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The role of peripheral oxytocin levels and alexithymia in relation to stress and comorbid mental illness in adults with and without autism spectrum disorder

vorgelegt von

Dr. Laura Irena Teresa Albantakis

aus

Ingolstadt, Deutschland

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First supervisor:	Prof. Dr. Leonhard Schilbach
Second supervisor*:*	Prof. Dr. Christoph Turck
Dean:	Prof. Dr. med. dent. Reinhard Hickel
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List of Abbreviations

ADHD	Attention deficit hyperactivity disorder
ADI-R	Autism Diagnostic Interview – Revised
ADOS	Autism Diagnostic Observation Schedule
ADP-IV	Assessment of DSM-IV Personality Disorders
AQ	Autism-Spectrum Quotient
ASD	Autism Spectrum Disorder
BDI-II	Beck Depression Inventory – II
CORT	Cortisol
EQ	Empathy Quotient
GAPD	General Assessment of Personality Disorder
HFA	High-functioning autism
LSAS	Liebowitz Social Anxiety Scale
MPIP	Max Planck Institute of Psychiatry
OCD	Obsessive-compulsive disorder
OCPD	Obsessive-compulsive personality disorder
OXT	Oxytocin
PD	Personality disorder
RME	Reading the Mind in the Eyes Test
TAS-20	Toronto Alexithymia Scale – 20

Contents

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with a prevalence of approximately 1 % across all ages (e.g. Baron-Cohen et al., 2009; Brugha et al., 2012). People affected by ASD show persistent deficits in social communication and social interaction as well as restricted and repetitive patterns of behavior, interests and activities (American Psychiatric Association, 2013).

Autism is a well-known disorder in child and adolescent psychiatry first described by Leo Kanner in 1943 and Hans Asperger in 1944. However, little is known about ASD in adulthood (Lai & Baron-Cohen, 2015; Lehnhardt et al., 2013). Most clinical and research work on ASD over the last decades has focused on early detection and early intervention in children in order to reduce disorder related symptoms and improve psychosocial functioning (Daniels, Halladay, Shih, Elder, & Dawson, 2014; Jones, Gliga, Bedford, Charman, & Johnson, 2014; Wong et al., 2015). While severity of autistic symptoms might decrease with age (Howlin, Moss, Savage, & Rutter, 2013; Magiati, Tay, & Howlin, 2014; Seltzer, Shattuck, Abbeduto, & Greenberg, 2004), clinical and social support are required in the majority of cases throughout the entire life (Howlin, Goode, Hutton, & Rutter, 2004; Levy & Perry, 2011). Most autistic individuals remain largely dependent on their family or social workers (Levy & Perry, 2011; Magiati et al., 2014) and do not find adequate employment despite good education and professional skills (Frank et al., 2018; Shattuck et al., 2012).

At least half of adult patients with ASD are diagnosed with concomitant psychiatric conditions especially depression and anxiety disorders (Albantakis et al., 2018; Lai & Baron-Cohen, 2015; Lehnhardt et al., 2013). Worst, suicide represents the second leading cause of death in young adults with high-functioning autism (Hirvikoski et al., 2016), highlighting the need for more awareness and therapeutic options for this patient population.

Still nowadays, only a limited number of clinical research institutions in Germany focus on ASD in adulthood (e.g. Michel et al., 2010; Roy, Dillo, Emrich, & Ohlmeier, 2009). In this regard, it is important to summarize and report clinical and research findings of ASD in adulthood, which have

been achieved during the last five years at the Max Planck Institute of Psychiatry and which are also part of this thesis.

At the beginning of the following chapter, the diagnostic assessment of ASD in adult patients will be described. The focus will be set on characteristic features of adults with ASD, common psychiatric comorbidities, relevant differential diagnoses, and psychosocial outcome. This information shall provide a basic understanding of clinical challenges and distinct features of autism in adulthood. In this context, published and unpublished work by the author of this thesis will be presented. At the end of the chapter, the thesis projects will be introduced including the aims of the thesis.

1.1 Definition of Autism Spectrum Disorder

In 2013, the American Psychiatric Association (APA) introduced the term "Autism Spectrum Disorder" (ASD) in its fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The diagnostic criteria for ASD according to DSM-5 are listed in Information Box 1. In short, ASD is characterized by social communication and interaction difficulties, restricted and repetitive behavior, and narrow interests (see Figure 1).

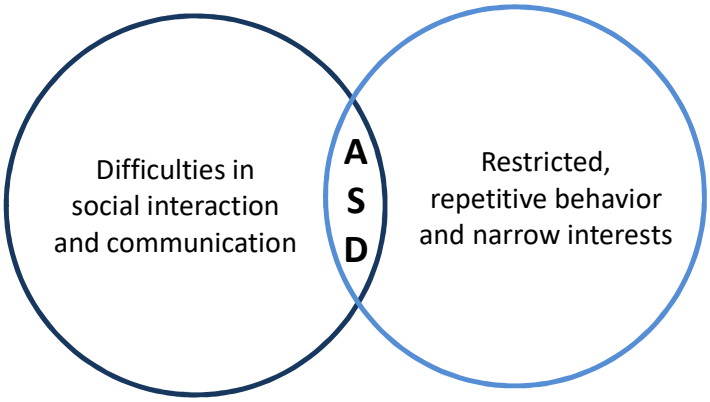

Figure 1. *Definition of autism spectrum disorder modified by Baron-Cohen (2008)*

Approximately 50 % of individuals with ASD possess at least average intelligence (Maenner et al., 2020). Originally the term "high-functioning autism (HFA)" described patients with an autistic disorder (ICD-10: F84.0) who were tested with no intellectual impairment (IQ > 70) but had a history of language delay. In recent years however, the term HFA has been extended, now including autistic individuals without intellectual impairment irrespective of a language delay in the past. On the one hand, this is due to the introduction of the umbrella term "autism spectrum disorder" in DSM-5, which does not further differentiate between "autistic disorder", "Asperger's syndrome", and "pervasive developmental disorder not otherwise specified". On the other hand, there are no clinical or neuropsychological criteria to reliably and objectively distinguish HFA from Asperger's syndrome in adulthood (Lehnhardt et al., 2013). Moreover, there seem to be no differences regarding the psychosocial outcome of adults with HFA and Asperger's syndrome (Howlin, 2003). Thus, the term

HFA is used in this thesis with its broader meaning including all patients with ASD without intellectual disability, irrespective of a language delay in childhood.

Information Box 1: Diagnostic criteria for autism spectrum disorder according to DSM-5 (APA, 2013)

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

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

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

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

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

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

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

Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.

1.2 Diagnostic assessment of ASD in adulthood

In this section, contents of the following publications are included:

- **Albantakis, L.**, Parpart, H., Krankenhagen, M., Böhm, J., Henco, L., Brandi, M.-L., & Schilbach, L. (2018). Autismus-Spektrum-Störungen (ASS) im Erwachsenenalter – Persönlichkeitsprofile und Begleiterkrankungen. *PTT – Persönlichkeitsstörungen; 22(01):56-71.*
- **Albantakis, L.** & Schilbach, L. (2020). Differentialdiagnostik von Störungen der sozialen Interaktion & Autismus im Erwachsenenalter. *Accepted for publication in Psychotherapie im Dialog (PiD) in May 2020*

Articles were originally written in German and have been translated into English for this thesis.

1.2.1 First assessment in adulthood

Since ASD is per definition a neurodevelopmental disorder with first symptoms typically appearing in the first 18 – 24 months of life (Guthrie, Swineford, Nottke, & Wetherby, 2013; Johnson et al., 2007), it is widely assumed that autistic individuals receive the diagnosis of ASD in early childhood. An early diagnosis is beneficial in order to install early intervention programs which would in turn help to reduce symptoms and improve the overall outcome of the autistic individual (Helt et al., 2008). Unfortunately, it is estimated that more than 40 % of autistic children, who already attend primary school, remain undiagnosed despite clinical symptoms and many of those reach adulthood without diagnosis (Baron-Cohen et al., 2009). The possibility of receiving an ASD diagnosis later in life has been acknowledged by the DSM-5 criteria (see Information Box 1; APA, 2013). There are multiple hypotheses why patients with ASD are not diagnosed until they reach adulthood. The most discussed reasons are briefly listed below:

Lack of awareness: Despite increasing public awareness for ASD in the last decades (Dillenburger, Jordan, McKerr, Devine, & Keenan, 2013), studies have shown that lack of knowledge and basic misconception of ASD are still common among (pre-)school teachers who represent key figures for identifying autism in early childhood (Barned, Knapp, & Neuharth-Pritchett, 2011;

Johnson, Porter, & McPherson, 2012; Liu et al., 2016). However, the perception and evaluation of the child by a third party can become essential to detect ASD in early childhood, when relatives of autistic individuals show social-communicative impairments themselves (Losh et al., 2009; Murphy et al., 2000; Piven, 1997). Consequently, parents of an autistic child might not identify abnormal behavior in their child due to own social-cognitive deficits. From clinical experience, it is quite common that parents consult specialists in ASD for a diagnostic assessment for themselves, after their child has been diagnosed with autism. In order to identify autistic symptoms at an early age, a greater importance should be attached to ASD in the training of (pre-) school teachers.

Misdiagnosis: Adults diagnosed with ASD later in life have often received the diagnosis of another psychiatric disorder before, including attention deficit hyperactivity disorder (ADHD), anxiety disorders, mood disorders, psychosis related disorders, and personality disorders (Geurts & Jansen, 2012). This is most likely due to the overlap of ASD related symptoms with other psychiatric conditions and the high comorbidity rate of psychiatric disorders in adults with ASD, potentially masking the underlying core condition (Happé et al., 2016). This aspect will be discussed in more detail in section 1.3.

Cognitive compensation mechanisms and camouflaging: Especially individuals with HFA acquire cognitive compensation mechanisms in order to respond adequately to social demands. These adaptation skills are usually trained by observing others and include e.g. copying proverbs, phrases for small talk, gestures and facial expressions (Lai & Baron-Cohen, 2015). The main objective is to “hide” ASD related deficits and to “be as neurotypical as possible”. Especially autistic women choose this strategy called “camouflaging” to fit in to society (Lai et al., 2017). However, the strategy is limited. In unfamiliar or “untrained” situations, autistic individuals cannot rely on learned techniques and demonstrate a lack of flexibility to adjust their behavior to the situation. Consequently, they feel exposed and mentally overstrained. The compensation strategies usually require high expenses which often lead to exhaustion, depression, and anxiety disorders (Lai et al., 2017). These comorbid psychiatric disorders are often the motivation to consult a psychiatrist or

psychotherapist. During the course of treatment when depressive or anxiety related symptoms decrease, the underlying core condition of ASD becomes more evident and patients are referred to an ASD specialist for a disorder related diagnostic assessment (Albantakis et al., 2018; Lai & Baron-Cohen, 2015).

Person environment-fit: This term describes the phenomenon that autistic individuals can succeed in life without much difficulty as long as they stay in an autism friendly environment (Lai & Baron-Cohen, 2015). This includes, for example, providing a daily structure, validating special interests and abilities, while respecting individual needs (Lai & Baron-Cohen, 2015). Leaving this environment, which usually happens in the transition phase from adolescence to adulthood, often entails social demands which exceed the limited capacities of the individual and reveal the underlying disorder (APA, 2013).

1.2.2 Introduction to diagnostic procedures of ASD in adulthood

In short, the diagnostic assessment of ASD in adulthood is very similar to the one in childhood or adolescence (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, 2015). It is mainly based on the assessment of the medical history with focus on early development and a behavioral observation by a clinician experienced with ASD (AWMF, 2015). An interview with a third party (e.g. parent, sibling, other family member) familiar with the developmental history of the patient can provide important information regarding abnormalities in early childhood. Otherwise, school reports or former medical records can also include indications for autistic behavior in the past (Albantakis & Schilbach, 2020; Albantakis et al., 2018; Lai & Baron-Cohen, 2015).

1.2.3 Diagnostic procedures of study projects

Patients recruited for study projects of this thesis, had a diagnostic assessment of ASD in adulthood at the “Outpatient or Day clinic for Disorders of Social Interaction” at the Max Planck Institute of Psychiatry (MPIP) in Munich. In both clinical institutions, the focus was set on the

diagnostic assessment and (psychotherapeutic) treatment of adults with HFA. In most cases, the contact to one of the clinical institutions at the MPIP was made by 1) the patient him-/herself, 2) a family member, 3) a clinical colleague or 4) a social worker by the employment office on behalf of the patient.

The diagnostic procedures at the MPIP followed the national autism guidelines (AWMF, 2015). As part of the diagnostic assessment, patients filled out a set of self-rating questionnaires including measures of autistic, empathetic, and alexithymic traits, a screening for relevant psychiatric comorbidities e.g. social phobia and depression, and differential diagnoses e.g. personality disorders. For more detailed information about the applied questionnaires, please refer to Information Box 2 “Questionnaires for the diagnostic assessment of ASD” and Information Box 3 “Questionnaires for relevant comorbidities and differential diagnoses in ASD”. Furthermore, the so called “gold standard” diagnostic tools for ASD were applied whenever possible, namely the “Autism Diagnostic Interview-Revised (ADI-R)” (Lord, Rutter, & Le Couteur, 1994) and the “Autism Diagnostic Observation Schedule” Module 4 (ADOS-2) (Hus & Lord, 2014). For further information, please refer to Information Box 4 “Gold standard diagnostic instruments in ASD”.

Information Box 2: Questionnaires for the diagnostic assessment of ASD

Autism-Spectrum Quotient (AQ)

AQ is a screening instrument for autistic traits in adults with at least average intelligence (Baron-Cohen, Wheelwright, Skinner, et al., 2001). It is a 50-item self-report questionnaire which covers five categories including social skill, attention switching, attention to detail, communication, and imagination with 10 items per category. Responses are given on a 4-point Likert scale ("definitely agree" to "definitely disagree") and dichotomized to indicate presence or absence of the symptoms. Scores range from 0 to 50 with higher scores indicating more autistic traits. Two cut-off scores were recommended in the past: to identify people who most likely have ASD, a cut-off of 26 would reduce false negatives, while a higher cut-off of 32 is likely to reduce false positives in a general population screen (Baron-Cohen, Wheelwright, Skinner, et al., 2001; Woodbury-Smith, Robinson, Wheelwright, & Baron-Cohen, 2005). In general, the AQ serves as a valid screening instrument for ASD but does not replace an in-depth diagnostic assessment. If the suspect of ASD exists and is further confirmed by high results in the AQ, the patient should be referred to a specialist experienced in ASD (Woodbury-Smith et al., 2005).

Empathy Quotient (EQ)

EQ is another screening instrument for empathetic traits which are supposed to be reduced in patients with ASD due to deficits in social cognition (Baron-Cohen & Wheelwright, 2004). It is a 60-item self-report questionnaire with 40 questions assessing empathy and 20 questions as filler or control items. Responses are given on a 4-point Likert scale ("strongly agree" to "strongly disagree"). On each empathy item a score of 2, 1, or 0 can be reached. Thus, scores range from 0 to 80 with higher scores indicating more empathetic traits. A cut-off of ≤ 30 was recommended to distinguish patients with ASD from controls (Baron-Cohen & Wheelwright, 2004).

Reading the Mind in the Eyes test (RME)

RME is an advanced theory of mind task involving mental state attribution and complex facial emotion recognition from photographs where only the eye region of the face is shown (Baron-Cohen et al., 2015; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). The revised version of the RME consists of 36 grey-scale pictures of people from magazines which were modified so that the main focus lies on the eye region. For each picture, four mental state terms are presented from which the participant has to choose the best one describing what the person on the picture might be thinking or feeling (Baron-Cohen et al., 2015; Baron-Cohen, Wheelwright, Hill, et al., 2001). For every correct answer, one point is given leading to a maximum score of 36. Multiple studies have shown that individuals with ASD score significantly lower than neurotypicals in the RME (Golan & Baron-Cohen, 2006; Holt et al., 2014; Lai et al., 2012; Lombardo, Barnes, Wheelwright, & Baron-Cohen, 2007; Losh et al., 2009; Wilson et al., 2014).

Information Box 3: Questionnaires for relevant comorbidities and differential diagnoses in ASD

Beck Depression Inventory (BDI-II)

BDI-II is a 21-item self-report questionnaire to measure severity of depression in adolescents and adults. The items assess depressive symptoms in relation to the diagnostic criteria for depressive disorders listed in the Diagnostic and Statistical Manual of Mental Disorders (4th ed.; American Psychiatric Association, 1994). Answers are given on a 4-point Likert scale ranging from 0 to 3 based on the severity of each item. The maximum score is 63 with higher scores representing greater severity of depressive symptoms (Beck, Steer, & Brown, 1996).

Liebowitz Social Anxiety Scale (LSAS)

LSAS is a validated instrument for screening and assessment of social phobic symptoms which can be used as self-report questionnaire or as clinician administered version (Fresco et al., 2001; Rytwinski et al., 2009). It contains 24-items including two subcategories of social interaction and performance situations which participants fear and/or avoid. Answers are given on a 4-point Likert scale ranging from 0 ("none" or "never") to 3 ("severe" or "usually") based on the severity or frequency of the symptomatology. The maximum score is 144 with higher scores representing greater severity and/or frequency. Scores of 50 to 64 are considered as "moderate social phobia", scores of 65 to 79 as "marked social phobia", scores of 80 to 94 as "severe social phobia", while scores equal and greater than 95 are interpreted as "very severe social phobia".

Toronto-Alexithymia-Scale-20 (TAS-20)

TAS-20 is a 20-item self-report instrument with three subscales including "difficulty describing feelings", "difficulty identifying feelings", and "externally oriented thinking" to evaluate alexithymic traits. Answers are given on a 5-point Likert scale ranging from 1 ("strongly disagree") to 5 ("strongly agree"). The total score and the categorical subscores are based on the sum of the according answers to the items. Scores ≤ 51 are considered as "non-alexithymia", scores of 52 to 60 as "possible alexithymia", while scores ≥ 61 are interpreted as "alexithymia" (Bagby et al., 1994).

Assessment of DSM-IV Personality disorders (ADP-IV)

ADP-IV can be used as a screening tool for personality disorders (PD). It is a self-report questionnaire with 94 items which assesses the trait and distress aspects of each criterion of DSM-4 related personality disorders (Schotte, de Doncker, Vankerckhoven, Vertommen, & Cosyns, 1998). The ADP-IV creates a personality profile but also allows classifying pathology into the different PD forms in a categorical and dimensional approach. Depending on the kind of PD different cut-off values were established (Doering et al., 2007; Schotte et al., 1998).

General Assessment of Personality Disorder (GAPD)

GAPD is a self-report questionnaire designed to evaluate general personality disorder. It measures self or identity problems and interpersonal dysfunction including the impact on psychosocial functioning (e.g. employment, relationships) (Hentschel, 2013; Hentschel & Livesley, 2013).

Information Box 4: Gold standard diagnostic instruments in ASD

Autism Diagnostic Interview – Revised (ADI-R)

ADI-R is a standardized, semi-structured interview which is conducted by a clinician experienced in ASD. The questions are usually addressed to a person familiar with the developmental history of the patient (e.g. parents, siblings or other caregivers). Focus of the interview is the patient's behavior with four to five years of age, as autistic symptoms are usually apparent at this time or a different time point when ASD related symptoms were most prominent. The ADI-R is comprised of 93 items referring to early development, language/communication, reciprocal social interactions, and restricted, repetitive behavior and interests. Scores are assigned on a scale ranging from 0 to 3 with higher numbers reflecting definite presence or greater severity of symptoms (Charman & Gotham, 2013; Lord et al., 1994).

Autism Observation Schedule (ADOS-2)

ADOS-2 is the only validated diagnostic instrument for adults with autism (Hus & Lord, 2014; Lai & Baron-Cohen, 2015). It is a semi-structured interview between (preferentially) a second independent examiner unfamiliar with the patient's history and the patient. The patient is asked to perform different tasks which aim to check for the diagnostic criteria for ASD while the social interaction and communication between the examiner and patient is observed. The interview is – with the patient's consent - recorded on video tape and later evaluated according to a specific scoring system. The cut-off value for ASD is at least seven points, while the value for autism is at least ten. However, research findings support clinical experience that people with HFA might not exceed the defined threshold for ASD in the high structured and well-defined observation situation of the ADOS-2 due to acquired cognitive compensation mechanisms (Lai et al., 2011). Therefore, ASD diagnosis should not be automatically excluded if the total score is below 7. For this reason, the ADOS-2 is not officially recommended as diagnostic instrument for adults in the national autism guideline (AWMF, 2015), but can be used as supporting information if required.

1.3. Psychiatric comorbidities and differential diagnoses in HFA

In this section, contents of the following publications are included:

- **Albantakis, L.**, Parpart, H., Krankenhagen, M., Böhm, J., Henco, L., Brandi, M.-L., & Schilbach, L. (2018). Autismus-Spektrum-Störungen (ASS) im Erwachsenenalter – Persönlichkeitsprofile und Begleiterkrankungen. *PTT – Persönlichkeitsstörungen; 22(01):56-71.*
- **Albantakis, L.**, Parpart, H., Thaler, H., Krankenhagen, M., Böhm, J., Zillekens, I.C., & Schilbach, L. (2018). Depression bei Erwachsenen mit Autismus-Spektrum-Störung. *Nervenheilkunde; 37(09): 587-593.*
- **Albantakis, L.** & Schilbach, L. (2020). Differentialdiagnostik von Störungen der sozialen Interaktion & Autismus im Erwachsenenalter. *Accepted for publication in Psychotherapie im Dialog (PiD) in May 2020*

The articles were originally written in German and have been translated into English for this thesis.

Psychiatric comorbidities are frequently observed in individuals with HFA and may change over lifespan regarding frequency and distribution. Most differential diagnoses can also be comorbid disorders in ASD, complicating the diagnostic assessment. While ADHD is the most common psychiatric comorbidity and differential diagnosis of ASD in childhood, the prevalence rates of comorbid depression and anxiety disorders increase in adolescence and adulthood (AWMF, 2015). In particular the transition phase from adolescence to adulthood is a critical time frame, when social demands and societal expectations increase, and individuals with ASD might struggle to meet these expectations in comparison to their neurotypical peers (Hendricks & Wehman, 2009; Volkmar, Jackson, & Hart, 2017). Here, people with HFA are at considerable risk of developing comorbid affective and anxiety disorders (Spain, Sin, Linder, McMahon, & Happé, 2018; Wigham, Barton, Parr, & Rodgers, 2017). In contrast to autistic individuals with intellectual disability, individuals with HFA possess the cognitive abilities to understand the life-long consequences they might have to face due to their autistic core condition (De-la-Iglesia & Olivar, 2015; Hedley, Uljarević, Foley, Richdale, &

Trollor, 2018; Volkmar et al., 2017). Furthermore, bullying is a relevant risk factor for developing comorbid depression and social phobia (De-la-Iglesia & Olivar, 2015; Hawker & Boulton, 2000), suicidal thoughts and suicidal attempts in individuals with ASD (De-la-Iglesia & Olivar, 2015; Holden et al., 2020; Mayes, Gorman, Hillwig-Garcia, & Syed, 2013; Mikami et al., 2009; Richa, Fahed, Khoury, & Mishara, 2014).

1.3.1 Attention deficit hyperactivity disorder

ADHD is the most common psychiatric comorbidity and most relevant differential diagnosis of ASD in childhood. ADHD is characterized by inattentiveness, hyperactivity and impulsiveness. Like ASD, it is a developmental disorder with onset in (early) childhood (AWMF, 2017). Contrary to ASD, the prevalence rate of ADHD decreases over the lifespan due to maturation processes in the brain (AWMF, 2017). While 5.3 % of children and adolescents fulfill the diagnostic criteria for ADHD, only 2.5 % of adults still do. In ASD, prevalence rates of approximately 1 % remain constant across all ages (Baron-Cohen et al., 2009; Brugha et al., 2012).

Delineating ASD and ADHD especially in childhood is challenging given the overlapping features of both disorders, e.g. inattention and hyperactivity, lack of social skills, and behavioral problems (Clark, Feehan, Tinline, & Vostanis, 1999; Mayes, Calhoun, Mayes, & Molitoris, 2012; Sturm, Fernell, & Gillberg, 2004). Furthermore, both disorders exhibit neurocognitive impairments such as deficits in executive functions (Corbett, Constantine, Hendren, Rocke, & Ozonoff, 2009; Happé, Booth, Charlton, & Hughes, 2006), low processing speed (Calhoun & Mayes, 2005), and learning disability in written expression among others (Mayes & Calhoun, 2007; Mayes, Calhoun, Mayes, & Molitoris, 2012). In patients with HFA, ADHD is often diagnosed first before ASD, but therapeutic interventions e.g. psychotherapy and medication improve ADHD related symptoms, uncovering the underlying core condition (Kentrou, de Veld, Mataw, & Begeer, 2019). In adulthood, prevalence rates of ADHD in ASD cases have been found to vary between 9 % and 36 % (Albantakis et al., 2018; Ghaziuddin, Weidmer-Mikhail, & Ghaziuddin, 2002; Hofvander et al., 2009).

1.3.2 Depression

Depression is one of the most relevant concomitant psychiatric conditions of ASD in adolescence and adulthood (Albantakis et al., 2018; De-la-Iglesia & Olivar, 2015; Hedley et al., 2018; Wigham et al., 2017). Depression is characterized by a depressed mood, loss of interest or pleasure in most activities, low self-esteem, physical changes such as significant weight loss or weight gain, low energy, sleep disturbances, anxiety, and a diminished ability to think or concentrate (APA, 2013; van den Bosch & Meyer-Lindenberg, 2019). Additionally, recurrent thoughts of death, suicidal ideation or a suicide attempt can occur (APA, 2013).

In adulthood, depression has been observed in 30 to 70 % of ASD cases (Ghaziuddin et al., 2002; Hofvander et al., 2009; Lugnegård, Hallerbäck, & Gillberg, 2011). In a study with 186 autistic patients at the MPIP (Albantakis et al., 2018), 50 % presented with a depressive disorder. Of those, 37.7 % had a moderate, 10.2 % a severe and 2.1 % a mild depression at the time of the diagnostic assessment. In line with work by Lugnegard et al. (2011), 70.9 % of autistic patients at the MPIP stated to have had at least one depressive episode in their lifetime (Albantakis et al., 2018). Suicidal ideation was reported by 14 % of patients at the time of the diagnostic assessment, while 38.7 % of patients stated to have experienced suicidal ideation once in their lifetime which was similar to findings by others (Strunz, Dziobek, & Roepke, 2013). In this context, 10.2 % had attempted suicide at least once in their life in accordance with previous observations (Lehnhardt et al., 2011). These prevalence rates highlight the importance of screening for comorbid depression in autistic adults including the assessment of suicidality (Albantakis et al., 2018). Suicide was found to be the second leading cause of death in young adults with HFA (Hirvikoski et al., 2016). Thus, an early assessment and prevention of risk factors increasing depression and suicidality should be installed to help autistic individuals and ultimately save lives.

1.3.3 Personality disorders

Personality disorders (PD) are one of the most relevant differential diagnoses for ASD in adulthood. A personality disorder (PD) is a mental illness in which individuals show an inflexible and

detrimental form of thinking, functioning and behaving (APA, 2013; Tyrer, Reed, & Crawford, 2015). Patients with PD have difficulties in interpreting situations and interacting with others, which can ultimately lead to conflicts and impairments in many aspects of life including relationships, work, and living conditions (APA, 2013; Tyrer, Reed, & Crawford, 2015). In general, the DSM-5 describes ten different forms of PDs. The most relevant ones as differential diagnoses for ASD are the schizoid, schizotypal, avoidant and obsessive-compulsive PD (Albantakis & Schilbach, 2020; Strunz et al., 2013).

Contrary to ASD where first core symptoms arise in early childhood (APA, 2013), PD related symptoms become more evident later in life, for instance in adolescence or early adulthood (Johnson, Cohen, Kasen, Skodol, & Oldham, 2008; Lugnegård, Hallerbäck, & Gillberg, 2012). In this context, a structured and comprehensive medical history including early childhood development can be fundamental to distinguish ASD from PDs (Albantakis & Schilbach, 2020; Lai & Baron-Cohen, 2015).

Furthermore, ASD is a disorder characterized by deficits in social interaction and communication as well as restricted, repetitive patterns of behavior, interests and activities (APA, 2013). PDs, however, mainly present with social-communicative impairments. While other research groups found that individuals with ASD might formally fulfil the diagnostic criteria for an obsessive-compulsive, schizoid or avoidant PD (Hofvander et al., 2009; Strunz, Dziobek, & Roepke, 2013), none of the 45 adult patients with ASD at the MPIP reached the diagnostic threshold for any PD in a preliminary study using the "Assessment of DSM-IV Personality Disorders" (ADP-IV) by Schotte and colleagues (Albantakis et al., 2018; Schotte et al., 2004). The personality profile of the autistic patients at the MPIP was further examined by the "General Assessment of Personality disorder" (GAPD) by Hentschel and Livesley (2013). Results from the autistic patients were compared with published data from patients with PD by Hentschel (2013) (see Figure 2). Adults with ASD described significantly more difficulties in intimacy and attachment (P1: "Intimacy and attachment") and in establishing and maintaining friendships (P2: "Affiliation"). Furthermore, autistic patients showed a

significantly lower “cooperativeness” (P4) or “lower capacity to work together with other people” than patients with PD (Albantakis et al., 2018; Hentschel, 2013). Given that autism is a neurodevelopmental disorder with onset in early childhood, these results suggest that social-communicative impairments seen in ASD are more profound than those observed in PD.

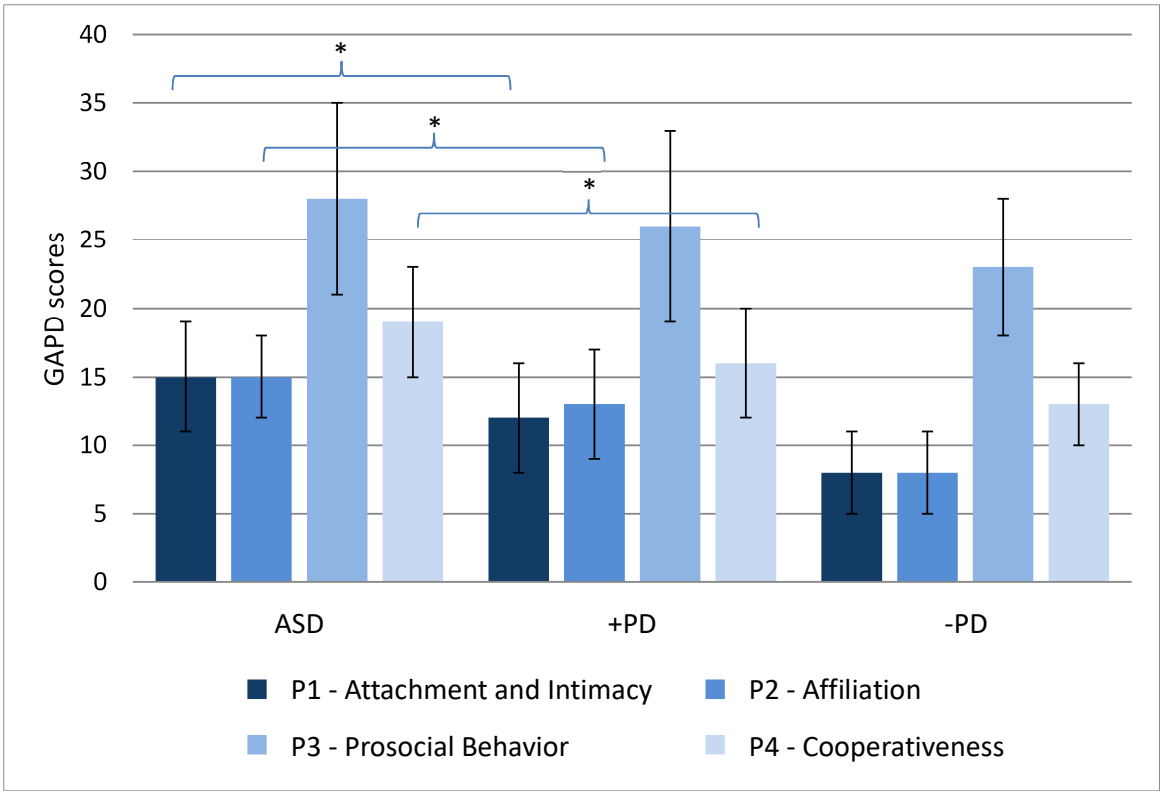

Figure 2. *Interpersonal pathology scales in adults with and without ASD*

This figure illustrates the differences of the interpersonal pathology scales between patients with autism spectrum disorder (ASD; *n*=63), personality disorder (+PD; *n*=75) and without personality disorder (-PD; *n*=75). Data are shown as mean values of scores obtained in the General Assessment of Personality Disorder (GAPD) ± Standard Error of Means.
*denotes significance of $p < 0.05$.

(modified from Albantakis et al., 2018)

Furthermore, autistic individuals unlike people with schizoid PD would like to socially engage with others e.g. establish friendships or romantic relationships (Dewinter, De Graaf, & Begeer, 2017; Müller, Schuler, & Yates, 2008; Strunz et al., 2017), contrary to general believes that autistic people prefer to be alone. However, autistic individuals often report not to know “how” to approach others adequately and feel easily overwhelmed by the situation (Byers, Nichols, & Voyer, 2013; Dewinter et

al., 2017; Müller et al., 2008; Strunz et al., 2017), leaving them (unwillingly) more socially isolated than neurotypicals.

Although behavioral patterns of people with avoidant or obsessive-compulsive PD (OC-PD) might resemble autistic characteristics, there are profound differences between these disorders (see Table 1). Furthermore, autistic individuals present more severe social-communicate impairments than people with avoidant PD or OC-PD (Fitzgerald, 2002; Lugnegård, Hallerbäck, & Gillberg, 2012). Despite certain overlaps of symptomatology seen in ASD and schizotypal PD (Barneveld et al., 2011; Hurst, Nelson-Gray, Mitchell, & Kwapil, 2007), autistic individuals do not over-interpret situations e.g. implicating a direct meaning to them, present with magical thinking or believe in superstitions. Quite the contrary, autistic individuals act rationally and make decisions based on facts (Brosnan, Lewton, & Ashwin, 2016; De Martino, Harrison, Knafo, Bird, & Dolan, 2008).

However, autistic individuals can also appear "arrogant" with a "know-it-all" attitude (Kirchner & Dziobek, 2014) given the expertise in their special interests and an insensitivity to social reputation (Izuma, Matsumoto, Camerer, & Adolphs, 2011; Kirchner & Dziobek, 2014). Thus, ASD related symptoms might be misinterpreted and wrongly attributed to narcissistic PD. Compared to autistic individuals, people with narcissistic PD are more extroverted, more open to experience and much less organized (Strunz et al., 2015). Furthermore, they present with reduced emotional empathy and intact cognitive empathy while opposite traits are found in people with ASD (Dziobek et al., 2008; Ritter et al., 2011).

1.3.4 Social phobia

Social phobia plays an important role as comorbid disorder but also differential diagnosis of ASD in adulthood. Patients affected by social phobia are usually afraid of social or performance situations in which they are exposed to unfamiliar people or possible scrutiny by others. They fear to act in a way that is embarrassing or humiliating for them (APA, 2013). Therefore, patients with social phobia usually try to avoid these situations or endure them while experiencing intense anxiety and distress (APA, 2013).

Despite a certain overlap of social phobic and autistic traits (Spain et al., 2018), distinct differences exist between these two disorders. Like patients with social phobia autistic individuals tend to avoid social situations. But unlike patients with social phobia, people with ASD are not afraid of a potential negative evaluation by others, but avoid social interactions due to the unpredictability and uncontrollability of the social encounter (Izuma et al., 2011; Tyson & Cruess, 2012). Furthermore, people with ASD present with repetitive and restricted patterns of behavior, interests or activities, while patients with social phobia do not show any of these symptoms (Spain et al., 2018). Irrespective of differences and overlaps between these two disorders, people with ASD can develop social phobia during life-span which is most likely due to negative experiences of social interactions with others (Kuusikko et al., 2008). 11.3 % of the MPIP sample had a comorbid social phobia (Albantakis et al., 2018), which is in line with results by others (Strunz et al., 2013), but less frequent than findings with rates up to 50 % (Bellini, 2004; Maddox & White, 2015; Spain et al., 2016).

1.3.5 Obsessive-compulsive disorders

Like social phobia, obsessive-compulsive disorders (OCD) need to be considered as important comorbid condition but also differential diagnosis. OCD are characterized by recurrent and persistent thoughts, urges or images that are experienced as intrusive and unwanted, causing anxiety or distress, and the attempts by the individual to ignore or suppress such thoughts, urges, or images, or to neutralize them with some thought or action (i.e., by performing a compulsion) (APA, 2013).

Although repetitive and restricted behavior observed in ASD might resemble OCD features, autistic patients do not experience it as intrusive, unwanted or detrimental (Neil & Sturmey, 2014). In contrast, most patients describe it as relaxing and calming (Howlin, 2004). Furthermore, the repetitive and restricted behavior is not applied in order to prevent or to control some dreaded event or situation, as it is commonly found in OCD (Neil & Sturmey, 2014). Nevertheless, it is possible that patients with ASD develop OCD as comorbid condition (Neil & Sturmey, 2014). In the

study with 186 patients from the MPIP (Albantakis et al., 2018), 7 % of autistic patients had comorbid OCD which was in line with other findings about OCD in adult ASD (Strunz et al., 2013).

1.3.6 Schizophrenia

Unlike depression or social phobia, schizophrenia is more often considered as differential diagnosis than as a comorbid condition of ASD in adulthood. Characteristic symptoms of schizophrenia are delusions, hallucinations, disorganized speech (e.g. derailment or incoherence), disorganized or catatonic behavior, and negative symptoms (i.e. affective flattening, alogia, or avolition) (APA, 2013). Additionally, patients demonstrate social or occupational dysfunction in one or more areas of life including work, interpersonal relationships, and self-care. The level of functioning is notably below the level achieved prior to the onset of the psychopathology (APA, 2013).

Prodromal stages and clinical courses with primarily negative symptoms or mild impairments are usually the forms of schizophrenia where symptoms might resemble autistic characteristics (Spek & Wouters, 2010). In particular, loss of interest, social withdrawal, hypersensitivity and irritability, often observed during the prodromal stages before psychotic symptoms arise (Klosterkötter, Hellmich, Steinmeyer, & Schultze-Lutter, 2001), might be difficult to delineate from ASD (Albantakis & Schilbach, 2020). Once again, a comprehensive assessment of early childhood development can provide clarity.

While ASD related symptoms are already observed from an early age on (APA, 2013), schizophrenic symptoms usually appear in late adolescence and early adulthood (Gogtay, Vyas, Testa, Wood, & Pantelis, 2011; Hafner et al., 1994). Information by third parties including parents, care givers, teachers, and friends can contribute to a better understanding of the pathological process (e.g. time of onset, kind and severity of symptomatology etc.) (Albantakis & Schilbach, 2020). Furthermore, autistic patients do not experience positive symptoms e.g. delusions, hallucinations or show paranoid tendencies (Spek & Wouters, 2010). Unlike schizophrenic patients, ASD patients do not suffer from disorganized formal thought processes like derailment or

incoherence. However, autistic individuals can experience hallucinations and delusional convictions, usually as transitory psychotic manifestations (Lehnhardt et al., 2013). In case ASD exists as core condition, the DSM-5 criteria suggest that the diagnosis of schizophrenia can only be given if prominent delusions or hallucinations persist for at least 1 month in addition to other required symptoms for the diagnosis of schizophrenia (APA, 2013).

According to a recent study, the risk of developing schizophrenia is 3.55-fold higher for autistic individuals than for non-autistic controls (Zheng, Zheng, & Zou, 2018). In a study from the MPIP (Albantakis et al., 2018), 1.6 % of patients suffered from comorbid schizophrenia. Findings from a recent meta-analysis suggest a prevalence rate of 6 % for “schizophrenia spectrum disorders” in ASD (Lugo Marín et al., 2018), while others have reported prevalence rates between 0.5 % and 6 % for schizophrenia in ASD (Skokauskas & Gallagher, 2009)

Table 1: Core symptoms of ASD in comparison with relevant differential psychiatric diagnoses

	ASD	Schizoid PD	Schizotypal PD	Schizophrenia	Avoidant PS	Social Phobia	OCPD	OCD	ADHD
Social interaction	●	●	●	●	●	●	●	●	●
Autistic characteristics									
Verbal communication	●	●	●	●	●	●	●	●	●
Nonverbal communication	●	●	●	●	●	●	●	●	●
Eye contact	●	●	●	●	●	●	●	●	●
Theory of mind	●[1]	●	●[2]	●[3]	●[3]	●[3]	●	●	●[5]
Interests/ rituals/ compulsions	●	●	●	●	●	●	●	●[4]	●
Concomitant symptoms/ prodromal symptoms									
Attention	●	●	●	●	●	●	●	●	●
Psychomotor function	●	●	●	●	●	●	●	●	●
Self-harm	●	●	●	●	●	●	●	●	●
Psychotic symptoms	●	●	●	●	●	●	●	●	●
Long-term manifestations									
Social interaction in childhood	●	●	●	●	●	●	●	●	●
Biographical stress factors	●	●	●	●	●	●	●	●	●

●: usually abnormal; ●: usually normal; ●: potential concomitant symptoms; ASD: Autism spectrum disorder; PD: Personality disorder; OCPD: Obsessive-compulsive personality disorder; OCD: Obsessive-compulsive disorder; ADHD: Attention deficit hyperactivity disorder.
[1] Hypomentalization, [2] suspicious-paranoid, [3] Hypermentalization, [4] ego-dystonic character, [5] due to attention deficit.

(modified from Lehnhardt et al., 2013)

Information Box 5: Comorbidities and differential diagnoses in ASD

- Approximately 50 % of adults with HFA experience comorbid depression and/or social phobia (at least once) in their lifetime.
- Other common psychiatric comorbidities include OCD and ADHD.
- Autistic people might formally fulfil the diagnostic criteria for a PD. To differentiate ASD and PD, onset and severity of symptoms need to be interrogated.
- Aside from deficits in social communication and interaction, people with ASD also present with repetitive and restricted behavior. A comprehensive assessment of the medical history including early development can help to distinguish ASD from other psychiatric conditions.
- The diagnosis of schizophrenia can additionally be given in ASD, if prominent delusions or hallucinations exist in addition to other relevant diagnostic criteria.

1.4. Psychosocial outcome

Although one in 100 people are autistic (e.g. Brugha et al., 2012), there is still limited research on psychosocial outcome measures in autistic individuals in adulthood (Kirby, Baranek, & Fox, 2016; Magiati, Tay, & Howlin, 2014). From the existing literature on this topic, psychosocial outcome values such as employment, marital status, and living conditions seem to vary among adults with ASD. This may be due to multiple factors such as the spectrum character of autism, cognitive abilities, language development, comorbid disorders, and family- or service-dependent support (Farley et al., 2009; Henninger & Taylor, 2013; Holwerda, van der Klink, Groothoff, & Brouwer, 2012; Howlin, Goode, Hutton, & Rutter, 2004; Kirby et al., 2016; Levy & Perry, 2011; Magiati et al., 2014; Scott et al., 2018).

For this thesis, a preliminary analysis of the psychosocial outcome in adult patients diagnosed with ASD at the MPIP was conducted. Information about school qualification, professional careers, employment, marital status, and living conditions of 122 autistic patients (68 % males) with an average age of 33.5 ± 10.4 years (18 – 60 years) was evaluated. The findings from this preliminary analysis will be reported in the following sections to exemplify psychosocial outcome measures from autistic patients in adulthood.

1.4.1 School qualification

Most patients with HFA (58.2 %) possessed a university qualification (see Figure 3). Only 0.8 % did not have a school-leaving qualification. Approximately a fourth of autistic patients provided a general certificate of secondary education.

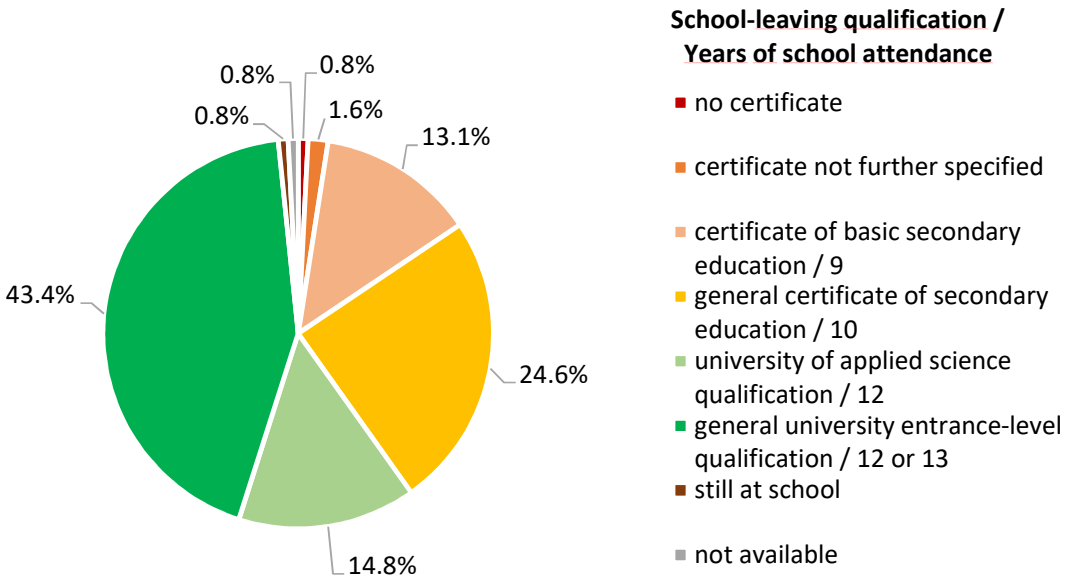

Figure 3. *Distribution of school leaving qualification in the ASD sample*

1.4.2 Professional qualification

Despite a high standard of school qualifications in average, approximately 16 % of autistic patients did not have any professional qualification (see Figure 4). Although 58.2 % of the ASD sample provided a university entrance qualification (see 1.4.1 School qualification), less than half of them went to college or university after high school.

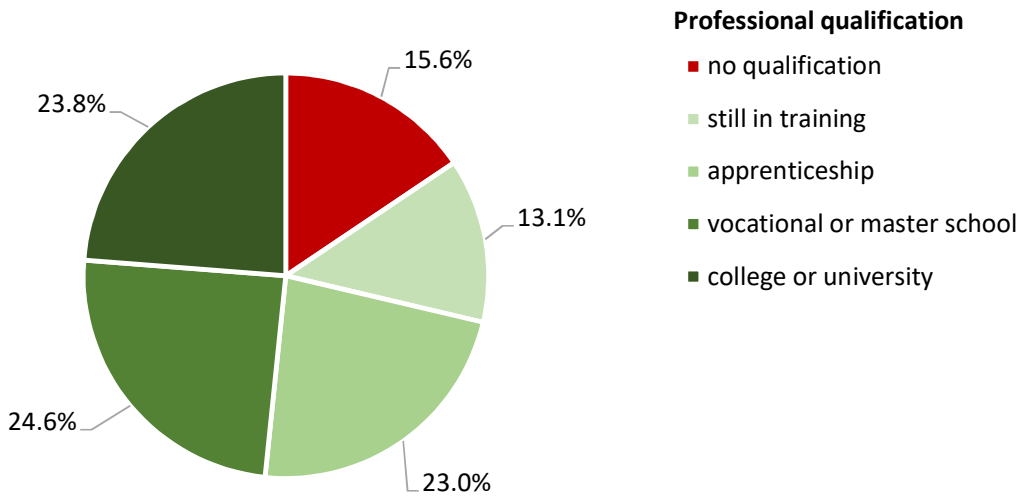

Figure 4. *Distribution of professional qualification in the ASD sample*

1.4.3 Employment status

Of the 122 autistic patients, 43.5 % did not pursue a professional career at the time of the diagnostic assessment at the MPIP (see Figure 5). This high rate is alarming given that only 0.8 % of patients did not have a school qualification and 58.2 % provided a university entrance qualification. Approximately 43 % of autistic patients worked in full-time. This percentage might seem promising. However, presumably only a limited number of patients worked in a job or in a job position according to their qualifications and interests (Frank et al., 2018; Scott et al., 2019; Vogeley, Kirchner, Gawronski, van Elst, & Dziobek, 2013).

Our findings from the MPIP regarding school qualification, professional qualification, and employment status in adults with ASD are in line with results by other research groups (Frank et al., 2018; Scott et al., 2019; Vogeley et al., 2013), demonstrating that people with ASD show difficulties in pursuing and maintaining employment despite good education and a high professional skill set. In this context, it is important to mention that people with HFA are aware of the discrepancy between their skills (i.e. their expertise and cognitive abilities) on the one hand, and the inability to unfold their potential on the other hand. Due to repeated frustration and failures in the work environment

in addition to the prospect of a life-long condition which cannot be healed at this stage, autistic patients are at risk of developing depressive comorbidities (Albantakis et al., 2018; Hedley et al., 2019; Vogeley et al., 2013). Therefore, it is of great importance to develop autism friendly work environments in which people with ASD get the opportunity to unfold their potential (Kirchner & Dziobek, 2014; Vogeley et al., 2013).

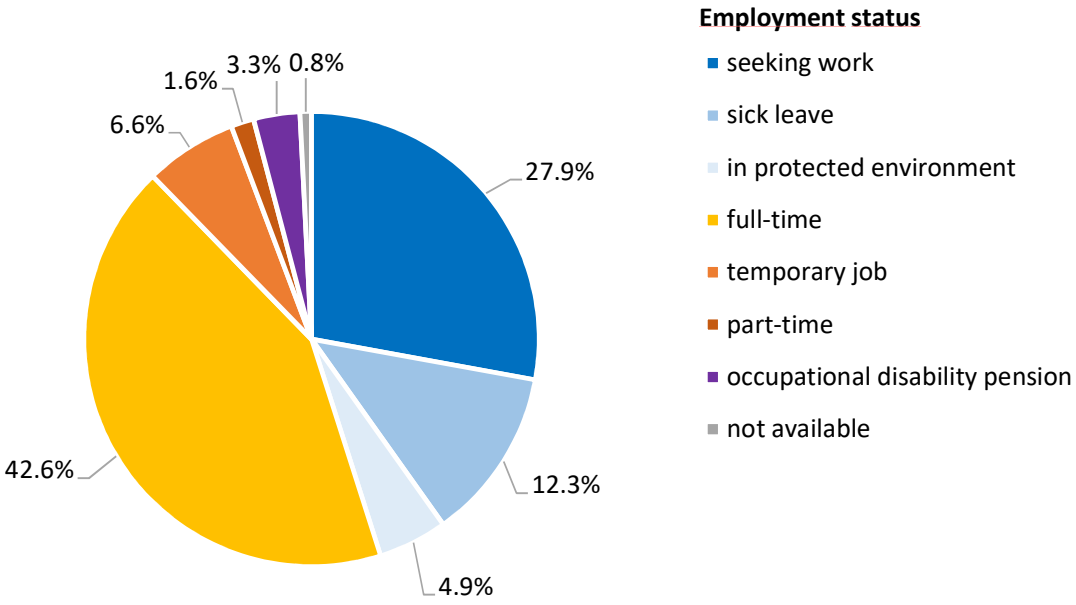

Figure 5. *Distribution of employment in the ASD sample*

1.4.4 Marital status

Contrary to general believes, autistic people are interested in romantic relationships (Cheak-Zamora, Teti, Maurer-Batjer, O'Connor, & Randolph, 2019; Strunz et al., 2017). Thus, approximately one third of the MPIP sample was in a relationship at the time of the diagnostic assessment (see Figure 6). It can be assumed that most of the patients had a neurotypical partner, considering that in a sample similar to this 80 % of autistic adults were in a romantic relationship with a non-autistic person (Strunz et al., 2017). In the study by Strunz et al. (2017), 44 % of the 229 patients with ASD (40 % male participants with an average age of 35 years) stated to have a partner.

In the sample from the MPIP, in which 68 % of autistic patients were male with an average age of 33.5 years, 28.9 % were in a romantic relationship. Male sex was found to be more often associated with no relationship experience (Byers et al., 2013; Strunz et al., 2017). Indeed, more female patients of the MPIP sample (33.3 %) were in a relationship compared to males. Byers and colleagues (2013) explained this phenomenon by referring to traditional, gender related roles. For instance, there may be higher social expectations for men to initiate the contact to a person they are romantically interested in, and for women to react to advances. While autistic men might struggle to meet these traditional expectations of "making the first move", women with ASD might have the advantage of succeeding with a more passive and introverted behavior.

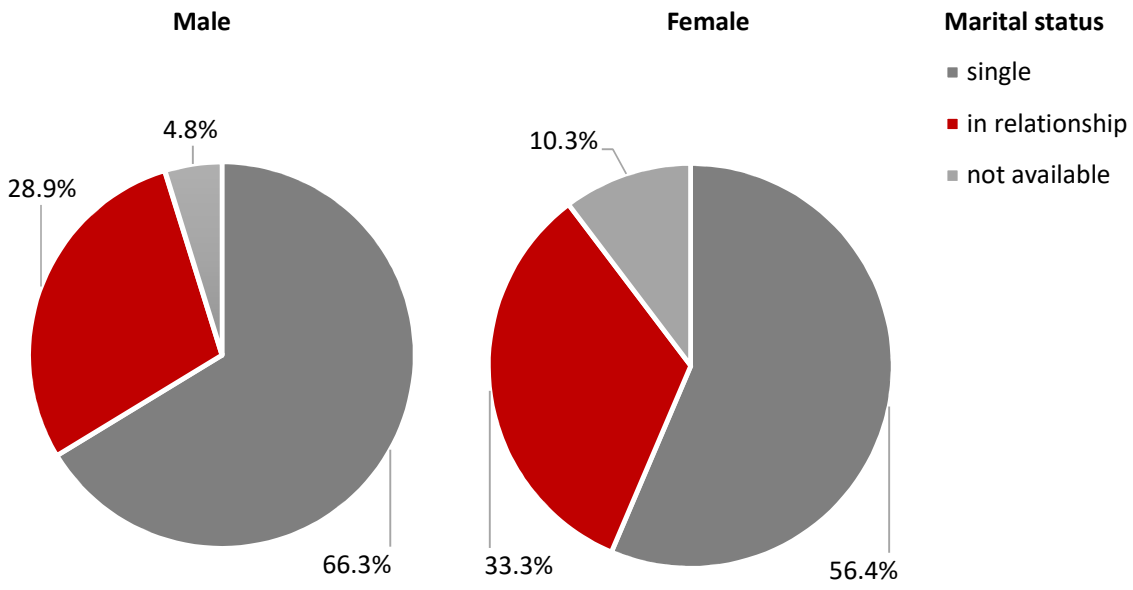

Figure 6. *Distribution of marital status in male and female patients with ASD*

1.4.5 Living conditions

Most patients with ASD lived either on their own (27.9 %), with a partner, children or as a family (31.2 %) or with their parents (31.1 %) (see Figure 7). Given the average age of 33.5 years, the percentage of patients still living with their parents appears relatively high for German standards. In fact, data from peers of the general (German) population extremely deviated from the ASD sample. Only a small percentage (men: 5 %, women: 2 %) still lived with their family, while the majority (men: 68 %, women: 73 %) lived with their partners (Weimann, 2010). In one of the very few articles which exist about psychosocial outcome values in autistic adults, the authors state that the majority of autistic individuals remain fully or largely dependent on parents or care givers, and require significant support for education, living arrangements and employment (Magiati et al., 2014). These observations are in line with findings of psychosocial outcome measures in adults with ASD from the MPIP. The lack of autonomy in the MPIP sample becomes strikingly evident when facing the high percentage of adults still living with their families (31.1 %) despite (at least) average intelligence and good education.

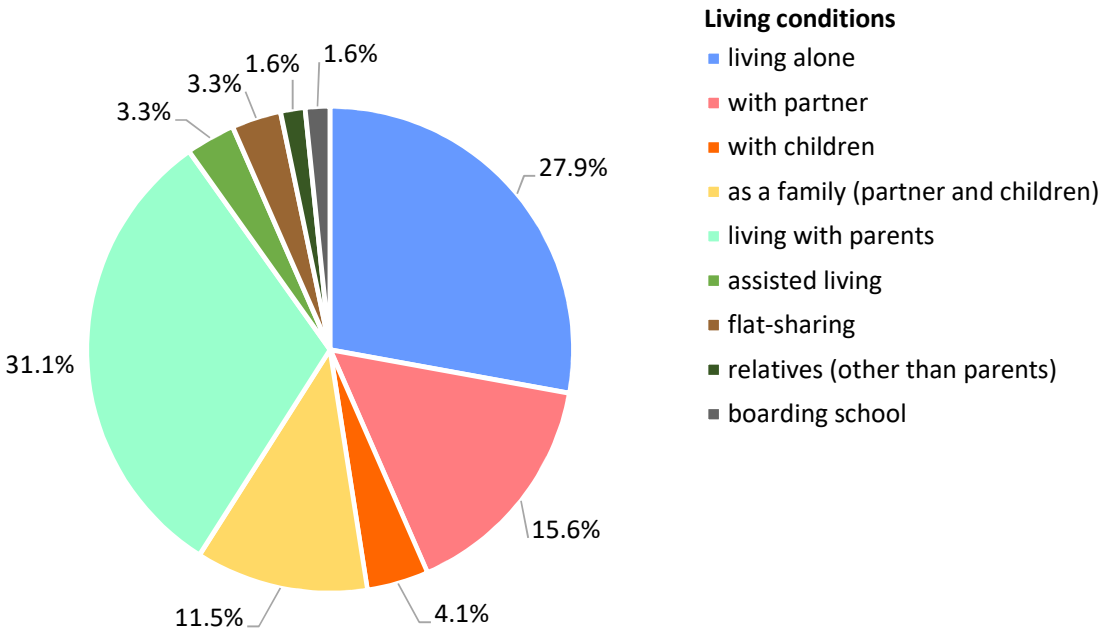

Figure 7. *Distribution of living conditions in the ASD sample*

Information Box 6: Psychosocial functioning in ASD

- Despite good education and professional qualifications approximately half of individuals with HFA do not find adequate employment.
- Repeated frustration and failures in the work environment can increase the risk for depression.
- Despite interest in romantic relationships only one third of autistic adults have a partner.
- Approximately one third of adults with ASD still live with their parents. This is in stark contrast to their neurotypical peers where only 2-5 % live with their parents.
- Adults with ASD require significant support in various areas of life.

1.5 Stress vulnerability in ASD

As described in the previous chapters, adults with HFA show high rates of comorbid depression and anxiety disorders, also referred to as "distress disorders" (Watson, 2005). Furthermore, autistic adults often stay behind their potential despite sufficient cognitive and language abilities resulting in low psychosocial functioning (Howlin, Goode, Hutton, & Rutter, 2004; Kirby, Baranek, & Fox, 2016; Levy & Perry, 2011; Magiati et al., 2014). Like the dimensional character of ASD, mental health and psychosocial outcome measures seem to vary among adults with HFA. While approximately half of all individuals with HFA are affected by comorbid mental illness and provide low psychosocial functioning, others show no clinically relevant impairments in this regard.

The stress-vulnerability model by Zubin and Spring (1977) defines that intrinsic vulnerability (e.g. genetic predisposition, abnormal brain function) in combination with psychosocial stressors (e.g. inter-personal or occupational stressors) can lead to mental illness (e.g. depression, anxiety disorders) (Goh & Agius, 2010). Since ASD is a predominantly neurobiological disorder with a complex, heterogeneous, multifactorial etiology involving genetic, epigenetic, immunological and environmental factors (Marotta et al., 2020; Parellada et al., 2014), it can be assumed that ASD itself represents an intrinsic vulnerability. Given the profound impairments in social interaction and communication in addition to the restricted and repetitive behavior of ASD (APA, 2013), it is likely that autistic individuals experience increased levels of stress in comparison to neurotypical peers. In particular, social-cognitive deficits may hinder autistic individuals to apply adequate emotion regulation strategies.

In recent years, the "tend and befriend" concept has attracted more interest in social neuroscience proposing that human beings tend to affiliate – to gather together and protect each other – in challenging situations (Baumeister & Leary, 1995; Taylor, 2006; Taylor, 2002). In this context, oxytocin (OXT) has been assigned an important role in stimulating affiliative behavior in response to stress (Taylor, 2006). Furthermore, OXT and social support have been shown to attenuate the biological and psychological stress response in human beings (Grewen, Girdler, Amico,

& Light, 2005; Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003). Conversely, negative encounters with social contacts or a lack of social support have been suggested to increase stress (Taylor, 2006).

Due to their social deficits, it is likely that autistic individuals are at risk of heightened levels of stress because they cannot sufficiently apply a "tend and befriend" behavior as response to stress. Furthermore, they may frequently be exposed to psychosocial stressors like bullying, social exclusion, lack of social support and unemployment (Frank, Jablotschkin, Arthen, Riedel, Fangmeier, Hölzel, & Tebartz van Elst, 2018; Holden et al., 2020; Strunz et al., 2017; Vogeley et al., 2013). These psychosocial stressors further increase stress in individuals with ASD, which can ultimately lead to distress disorders such as anxiety disorders and depression. These factors might turn into a vicious circle with mental illness aggravating social impairments and consequently exacerbating psychosocial stressors (see Figure 8).

In order to prevent chronic stress and comorbid mental illness in ASD, it is essential to identify risk factors which increase the stress vulnerability in adults with ASD. For this thesis, two constructs have been investigated which have been associated with deficits in social interaction and communication in context of autism, stress-coping and mental illness. For each construct an independent study has been designed and conducted.

In the first study (see Section 2.3), the role of OXT in ASD in relation to stress has been investigated, while in the second study (see Section 3.3), it has been tested whether alexithymia represents a risk factor for comorbid mental illness in adults with ASD.

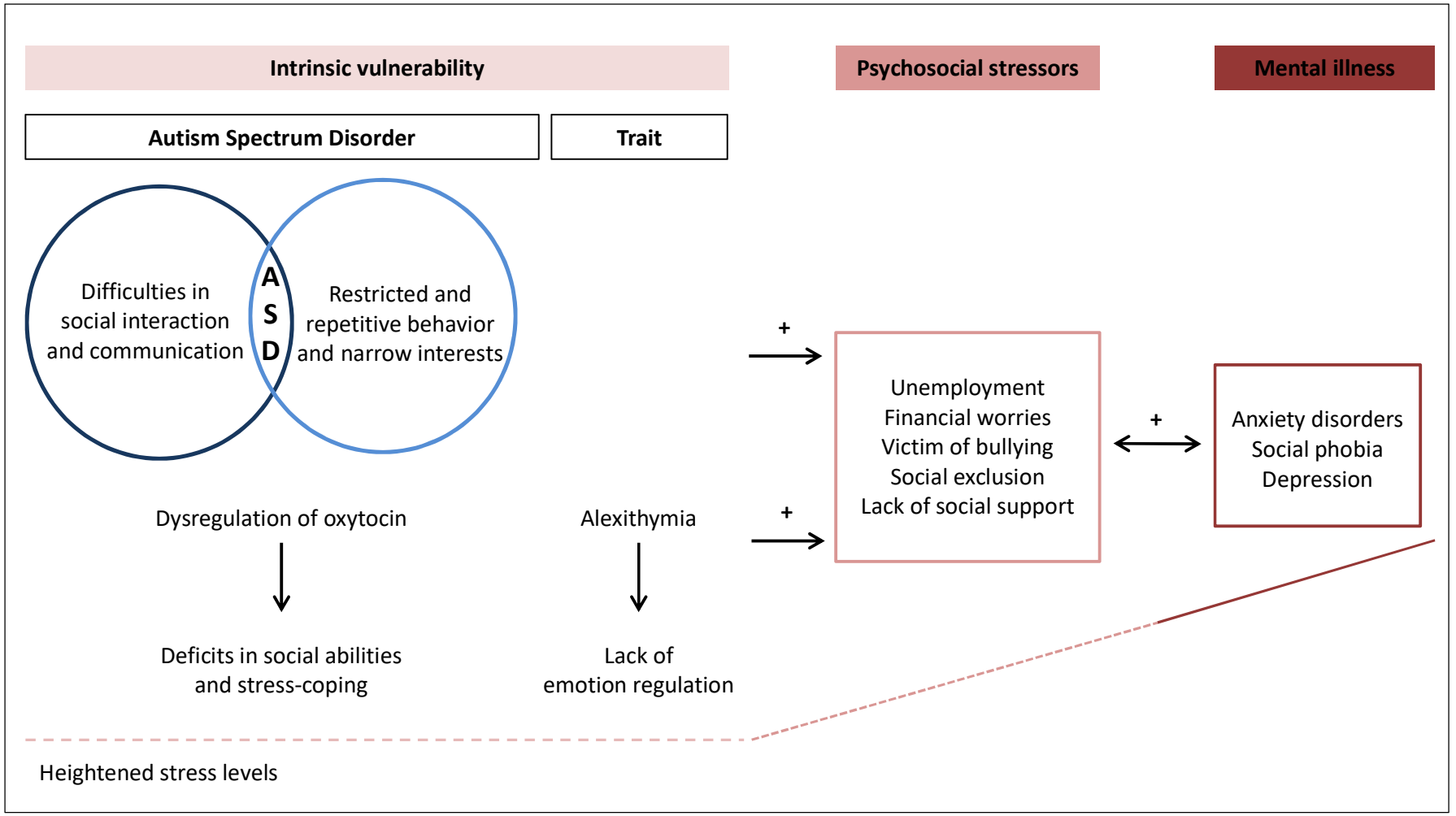

Figure 8. *Simplified stress vulnerability model for comorbid distress disorders in ASD with focus on oxytocin and alexithymia*

Dysregulation of oxytocin (as suggested underlying pathomechanism of autism spectrum disorder) and potential co-existing traits like alexithymia increase the intrinsic vulnerability for comorbid mental disorders. Due to deficits in social abilities, stress-coping and insufficient emotion regulation strategies autistic individuals are at risk of various psychosocial stressors which further increase the risk of comorbid mental illness.

1.6 Oxytocin

Several neurotransmitter systems have been suggested to be part in the etiological processes of ASD including e.g. gamma aminobutyric acid (GABA), glutamate, serotonin, dopamine, and oxytocin (OXT) (Marotta et al., 2020).

In the last decade, OXT has gained considerable interest as treatment option for various psychiatric conditions including ASD (e.g. Cochran, Fallon, Hill, & Frazier, 2013; Kirsch, 2015). This is due to its role as a modulator of social behaviors on the one hand, and anxiety and stress-coping on the other (Lee et al., 2009; Neumann & Landgraf, 2012; Neumann & Slattery, 2016). Given the profound social and emotional impairments seen in ASD, a deficiency of OXT has been hypothesized as underlying pathomechanism for autism (Modahl, Fein, Waterhouse, & Newton, 1992). According to this theory, the application of exogenous OXT should compensate for this OXT deficit and ultimately improve social abilities in patients with ASD.

Initial studies administering single doses of OXT were successful by enhancing various social skills such as social information processing, emotion recognition, and social learning (Andari et al., 2010; Guastella et al., 2010; Hollander et al., 2007). However, results from clinical trials with repeated applications of OXT over a longer period were inconsistent. While some studies observed a clinical efficacy of OXT treatment in autistic patients (Watanabe et al., 2017; Yatawara, Einfeld, Hickie, Davenport, & Guastella, 2016), others did not find any advantage of OXT application over placebo administration (Dadds et al., 2014; Guastella et al., 2015; Munesue et al., 2016). Thus, it was hypothesized that inter-individual differences of endogenous OXT might contribute to the equivocal responses seen after OXT application (Parker et al., 2017).

Consistent with the OXT deficiency theory (Modahl et al., 1992), Parker et al. (2017) suggested that individuals with lower peripheral pre-treatment OXT concentrations would experience greater social improvements from OXT application. Indeed, the researchers showed that autistic children with lowest pre-treatment plasma OXT concentrations were those who had the

most benefit from OXT treatment (Parker et al., 2017). Thus, the assessment of peripheral OXT may be useful to identify OXT treatment responders.

Aside from therapeutic aspects, peripheral OXT concentrations have been considered as diagnostic markers for ASD. According to the OXT deficiency theory (Modahl et al., 1992), it was assumed that autistic individuals had lower peripheral OXT levels than neurotypical peers. While some studies could confirm this hypothesis (Andari et al., 2010; Husarova et al., 2016; Modahl et al., 1998), others found either no group related differences (Miller et al., 2013; Parker et al., 2014; Taurines et al., 2014) or even higher levels of peripheral OXT in patients with ASD compared to controls (Jacobson et al., 2014; Jansen et al., 2006). Most studies examining peripheral OXT levels in ASD have addressed their research questions to children and adolescents. Only two studies have included adults in their research with contradictory results (Andari et al., 2010; Jansen et al., 2006). These two studies provided a limited sample size with a strong sex bias towards male participants.

Given the inconsistencies of study results, it is likely that confounding factors have been neglected when assessing peripheral OXT concentrations. Although often disregarded, methodological aspects such as choice of biomaterial, experimental set-up (baseline vs. stimulation), and analysis method have been identified to cause considerable variance in OXT measures (McCullough, Churchland, & Mendez, 2013). Furthermore, biological factors such as age, stage of development including hormonal status, and medication might have an impact on peripheral OXT concentrations, most of which have not been taken into account in previous studies.

Thus, the peripheral assessment of OXT in people with ASD, in particular in autistic adults, has not been sufficiently evaluated yet. Since the diagnostic procedure of ASD is still very complex and time-consuming and primarily based on the clinical experience of the practitioner (AWMF, 2015), an objective marker for ASD would be an important breakthrough for ASD diagnostics. Therefore, I investigated the applicability of peripheral OXT as indicator for ASD in a structured and comprehensive study design considering methodological aspects and biological factors for my thesis.

1.7 Alexithymia

Alexithymia is a subclinical condition which is characterized by impaired identification and description of own emotions and those of others. Furthermore, people with high alexithymic traits show an externally oriented thinking style and a reduced capacity to fantasize and imagine (Nemiah et al., 1976; Krystal, 1988; Samur et al., 2013; Taylor et al., 1997; Timoney and Holder, 2013). Developmental dysfunctions of limbic structures have been suggested as underlying cause of alexithymia. These include the anterior cingulate cortex and anterior insula, which are involved in the subjective experience of emotion, affect recognition, and empathy (Bird & Cook, 2013; Etkin, Egner, & Kalisch, 2011; Lane, Ahern, Schwartz, & Kaszniak, 1997; Singer, Critchley, & Preuschoff, 2009). Given its etiology, alexithymia is considered a trait and not a state-related condition with dimensional character (Hemming, Haddock, Shaw, & Pratt, 2019).

High alexithymic traits have been found in the general population and to a higher percentage in patients with psychiatric disorders including autism (Fietz, Valencia, & Silani, 2018; Franz et al., 2008; Salminen, Saarijärvi, Äärelä, Toikka, & Kauhanen, 1999). Approximately 50 % of individuals with ASD have been diagnosed with concomitant alexithymia (Hill, Berthoz, & Frith, 2004; Milosavljevic et al., 2016). It has been argued that alexithymic traits resemble autistic features especially those involving emotional processes (Cook, Brewer, Shah, & Bird, 2013; Starita, Borhani, Bertini, & Scarpazza, 2018). Furthermore, an overlap between these two conditions has been suggested (Fitzgerald & Bellgrove, 2006; Poquérusse, Pastore, Dellantonio, & Esposito, 2018). Aside from trait-related similarities, both ASD and alexithymia have etiologically been associated with the oxytonergic and serotonergic system and dysfunctions of brain regions such as the amygdala, cingulate, and prefrontal cortex (Donovan & Basson, 2017; Elagoz Yuksel, Yuceturk, Faruk Karatas, Ozen, & Dogangun, 2016; Muller, Anacker, & Veenstra-VanderWeele, 2016; Poquérusse et al., 2018).

Due to the equivocal results from numerous emotion recognition and empathy studies, Bird and Cook (2013) suggested that discrepancies in study findings would be associated with inter-individual differences of alexithymic levels in autistic participants. Both researchers hypothesized

that “emotional symptoms of autism” were rather due to the high rate of concomitant alexithymia in ASD than to autism per se (Bird & Cook, 2013). In fact, Cook and colleagues (2013) could confirm their “alexithymia hypothesis” by showing that alexithymia and not autism was associated with impaired emotion attribution. More precisely, after matching groups according to levels of alexithymia, participants with ASD did not show any deficits in emotion recognition in comparison with controls. Furthermore, the researchers suggested that alexithymia would not affect the ability to detect facial expressions but the ability to interpret their emotional content (Cook, Brewer, Shah, & Bird, 2013). In line with these findings are results from other studies investigating the role of alexithymia in interoception (Mul, Stagg, Herbelin, & Aspell, 2018; Shah, Hall, Catmur, & Bird, 2016) and production of facial expressions in autistic individuals (Trevisan, Bowering, & Birmingham, 2016). Moreover, alexithymic traits were more predictive of empathy deficits and reduced eye-fixations than autism severity (Bird, Press, & Richardson, 2011; Bird et al., 2010). Taken together, current research suggests that emotional impairments seen in ASD are more likely to be due to alexithymia than autism.

Aside from autism, alexithymia is frequently observed in psychiatric conditions commonly found in ASD such as depressive and anxiety disorders (Berardis et al., 2008; Hemming et al., 2019; Leweke, Leichsenring, Kruse, & Hermes, 2012; Turk, Heimberg, Luterek, Mennin, & Fresco, 2005). In fact, alexithymia and concomitant psychopathologies have similar prevalence rates of approximately 50 % in ASD (Albantakis et al., 2018; Hill et al., 2004; Lehnhardt et al., 2013; Milosavljevic et al., 2016). Since alexithymia is considered a psychopathological trait and not a state related condition (Hemming et al., 2019), it is likely that alexithymic traits may contribute to the development of comorbid psychopathology frequently observed in ASD. Or in other words, alexithymia may act as a vulnerability factor for concomitant psychopathologies in autistic individuals. In this case, this would have direct diagnostic and therapeutic implications for ASD. Therefore, in the second study of this thesis I investigated whether and to what extent alexithymic traits predict depressive and social phobic symptoms in adults with and without autism.

1.8 Aims of the thesis

In this thesis, I investigated potential causes of stress vulnerability in adults with HFA, focusing on OXT and alexithymia as potential factors to increase stress and thus, mental comorbidities.

Starting from a neurobiological perspective, the first study examined the responsiveness of the OXT system in autistic adults during a physiological stress task under consideration of methodological aspects and common characteristics of adults with ASD in comparison to neurotypical peers. The main aim of the study was to examine whether OXT release would be impaired under stress in participants with as opposed to without ASD, which would provide support for the hypothesis that OXT dysregulation contributes to stress vulnerability in autism.

In the second study, I investigated the contribution of autistic and alexithymic traits as potential risk factors for psychiatric comorbidities frequently seen in ASD such as depression and social phobia. For this study, adults with ASD, patients with disorders of social interaction and neurotypical peers were included in order to develop a dimensional approach, since both traits are considered dimensional. The main aim of this study was to reveal which traits would be risk factors for mental illness in order to increase awareness and offer individualized therapeutic treatments.

2. Peripheral oxytocin levels in adults with and without autism

2.1 Summary

This chapter includes the first thesis study in which the responsiveness of the OXT system was examined in adults with ASD and neurotypical peers. A deficiency of OXT has previously been suggested as underlying pathomechanism of ASD (Modahl et al., 1992). Studies investigating peripheral OXT concentrations in autistic individuals in comparison with healthy controls have found equivocal results (e.g. Jacobson et al., 2014; Modahl et al., 1998; Parker et al., 2014). Most of these studies assessed OXT levels under baseline conditions. However, it is unclear whether baseline levels reflect central nervous system processes. Thus, stimulation-based tasks have been recommended to implement in the study design in order to assess the responsiveness of the OXT system rather than baseline levels alone (Landgraf & Neumann, 2004; Neumann & Landgraf, 2012; Valstad et al., 2017). Furthermore, most previous studies have only included autistic children leaving the question of dysregulated OXT levels unresolved for adults with autism.

Therefore, in the thesis study, the focus was on adults with ASD (*n* = 33) and a physical exercise-based stimulation task was implemented in order to conduct pre-post comparisons of OXT concentrations from saliva and plasma samples with those from healthy controls (*n* = 31).

Furthermore, the change of peripheral OXT was investigated in relation to the induced stress response as measured by cortisol levels, because previous work suggests a coordinated response of both OXT and stress systems.

The findings indicate that a stimulation-based task is indeed required in order to reveal group related differences because OXT concentrations were found to be higher in adults with autism post-exercise as compared to healthy controls. Interestingly, this observation was only observed in the subgroup of patients whose physiological stress response as measured by cortisol was absent.

Furthermore, positive associations between the temporal dynamics of peripheral OXT and cortisol concentrations were found in healthy participants, which has previously been related to tend-and-befriend behavior (Taylor, 2006), while these associations were negative in autistic adults, which might suggest that autistic individuals benefit less from prosocial processes in situations of stress.

The present study, therefore, provides important new insights into the dynamics of the OXT system in adults with ASD and coordinated functioning with the hypothalamic–pituitary–adrenal (HPA) axis and stress responses.

2.2 Contributions

Authors:

Albantakis, L., Brandi, M.-L., Brückl, T., Gebert, D., Auer, M.K., Kopczak, A., Stalla, G.K., Neumann, I.D., Schilbach, L.

Contributions:

The author of this thesis is the first author of the publication. Laura Albantakis and Marie-Luise Brandi designed the research. Laura Albantakis provided the data from the study participants (healthy controls and autistic patients). Laura Albantakis performed the computational data analysis with help of Marie-Luise Brandi and Tanja Brückl. Dorothea Gebert, Matthias Auer, Anna Kopczak, and Günther Stalla designed the original experimental set-up of the ergometer task, which was modified and extended by Laura Albantakis. Inga Neumann advised on the experimental set-up and the sample collection. Laura Albantakis wrote the manuscript. All authors reviewed and edited the manuscript. Leonhard Schilbach was the supervisor of the project and provided funding.

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2.3 Physical exercise elicits differential oxytocin and cortisol responses in adults with and without autism

Albantakis L.[1,2], Brandi M.-L.[1], Brückl T.[3], Gebert D.[4], Auer M.K.[5], Kopczak A.[6], Stalla G.K.[5,7], Neumann I.D.[8], Schilbach L.[1,2,9]

[1] Max Planck Institute of Psychiatry – Independent Max Planck Research Group for Social Neuroscience, Kraepelinstr. 2-10, 80804, Munich, Germany

[2] International Max Planck Research School – Translational Psychiatry, Kraepelinstr. 2-10, 80804, Munich, Germany

[3] Max Planck Institute of Psychiatry – Translational Research in Psychiatry, Kraepelinstr. 2-10, 80804, Munich, Germany

[4] Neurological Specialty Hospital for Movement Disorders/Parkinson's Disease, Straße nach Fichtenwalde 16, 14547, Beelitz, Germany

[5] Medizinische Klinik and Poliklinik IV, LMU Klinikum, Ziemssenstr. 1. 80336, Munich, Germany.

[6] Institute for Stroke and Dementia Research, University Hospital, LMU Munich, Feodor-Lynen-Straße 17, 81377, Munich, Germany

[7] Medicover Neuroendokrinologie, Orleansplatz 3, 81667, Munich, Germany

[8] Department of Behavioural and Molecular Neurobiology, University of Regensburg, Universitätsstr. 31, 93053, Regensburg, Germany

[9] Ludwig-Maximilians-Universität München, Geschwister-Scholl-Platz 1, 80539, Munich, Germany

Corresponding author:

Dr. Laura Albantakis

Max Planck Institute of Psychiatry

Kraepelinstr. 2-10

80804 Munich

laura_albantakis@psych.mpg.de

Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disorder, whose core symptoms consist of deficits in social interaction and communication as well as restricted and repetitive behavior. Brain oxytocin (OXT) has been associated with various prosocial behaviors, and might, therefore, be involved in the pathogenesis of disorders associated with socio-emotional dysfunctions such as ASD. However, significant associations between central and peripheral OXT levels may only be present in response to physiological or stressful stimuli, but were not shown under baseline conditions. In this study, we, therefore, investigated salivary and plasma OXT in response to physical exercise in adults with ASD (n = 33, age: 20-53 years) without intellectual impairment (IQ > 70) and neurotypical controls (n = 31, age: 18-60 years). To stimulate the OXT system, we used rapid cycling and measured cortisol (CORT) concentrations to monitor the physiological stress response. Neither salivary (p = .469) nor plasma (p = .297) OXT concentrations significantly differed between groups at baseline. After physical exercise, we observed increased plasma OXT concentrations in patients with ASD compared to neurotypicals (p = .030), but only when a physiological stress reaction as measured by CORT was absent in patients. When age was added to the statistical model, the group effect did not remain significant. In contrast to blood OXT, saliva OXT remained unchanged both in neurotypicals and in patients with ASD. Correlations between changes of peripheral OXT and CORT concentrations were positive in neurotypicals, while they were negative in autistic individuals indicating a potential dysregulation of the interaction between the OXT and stress system in ASD. Social anxiety traits were predictive of plasma, but not saliva OXT concentrations in neurotypicals at baseline, while a combination of traits related to alexithymia, empathy and social anxiety explained variance of plasma OXT concentrations in autistic patients.

Keywords

Autism spectrum disorder, oxytocin, cortisol, stress

Introduction

Autism spectrum disorder (ASD) is defined by persistent impairments of social communication and interaction as well as repetitive and restricted patterns of behaviors, activities, and interests (American Psychiatric Association, 2013). The existing diagnostic assessment of ASD is still very complex and time-consuming. It is mostly based on behavioral observation and a detailed exploration of the early development by specialists trained in ASD (Hayes, Ford, Rafeeque, & Russell, 2018). While autism is ideally diagnosed at an early age, when intervention programs can significantly improve symptoms (e.g. Helt et al., 2008), reality shows that at least 40 % of autistic children in the primary school population remain undiagnosed (Baron-Cohen et al., 2009). Especially autistic individuals with at least average intelligence, also referred to as persons with high-functioning autism (HFA), can reach adulthood without being tested for ASD due to cognitive compensation mechanisms and favorable environmental factors (Lai & Baron-Cohen, 2015). Due to the high comorbidity rate of psychiatric conditions (e.g. depression, social phobia, and alexithymia) potentially overlapping the core symptoms of ASD, the diagnostic assessment is further complicated (Albantakis et al., 2018; Lai & Baron-Cohen, 2015). For these reasons, the development of objective and observer-independent markers would be an important break-through for autism diagnosis, but could also be relevant for treatment decisions.

Until today, the exact etiology of ASD remains poorly understood (Bhandari, Paliwal, & Kuhad, 2020). The neuropeptide oxytocin (OXT), which has been frequently linked with ASD in recent years, has received considerable interest as a modulator of social behaviors on the one hand, and anxiety and stress-coping on the other (Neumann & Landgraf, 2012; Neumann & Slattery, 2016). OXT is primarily synthesized in the magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus, then transported to the posterior pituitary gland, and finally released into the blood stream (Jurek & Neumann, 2018). OXT is also released via widely distributed pathways within distinct brain regions in response to social or stressful stimuli as revealed in laboratory animals, where it acts as a neuromodulator (Jurek & Neumann, 2018). In humans, OXT is

mostly measured in the periphery, i.e. in different body fluids such as plasma, saliva or urine (McCullough, Churchland, & Mendez, 2013).

Due to the core symptomatology of ASD, a deficiency of the OXT system has been suggested as an underlying cause of autism (Modahl et al., 1992). Analyses of peripheral OXT concentrations in autistic individuals, however, showed mixed results with lower (Andari et al., 2010; Modahl et al., 1998), higher (Jacobson et al., 2014; Jansen et al., 2006), or similar OXT values compared to neurotypicals (Parker et al., 2014; Taurines et al., 2014). Importantly, the temporal dynamics of peripheral OXT release may substantially differ from that of central release in a stimulus-dependent way (Landgraf & Neumann, 2004; Neumann & Landgraf, 2012). While both central and peripheral OXT release was observed during birth, suckling, mating, physical exercise or experimentally induced stress, no correlation was found under baseline conditions (Landgraf & Neumann, 2004; Neumann & Landgraf, 2012; Valstad et al., 2017). Thus, previous findings observed solely at baseline need to be treated with caution as it is unclear whether they reflect the OXT (dys)regulations of the brain. Several stimuli like sexual self-stimulation (De Jong et al., 2015), psychosocial stress (Bernhard et al., 2018; De Jong et al., 2015), and physical exercise (De Jong et al., 2015; Gebert et al., 2018; Hew-Butler et al., 2008) have been identified to reliably increase peripheral OXT concentrations. In adults with ASD, however, a commonly used psychosocial stress task like public speaking has failed to induce a peripheral OXT change (Jansen et al., 2006).

In this study, we therefore, chose physical exercise in form of rapid cycling (ergometry) as OXT-inducing stimulus. Apart from stimulating OXT secretion, this procedure also allows to elicit stress responses measurable as cortisol (CORT) increase. This is important because an increase of CORT might be essential to stimulate OXT concentrations (Brown et al., 2016; Torner et al., 2017). To ensure the successful individual stress response a cut-off of ≥ 15.5 % CORT baseline-to-peak increase was defined (Miller, Plessow, Kirschbaum, & Stalder, 2013). More precisely, participants reaching a CORT post-stress-to-baseline quotient of at least 1.155 were defined as CORT responders, while others below this quotient were CORT non-responders to the physical challenge.

Plasma has been the biomaterial of choice to measure OXT given the modestly invasive character and its good temporal resolution (De Jong et al., 2015; McCullough et al., 2013). However, people with ASD often suffer from sensory issues (Crane, Goddard, & Pring, 2009), thus a less invasive method, e.g. saliva collection, would be advantageous. While measures of basal OXT in saliva have repeatedly been shown to be reliable (e.g. Grewen et al., 2010; White-Traut et al., 2009), the sensitivity of saliva samples to detect dynamic changes in OXT levels in response to relevant physiological and psychological challenges needs to be further examined (De Jong et al., 2015). Therefore, we decided to collect both plasma and saliva samples to measure peripheral OXT.

In this study, we pursued four main aims: First, we tested whether the peripheral OXT concentrations of adult individuals with HFA were altered compared to those of neurotypicals under baseline conditions. Second, we examined peripheral OXT concentrations for group-related effects after physical exercise. Third, we focused on the correlation between peripheral CORT and OXT concentrations, as recently found in neurotypicals (Bernhard et al., 2018; De Jong et al., 2015; Engert et al., 2016). Fourth, we tested, whether the behavioral phenotype (e.g. autistic or anxious traits) was associated with peripheral OXT concentrations measured at baseline. Implementing this approach, we aimed at integrating the complex behavioral characteristics of our participants, especially of those with ASD and comorbid psychiatric conditions, into our analysis.

Subjects and methods

Study sample

Seventy-seven participants, aged 18 to 60 years, were recruited in the time between October 2017 and April 2019 at the Max Planck Institute of Psychiatry (MPIP). Thirteen participants were excluded from the study due to cardiovascular risks (*n* = 7), exceedance of cut-off values in psychometric questionnaires (this applies to alleged neurotypicals, *n* = 5), or intake of hormonal contraception (*n* = 1), leaving 64 participants for the final data analyses (Table 1). Neurotypical controls were recruited through an online study application system on the institute's website. Individuals with autism were either recruited through the "Outpatient and Day Clinic for Disorders of

Social Interaction" at the MPIP (*n* = 28) or the online system (*n* =5). Neurotypical controls (*n* = 31) were defined as adults without any history of psychiatric or neurological disorders. Before inclusion in the study, the medical history of potential candidates was taken following a physical examination. They were excluded from the study in case of a suspected somatic, psychiatric or neurological disorder. Autistic patients (*n* = 33) received a diagnostic assessment of ASD according to the German national autism guidelines (AWMF, 2015). Only patients who met the DSM-5-criteria for ASD were allowed to participate in the study. Since participants with ASD did not present with any intellectual impairment and IQ values < 70 were used as an exclusion criterion, patients were regarded as high-functioning (HFA). Exclusion criteria consisted of any serious somatic illness (e.g. diabetes, diseases of the cardiac, pulmonary, renal or hepatic system, chronic inflammatory diseases etc.), a diagnosis of schizophrenia in the present or past, IQ value < 70, breast-feeding, pregnancy and the use of hormonal contraception and/or sex hormones to control for potential hormonal effects on OXT. All study participants provided written informed consent. Ethical approval was granted by the Ethics Committee of the Ludwig-Maximilians-University (LMU) Munich (Project number: 712-15). All procedures were performed in accordance with the Declaration of Helsinki. Participants could withdraw from the study at any time and were financially compensated for their time.

Diagnostic procedures

Medical and psychosocial histories from patients were assessed in interviews conducted by a psychologist or psychiatrist experienced in ASD according to the national autism guidelines (AWMF, 2015). Approximately 61 % of autistic individuals presented with psychiatric comorbidities known to be common for adults with HFA (Supplementary Table 1; Albantakis et al., 2018; Lai & Baron-Cohen, 2015). 51.5 % of patients took psychiatric medication on a regular basis (Supplementary Table S1). A reduction of medication and stop of intake prior to the study participation would have caused a disruption of familiar procedures in the patients' everyday lives, causing psychological stress and potentially confounding with the experiment's measures. Therefore, patients were asked not to take the medication in the morning prior to the experiment but afterwards. Participants of both groups

filled out questionnaires to assess social functioning including depressive, social phobic and alexithymic traits (Table 1). The "Autism-Spectrum Quotient (AQ)" (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001) was used to evaluate autistic traits while the "Empathy Quotient (EQ)" (Baron-Cohen & Wheelwright, 2004) measured levels of empathy. The "Liebowitz Social Anxiety Scale (LSAS)" (Fresco et al., 2001) and "Beck Depression Inventory-II (BDI-II)" (Beck, Steer, & Brown, 1996) provided information of present severity of social phobic and depressive symptoms, respectively. The "Toronto Alexithymia Scale" with 20 Items („TAS-20") (Bagby, Parker, & Taylor, 1994) reflected levels of alexithymia. As expected, neurotypical and autistic participants significantly differed in all psychometric measures (Table 1).

Table 1

Characteristics of study participants

Variables	Neurotypicals	ASD	Statistics
	n (%)	*n* (%)	*p*
Sex			.077
Male	11 (35.5)	19 (57.6)	
Female	20 (64.5)	14 (42.4)	
	M (SD)	*M (SD)*	*p*
Age (years)	31.0 (11.7)	36.82 (10.7)	.043*
BMI (kg/m^2)	23.1 (4.9)	23.91 (4.1)	.492
Urine osmolality (mosm/kg)	767.3 (216.9)	773.53 (179.4)	.903
AQ	13.7 (5.3)	35.4 (9.8)	< .001**
BDI-II	4.5 (5.2)	13.2 (11.6)	< .001**
EQ	46.5 (11.3)	19.1 (12.6)	< .001**
LSAS	23.4 (15.4)	73.1 (25.0)	< .001**
TAS-20	41.2 (9.3)	58.8 (9.5)	< .001**

Neurotypicals: *n* = 31; Autism Spectrum Disorder (ASD): *n* = 33. AQ: Autism-Spectrum Quotient; BDI-II: Beck Depression Inventory – II; EQ: Empathy Quotient; LSAS: Liebowitz Social Anxiety Scale; TAS-20: Toronto Alexithymia Scale with 20 Items.
*denotes significance with $p < .05$. **denotes significance with $p < .001$.

Physical exercise as stress paradigm

Participants arrived at the outpatient unit of the MPIP at 8:30 am in a fasting state (> 12 h). After a physical examination, the experiment started (Figure 1).

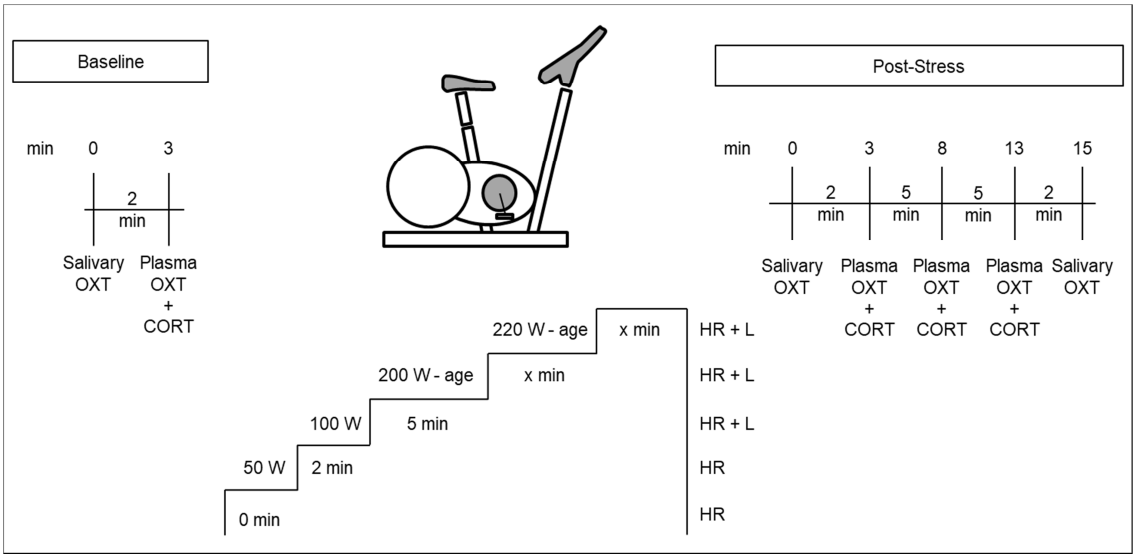

Figure 1. *Experimental set-up*

Heart rate (HR) was measured at the start (0 min) and 2 min after the start of the cycling. HR and lactate levels (L) were measured 7 min after the start of the cycling and before stop of the cycling depending on the individual performance.

First, salivary OXT was collected using a cylindrical chewing swab (see 2.4, Sarstedt, S-Salivette, Cat.nr.: 51.1534.500), on which participants were instructed to chew for approximately 2 mins for sufficient saliva absorption. Then (+3 min), plasma was taken for plasma OXT and CORT analyses. After the baseline sample collection, participants exercised on a bicycle ergometer (Kettler Ergometer TXl, Germany) according to a strict protocol (Gebert et al., 2018). In summary, participants exercised for ≥ 7 min, and then stopped either a) when lactate levels reached ≥ 4 mmol/l (considered to be the anaerobic threshold (Beneke, 1995)), or b) if lactate continuously remained < 4 mmol/l, then it was stopped when participants either reached physical exhaustion or after overall 25 min of exercise (Gebert et al., 2018). After the stress task, salivary OXT samples were taken at +1 and at +15 min post-stress. Plasma samples were taken at +3, +8, and +13 min post-stress for plasma OXT and CORT analyses. The time points were chosen to monitor the OXT

concentrations over time considering the half-life of OXT, which is supposed to be 4-10 min in human beings (Leng & Sabatier, 2016). All blood and saliva samples were collected within a strict time frame (9.00 am – 10.30 am) according to protocol. In addition to the heart rate, lactate in capillary blood was measured repeatedly (Lactate Pro2, Japan (Pyne, Boston, Martin, & Logan, 2000)) in order to monitor for individual exertion during the experiment (Figure 1).

Quantification of plasma CORT, salivary and plasma OXT

Sample preparation

Saliva was taken into collection tubes (Sarstedt, S-Salivette, Cat.nr.: 51.1534.500) and transported at room temperature. Then saliva was centrifuged at 4°C for 15 minutes with 2500 x g. After centrifugation the samples were aliquoted into 2D-barcode tubes (Brooks, fluidX, Cat.nr.: 68-0703-12) and stored at -80°C. Plasma was taken into blood collection tubes (Sarstedt, S-Monovette K3E 2.7 ml or 7.5 ml, Cat.nr.: 01.1605.001). Immediately after blood collection the tubes were transported in a cooling box. Then plasma was centrifuged at 4°C for 15 minutes with 2500 x g. The supernatant was filled into a 4 ml tube (Sarstedt, 92 x 15.3 mm, PP, Cat.nr.: 62.611) and centrifuged again. After centrifugation the samples were aliquoted into 2D-barcode tubes (Brooks, fluidX, Cat.nr.: 68-0703-12) and stored at -80°C.

OXT analysis

All salivary and plasma OXT concentrations were quantified by an external laboratory (RIAgnosis, Sinzing, Germany) using radioimmunoassay (RIA) as previously described (De Jong et al., 2015). The analysis was performed on encoded samples without providing any additional information (including times of sample collection, matching pairs of saliva and plasma etc.). According to the provider, saliva samples (300 µl) were evaporated (Concentrator, Eppendorf, Germany) prior to analysis. Plasma samples (0.5 ml) were kept at -20°C until extraction using LiChroprep® Si60 (Merck) heat-activated at 690°C for 3 hours. 20 mg of LiChroprep® Si60 in 1 ml distilled water were added to the sample, mixed for 30 min, washed twice with distilled water and 0.01 mol/l HCl, eluded with 60 % acetone and evaporated as described above. To both, evaporated

saliva samples and plasma extracts, 50 µl of assay buffer was added followed by 50 µl antibody raised in rabbits against OXT. Finally, after 60-min pre-incubation, 10µl of 125I-labeled OXT was added. The detection limit of the RIA was in the 0.1–0.5 pg/sample range depending on the age of the tracer. Intra- and inter-assay variabilities were < 10 % and cross-reactivities with related peptides < 0.7 %. All samples were assayed in the same batch. Serial dilutions of samples containing high levels of endogenous OXT run strictly parallel to the standard curve indicating immuno-identity.

CORT analysis

Plasma CORT was determined by using an Enzyme-linked Immunosorbent Assay (ELISA) kit (RE52061, TECAN, IBL Hamburg, Germany). The Standard Range was 20 - 800 ng/ml. The analytical sensitivity (limit of detection) is 2.46 ng/ml, the 2 SD functional sensitivity is 4.03 ng/ml and the mean concentration is < 20 % CV; cross-reactivity of other substances tested < 0.01 %; intra-assay < 3.48; inter-assay < 3.42.

Statistics

Data processing and statistical analyses were performed in IBM SPSS 25.0 (IBM Corp., Armonk, NY, USA), Matlab (R2010a, The MathWorks, Inc., Natick, MA, USA), and Perseus (http://www.biochem.mpg.de/5111810/perseus). Missing values of OXT, CORT and psychometric measures (< 7 %) were imputed with Perseus (http://www.biochem.mpg.de/5111810/perseus) using normal distribution with width 0.3 and down shift 0. Descriptive data were compared by Chi^2 -tests (sex) or t-tests. To analyze dimensional measures of OXT, all OXT measures were transformed by natural logarithmic transformation to achieve a normal distribution. After transformation, OXT measures were normally distributed. For easier interpretation of results, most tables and figures show the original, non-transformed data. Univariate analyses were performed to test for effects of group and sex as between-subject factors and age as covariate on baseline CORT and OXT concentrations. Repeated measures analyses of variance (rmANOVA) were conducted to test for effects of time as within-subject factor and group (Neurotypicals vs. ASD patients) as between-subject factor on CORT and OXT reactivity. In addition, the influence of sex and age on time and

group effects of CORT and OXT reactivity was investigated. Sex (males vs. females) was included as between-subject factor in rmANOVAs first, while age was entered as covariate second, to test for sex effects and age effects on CORT and OXT stress response, respectively. Greenhouse Geisser corrections were implemented when necessary. In case Greenhouse Geisser corrections exceeded .75, Huynh-Feldt corrections were used (Field, 2018). Differences in CORT and OXT reactivity ($p < .05$) were followed by post-hoc Bonferroni-corrected pair-wise comparisons. Participants qualifying as stress responders for CORT were defined by a cut-off of ≥ 15.5 % baseline-to-peak increase (Miller et al., 2013). The CORT peak was reached at the third time point after the physical exercise (CORT +13 min). Thus, a quotient of the CORT concentrations +13 min/ baseline ≥ 1.155 was defined as CORT response (= 1) with participants being CORT responders to the physical challenge. Otherwise, participants were identified as CORT non-responders (= 0). The OXT and CORT responses were operationalized as a change score (ΔOXT and ΔCORT, respectively) by subtracting the baseline value from the concentrations at different time points of the sample collection (Table 2; Engert et al., 2016).

Table 2

Δ *values for OXT and CORT concentrations*

Δ Values	**Minute**	**Calculation**	**Material**
ΔOXT-1	+1	post-stress – baseline	Saliva
ΔOXT-3	+3	post-stress – baseline	Plasma
ΔOXT-8	+8	post-stress – baseline	Plasma
ΔOXT-13	+13	post-stress – baseline	Plasma
ΔOXT-15	+15	post-stress – baseline	Saliva
ΔCORT-3	+3	post-stress – baseline	Plasma
ΔCORT-8	+8	post-stress – baseline	Plasma
ΔCORT-13	+13	post-stress – baseline	Plasma

CORT: Cortisol; OXT: Oxytocin.

Correlations between ΔOXT and ΔCORT were calculated using pairwise Spearman-correlations (no logarithmic transformations were possible due to negative values). Linear regression analyses were performed to reveal associations between the behavioral phenotype, by using the psychometric measures, and peripheral OXT concentrations at baseline. First, backwards selection was applied to identify the most parsimonious model. This approach allowed us to observe the relative impact of psychometric measures on OXT concentrations, even if they were not included in the final models. Second, the analyses were performed with the variables of the most parsimonious model with the enter method and 1,000 resamples bootstrapping to provide more robust statistics (Field, 2018). The reason for this second approach was that tests of normality revealed that relevant measures (AQ, BDI-II, EQ, LSAS, TAS-20) were not normally distributed, and data transformation failed to improve skewness.

Results

Baseline concentrations of CORT, salivary and plasma OXT concentrations

An overview of baseline concentrations of CORT, salivary and plasma OXT concentrations can be found in Table 3.

Table 3

Descriptives of baseline concentrations of CORT, salivary and plasma OXT concentrations

Variables	Neurotypicals		ASD	
	Females	Males	Females	Males
	n = 20	*n* = 11	*n* = 14	*n* = 19
	M (SD)	*M (SD)*	*M (SD)*	*M (SD)*
CORT (ng/ml)	117.32 (31.65)	153.73 (26.69)	117.60 (38.85)	141.12 (46.04)
Salivary OXT (pg/ml)	0.97 (.23)	1.01 (.19)	0.99 (.19)	1.09 (.36)
Plasma OXT (pg/ml)	2.96 (1.23)	2.36 (1.09)	3.03 (.79)	2.81 (1.20)

CORT: Cortisol; OXT: Oxytocin; Neurotypicals: *n* = 31; Autism Spectrum Disorder (ASD): *n* = 33.

Plasma CORT

There was neither a significant main effect of group on CORT baseline concentrations ($F(1,59) = .19$, $p = .667$), nor of age ($F(1,59) = .36$, $p = .554$) nor of the interaction of group x sex ($F(1,59) = .46$, $p = .502$), while the main effect of sex was significant ($F(1,59) = 8.37$, $p = .005$), with men (mean CORT = 145.74 ng/ml, SD = 39.99) presenting significantly higher CORT concentrations than women (mean CORT = 117.43 ng/ml, SD = 34.22) at baseline.

Salivary OXT

There was neither a significant main effect of group on salivary OXT baseline concentrations ($F(1,59) = .53$, $p = .469$), nor of sex ($F(1,59) = .92$, $p = .341$), nor of the interaction of group x sex ($F(1,59) = .08$, $p = .783$), nor of age ($F(1,59) = .12$, $p = .731$).

Plasma OXT

There was neither a significant main effect of group on plasma OXT baseline concentrations ($F(1,59) = 1.11$, $p = .297$), nor of sex ($F(1,59) = 2.88$, $p = .095$), nor of the interaction of group x sex ($F(1,59) = .20$, $p = .656$), nor of age ($F(1,59) = .04$, $p = .851$).

Correlation between baseline plasma and saliva OXT

There was no correlation between plasma and saliva OXT concentrations at baseline (Supplementary Table S2).

Correlation between baseline OXT and baseline CORT

In the neurotypical group, while baseline plasma OXT concentrations did significantly correlate with baseline plasma CORT levels (r = -.39, p = .032) baseline salivary OXT concentrations did not (r = .05, p = .798). In the ASD group, neither baseline salivary (r = -.07, p = .708) nor baseline plasma OXT concentrations correlated with CORT levels (r = .20, p = .278).

Validity of the stress paradigm

Heart rates and lactate levels significantly increased during the stress paradigm in each group, respectively ($p < .001$; Supplementary Table S3). Physiological parameters before and during the physical exercise did not significantly differ between groups (Table 4).

Table 4

Physiological values before and during stress-paradigm

Physiological values	*N*	*Neurotypicals*	*ASD*	*Statistics*
	Neurotypicals/ASD	*Mean (SD)*	*Mean (SD)*	*p*
Pulse (1/min)				
Baseline	31/33	76.30 (15.34)	83.13 (18.49)	.414
50 W	28/33	100.7 (18.3)	98.8 (16.9)	.682
100 W	27/32	118.5 (26.8)	121.2 (25.5)	.697
Submaximal W	25/27	140.1 (29.2)	142.4 (28.7)	.777
Maximal W	11/9	148.5 (24.6)	148.8 (27.0)	.978
Final*	29/29	145.2 (30.3)	150.2 (27.0)	.510
Lactate (mmol/l)				
100 W	31/32	3.49 (2.7)	3.0 (1.8)	.366
Submaximal W	26/28	5.60 (3.2)	5.70 (2.6)	.900
Maximal W	11/10	5.30 (3.5)	5.27 (3.1)	.979
Final*	31/33	6.4 (3.0)	6.3 (2.5)	.838
Duration of exercise (min) with stop at				
100 W	30/33	7.17 (.69)	7.12 (.66)	.790
Submaximal W	25/30	11.78 (1.29)	11.72 (1.19)	.851
Maximal W	10/10	18.15 (1.73)	17.50 (2.0)	.449
Final*	31/33	13.23 (4.92)	13.24 (5.0)	.989

Neurotypicals: $n = 31$; Autism Spectrum Disorder (ASD): $n = 33$.
Min: minute; W: wattage; Submaximal W: 200 – age; Maximal W: 220 – age.
*Individual maximal values taken before exercise was stopped due to physical exhaustion.
Statistics: Unpaired t-tests were performed to test for group related differences.

The physical stressor induced the defined CORT response (CORT quotient ≥ 1.155, see *2.5*) in 11 out of 31 neurotypicals and 18 out of 33 autistic patients. RmANOVA revealed a significant effect of factor time on CORT concentrations ($F(1.68, 100.89) = 11.74$, $p < .001$) with increasing CORT levels

over time. There were neither any significant effects by group and sex as between-subject factors nor by any interactions between time, sex, and group on CORT concentrations (Supplementary Tables S4a and b). When including age as covariate (Supplementary Table S4c), time did not have a significant main effect on CORT concentrations any more $F(1.68, 99.30) = 1.12$, $p = .321$. There were neither any significant effects by group and sex as between-subject factors nor by any interactions (Supplementary Table S3c). Age did not have a significant effect on CORT concentrations either ($F(1, 59) = .06$, $p = .801$).

Salivary and plasma OXT concentrations in response to the stress paradigm

Salivary OXT

Salivary OXT concentrations did not change over time in both CORT non-responders ($F(2, 62) = 1.73$, $p = .187$) and CORT responders ($F(2, 50) = 1.98$, $p = .149$), and there were no differences between ASD and control group, or between males and females (Supplementary Tables S5a and b). When including age as covariate, time remained non-significant in both CORT non-responders ($F(2, 60) = 0.33$, $p = .718$) and CORT responders ($F(2, 48) = 0.32$, $p = .728$). As before, there were no differences between ASD and control group, or between males and females (Supplementary Table S5c). Age did not have a significant effect on salivary OXT concentrations either (CORT non-responder: $F(1, 30) = 0.09$, $p = .766$; CORT responder: $F(1, 24) = 0.19$, $p = .670$).

Plasma OXT

Plasma OXT concentrations did not change over time in both CORT non-responders ($F(2.80, 86.69) = 2.11$, $p = .109$) and CORT responders ($F(3, 75) = 0.27$, $p = .847$). However, a significant difference between ASD and controls was found in the CORT non-responder subsample ($F(1, 31) = 5.14$, $p = .030$), with elevated levels in the ASD group. There was no significant effect found on concentrations of the CORT responder subsample ($F(1, 25) = 0.12$, $p = .738$). Factor sex was non-significant in both CORT subsamples (non-responder: $F(1, 31) = 0.54$, $p = .470$; responder: $F(1, 25) = 1.66$, $p = .210$). None of the interactions between factors age, time, sex, and group were significant (Figure 2 and Supplementary Tables S6a and b). When including age as covariate, the effect of group

did not remain significant (CORT non-responder: $F(1, 30) = 3.38$, $p = .076$; CORT responder: $F(1, 24) = 0.06$, $p = .802$). Neither age (non-responder: $F(1, 30) = 0.91$, $p = .347$; responder: $F(1, 24) = 0.11$, $p = .746$), nor sex nor any interaction had a significant effect on plasma OXT concentrations in any CORT subsample (Supplementary Table S6c).

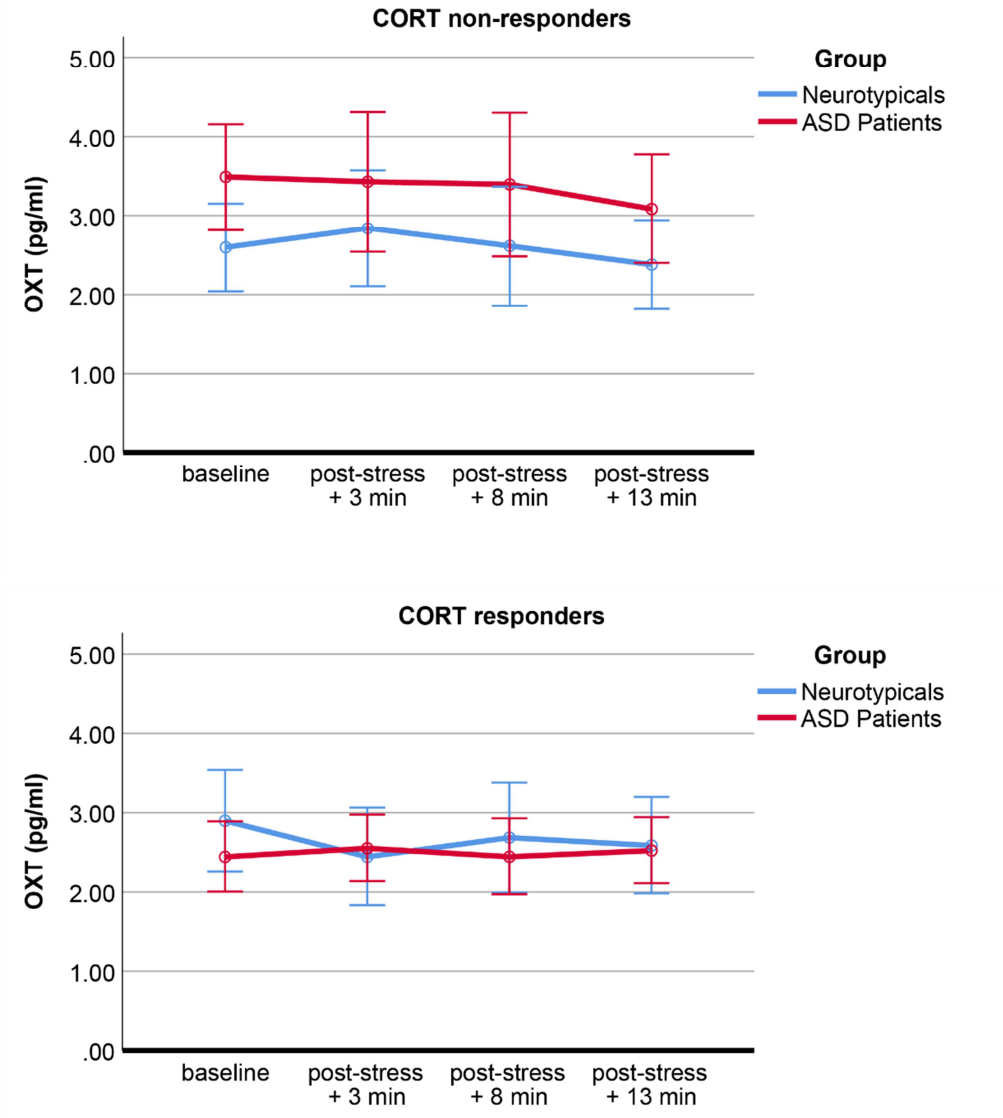

Figure 2. *Plasma OXT concentrations before and after stress paradigm among CORT non-responders and CORT responders*

Oxytocin (OXT) concentrations are illustrated over time for the subsample of CORT non-responders (quotient of the CORT concentrations +13 min/ baseline < 1.155) and CORT responders (quotient of the CORT concentrations +13 min/ baseline ≥ 1.155). When adding age as covariate, the group effect of neurotypicals and patients with autism spectrum disorder (ASD) did not reach significance any more. For both panels, data are shown as means ± Standard Error of Means.

Correlation between plasma and saliva OXT

There was no correlation between plasma and saliva OXT concentrations at any time point after the exercise (Supplementary Table S2).

Correlation between ΔOXT and ΔCORT concentrations

In neurotypicals, ΔOXT-15 and ΔCORT-13 were *positively* correlated in absence of a CORT response (r_s = .49, p = .028; Supplementary Table S7a and Supplementary Figure S1a), while in autistic individuals, ΔOXT-1 and ΔCORT-3 (r_s = -.586, p = .022), ΔOXT-3 and ΔCORT-8 (r_s = -.621, p = .013), and ΔOXT-3 and ΔCORT-13 (r_s = -.596, p = .019), were *negatively* correlated in absence of a CORT response (Supplementary Table S7b and Supplementary Figures S1b-d).

Behavioral measures as predictors of basal OXT concentrations

The behavioral measures applied in this study were rather trait than state related. Therefore, to test for associations between behavioral characteristics and peripheral OXT concentrations, we performed the linear regression analyses only with basal OXT levels.

In neurotypicals, a model including LSAS and TAS-20 scores explained 21.3 % of variance of basal plasma OXT concentrations (F(2,28) = 3.79, p = .035), while only LSAS scores were significant predictors (LSAS [-.063; -.016]: β = -.04, p = .005) and TAS-20 scores were not [-.026; .076]: β = .03, p = .322). In autistic individuals, a model including EQ, TAS-20 and LSAS scores explained 24.9 % of variance of basal plasma OXT concentrations (F(3,29) = 3.20, p = .038), while no single psychometric measure was identified as significant predictor of basal plasma OXT concentrations (EQ [-.029; 048]: β = .03, p = .124; LSAS [.003; .041]: β = .02, p = .054; TAS-20 [-.099; 005]: β = .05, p = .085).

No significant models could be established with basal salivary OXT concentrations as dependent variable neither in neurotypicals nor in patients with ASD.

Discussion

The present study examined the OXT response to physical exercise as a stress-inducing task in neurotypical compared to autistic adults. Four main study aims were hereby addressed: First, we compared basal peripheral OXT concentrations, but found no significant differences between neurotypical and autistic individuals neither in salivary nor plasma OXT values. Second, we examined OXT responses in saliva and plasma after physical exercise and found autistic patients presenting significantly higher post-stress levels of plasma OXT than neurotypicals, when lacking a stress-induced increase in CORT concentrations (CORT quotient < 1.155). However, when age was included as covariate into the model, this group effect failed to reach statistical significance. Third, in absence of a CORT response, the stress-induced rise in salivary OXT was found to be correlated with the stress-induced rise in saliva CORT levels in neurotypicals, while in autistic patients an indirect correlation was found, i.e. higher increases in OXT concentrations were related to decreases in CORT concentrations in both saliva and plasma. Fourth, we identified levels of social anxiety as significant predictors of plasma OXT concentrations at baseline in neurotypicals with a higher degree of social anxiety predicting lower OXT levels. In autistic individuals, a combination of alexithymic, empathetic and socially anxious traits predicted OXT levels at baseline indicating a more complex behavioral phenotype in the study participants with ASD. This is likely due to the dimensional character of the underlying autism spectrum condition and the high rate of psychiatric comorbidities among autistic patients.

The majority of previous studies have focused on children and adolescents with equivocal results (e.g. Jacobson et al., 2014; Modahl et al., 1998; Parker et al., 2014), when investigating peripheral OXT concentrations in ASD under baseline conditions. So far, only two studies have examined peripheral OXT levels in autistic adults with contrasting results. While Andari et al. (2010) found significantly lower basal OXT concentrations in 13 adults with ASD compared to neurotypical controls, Jansen et al. (2006) observed increased levels of peripheral OXT in 10 autistic individuals at baseline. In this regard, our findings add to previous literature of peripheral OXT concentrations in

adults with ASD by reporting no group-related differences under baseline conditions in a much bigger sample of 33 autistic adults. These results are in line with observations in children and adolescents with ASD (e.g. Parker et al., 2014; Taurines et al., 2014), and further support the notion that differing OXT *baseline* levels do not represent a defining feature of autism.

While Jansen et al. (2006) implemented a public speaking task as OXT stimulus with no significant effect on peripheral OXT concentrations in autistic adults, we chose rapid cycling as stimulus for our study. Against our expectations, after physical exercise, we found significantly higher plasma OXT concentrations in autistic individuals than in neurotypicals. This supports the assumption that a stimulating task is required in order to reveal group related differences of the OXT responsiveness. However, this group effect was only observed in the subsample of ASD and neurotypicals who did not show the defined CORT response to exercise. As concluded from adrenalectomized rats, glucocorticoids seem to inhibit the stress-induced secretion of OXT into blood (Torner et al., 2017), but seem essential for OXT release within the hypothalamus .This could indicate that the intensity of the applied stimulus need to be moderate and should not induce a physiological stress response. This would be in line with previous findings of an OXT increase during a “moderate running” task in healthy participants (De Jong et al., 2015). However, the results did not hold up when including age as factor in our statistical model. Thus, these observations need to be interpreted with caution. Nevertheless, the results are surprising for two reasons: first, we expected lower OXT concentrations in patients with ASD compared to neurotypicals, bearing in mind the hypothesis of an OXT deficiency in ASD (Modahl et al., 1992). Secondly, we assumed that we would reveal group-related differences in the subsample of CORT responders than among CORT non-responders because individuals with autism have been shown to exhibit heightened stress responses to experimental procedures (Lam, Aman, & Arnold, 2006).

Regarding the temporal dynamics of peripheral OXT and CORT concentrations, we found positive correlations between ΔOXT and ΔCORT concentrations in neurotypicals which was in line with previous studies (Bernhard et al., 2018; De Jong et al., 2015; Engert et al., 2016). However, we

found these associations only in the subgroup of CORT non-responders, meaning in the absence of the defined physiological stress response. One explanation might be that due to the circadian rhythm of CORT (Oster et al., 2017), the baseline CORT concentrations in our experiment were higher compared to the CORT concentrations in other studies because samples were collected in the morning and not in the afternoon. Thus, in order to reach a CORT response, indicating a successful physiological stress induction, by using the cut-off of ≥ 1.155 baseline-to-peak CORT ratio, the CORT concentrations would have to raise much higher during the physical exercise to compensate for higher morning CORT levels. According to the stress buffer theory, which suggests that OXT would be released as a buffer for the induced CORT increase (Engelmann et al., 2004; Neumann, 2002), it could be that the stress buffering effect was already reached under low CORT concentrations in our study, while the effect was depleted when CORT levels increased.

Contrary to the neurotypical participants, we found a negative correlation between ΔOXT and ΔCORT concentrations in the absence of a CORT response in saliva and plasma of autistic patients suggesting that OXT might not be sufficiently released to buffer the CORT increase or might even be suppressed in ASD. Correlations between ΔOXT and ΔCORT concentrations were found at similar time points, indicating dynamic changes of both target measures took place simultaneously or with a minor delay of time (Engert et al., 2016). It also implicates that the time points of sample collection matter in order to find significant effects in OXT and CORT concentrations.

In addition to biological factors (e.g. sex, age and peripheral CORT concentrations), we looked for potential associations between behavioral traits and peripheral OXT concentrations. In line with former results (Carson et al., 2015; Weisman et al., 2013), a higher degree of social anxiety was associated with lower basal plasma OXT concentrations in neurotypicals. In autistic participants, a conglomeration of alexithymic, empathetic and social phobic traits was found to explain 24.9 % of variance of basal plasma OXT concentrations reflecting the complex phenotype of autistic adults. Contrary to neurotypicals, a higher degree of social anxiety was associated with higher basal plasma

OXT concentrations in patients with ASD. Furthermore, increasing empathic and alexithymic traits were associated with an increase of basal plasma OXT concentrations.

Contrary to results by other research groups (Feldman et al., 2010; Grewen et al., 2010), we did not observe correlations between salivary and plasma OXT concentrations at any time. A possible explanation could be that enzyme immunoassays (EIA) were used to measure OXT in unextracted (Feldman et al., 2010) and extracted plasma (Grewen et al., 2010), while we measured OXT in extracted plasma with RIA. An extracting or non-extracting process prior to analysis as well as the kind of assay (EIA or RIA) used to assess OXT can lead to great discrepancies of measured OXT concentrations (McCullough et al., 2013). Based on our results, we strongly advise to pay attention to methodological details as more and more researchers tend to equate results reported in different materials with different methods (McCullough et al., 2013).

Limitations

There are some limitations in our study which need to be considered. First, neurotypicals and autistic patients were not ideally matched regarding age and sex distribution which is a common challenge in clinical trials with naturalistic designs (Fogel, 2018). However, sex was considered as between-subject factor and age as covariate in the univariate and rm-ANOVAs. There was neither a sex nor an age-related effect on OXT concentrations. However, when entering age as covariate into the rm-ANOVA for plasma OXT in the last step, the described group effect turned non-significant. So far, the existing research of age effects on peripheral OXT concentrations in human beings is limited and inconsistent. While some found age-related changes on peripheral OXT concentrations (Modahl et al., 1998), others did not (Andari et al., 2010; Taurines et al., 2014). Therefore, the age effect on peripheral OXT concentrations needs to be re-evaluated in a bigger sample.

Second, the high rate of psychiatric comorbidities adequately represents the autistic phenotype in adulthood and stands for a very naturalistic study design (Albantakis et al., 2018; Lai & Baron-Cohen, 2015). Given the limited sample size of 33 autistic patients, we did not control for potential psychotropic effects on CORT and OXT concentrations. A binary categorical division

(psychopharmacological intake: *yes/no*) appeared as no appropriate solution for this potential confounding factor because the prescribed substances varied among patients (Supplementary Table S1) targeting different neurotransmitter systems. Including each drug as covariate alternatively, did not appear useful either, as various different drugs were taken with different dosages (Supplementary Table S1). Therefore, we only reported this information without further including it into our analyses. However, existing research on the prescribed medication in this study suggested that it does not affect peripheral OXT concentrations (Keating et al., 2013; Taurines et al., 2014). In this regard, the effect of psychiatric medication might not have had such an important impact on the peripheral OXT concentrations overall.

Third, the sample collection and stress paradigm were carried out in the morning. CORT concentrations are known to follow a circadian rhythm with higher levels in the morning following a decrease over the day (Oster et al., 2017). Material for CORT analyses was taken from the same samples as for OXT plasma analyses (Figure 1), so concentrations were measured before and after the stress task. However, we could not control for the biological circadian rhythm of CORT which might have additionally influenced the CORT concentrations measured in relation to the paradigm.

Conclusions

The present study has helped to extend our understanding of the OXT and stress system in autistic adults and neurotypicals. In line with previous studies, we found no evidence for group-related differences of peripheral OXT concentrations at baseline. After physical exercise, however, plasma OXT concentrations were significantly higher in autistic participants when the physical stressor had not induced an increase in CORT levels, while no such group-related differences were found under a CORT response. However, these observations did not hold up when including age as factor in the statistical model. Thus, these findings need to be interpreted with caution. Correlations between changes of peripheral CORT and OXT concentrations were also only observed in absence of a physiological stress response: in neurotypicals, the correlation was positive such that higher CORT were associated with higher OXT levels while in autistic patients, the correlation was negative

suggesting a dysregulation of the link between OXT and CORT system in ASD. Furthermore, levels of social anxiety were predictive of basal plasma OXT concentrations in neurotypicals, while a combination of psychometric measures including alexithymia, empathy and social anxiety was identified in autistic participants, highlighting the complex phenotype of autistic adults.

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Supplementary Material

Table S1

Psychiatric comorbidities and psychiatric medication in autistic patients

Variables	Total	Male	Female
	n (%)	*n* (%)	*n* (%)
Psychiatric comorbidities			
At least one comorbid psychiatric disorder	20 (60.6)	11 (33.3)	9 (27.3)
Unipolar depression	18 (54.6)	9 (27.3)	9 (27.3)
Social Phobia	3 (9.1)	3 (9.1)	0 (0.0)
OCD	1 (3.0)	0 (0.0)	1 (3.0)
ADHD	5 (15.2)	3 (9.1)	2 (6.1)
Alexithymia	17 (51.5)	8 (24.2)	9 (27.3)
Psychiatric medication	17 (51.5)	9 (27.3)	8 (24.2)
Antidepressants	13 (39.4)	6 (18.2)	7 (21.2)
Amitripytline	1 (3.0)	0 (0.0)	1 (3.0)
Bupropion	1 (3.0)	0 (0.0)	1 (3.0)
Escitalopram	2 (6.1)	1 (3.0)	1 (3.0)
Mirtazapine	2 (6.1)	0 (0.0)	0 (0.0)
Sertraline	2 (6.1)	0 (0.0)	2 (6.1)
Tianeptine	2 (6.1)	0 (0.0)	2 (6.1)
Trimipramine	1 (3.0)	1 (3.0)	0 (0.0)
Venlafaxine	3 (9.1)	3 (9.1)	0 (0.0)
Neuroleptics	5 (15.2)	3 (9.1)	2 (6.1)
Quetiapine	4 (12.1)	2 (6.1)	2 (6.1)
Risperidone	1 (3.03)	1 (3.0)	0 (0.0)
Stimulants	5 (15.2)	2 (6.1)	3 (9.1)
Methylphenidate	3 (9.1)	2 (6.1)	1 (3.0)
Atomoxetine	2 (6.1)	0 (0.0)	2 (6.1)

Note. Percentages refer to the entire sample of patients with Autism Spectrum Disorder (ASD; *n* = 33). Psychiatric comorbidities were diagnosed according to ICD-criteria, except alexithymia. Alexithymia was confirmed with a score ≥ 61 according to Bagby et al.(1994). OCD: Obsessive compulsive disorder. ADHD: Attention deficit hyperactivity disorder.

Table S2

Correlation between salivary and plasma OXT concentrations

		Saliva OXT baseline	Plasma OXT baseline	Saliva OXT +1min	Plasma OXT +3min	Plasma OXT +8min	Plasma OXT +13min	Saliva OXT +15min
Saliva OXT baseline	*r*	1.00	-.05	.502	.04	.02	-.02	.440
	p-value		.697	<.001**	.770	.902	.884	<.001**
	N	64	64	64	64	64	64	64
Plasma OXT baseline	*r*	-.05	1.00	-.05	.599	.842	.672	.22
	p-value	.697		.694	<.001**	<.001**	<.001**	.085
	N	64	64	64	64	64	64	64
Saliva OXT +1min	*r*	.502	-.05	1.00	-.02	.09	-.02	.601
	p-value	<.001**	.694		.889	.469	.850	<.001**
	N	64	64	64	64	64	64	64
Plasma OXT +3min	*r*	.04	.599	-.02	1.00	.672	.648	.04
	p-value	.770	<.001**	.889		<.001**	<.001**	.745
	N	64	64	64	64	64	64	64
Plasma OXT +8min	*r*	.02	.842	.09	.672	1.00	.658	.306
	p-value	.902	<.001**	.469	<.001**		<.001**	.014*
	N	64	64	64	64	64	64	64
Plasma OXT +13min	*r*	-.02	.672	-.02	.648	.658	1.00	.15
	p-value	.884	<.001**	.850	<.001**	<.001**		.246
	N	64	64	64	64	64	64	64
Saliva OXT +15min	*r*	.440	.22	.601	.04	.306	.15	1.00
	p-value	<.001**	.085	<.001**	.745	.014*	.246	
	N	64	64	64	64	64	64	64

OXT: Oxytocin in pg/ml.

*. denotes unadjusted p-value $p < .05$.

**. denotes *p*-value adjusted with Bonferroni correction for multiple testing with a significance $p < .001$.

Table S3

Significant changes of heart rate and lactate levels as response to stress task

Variables	Neurotypicals			ASD		
	n	*F*	*p*	*n*	*F*	*p*
HR - 100 W	25	47.99	< .001	31	59.82	< .001
HR - submaximal W	21	74.15	< .001	26	65.85	< .001
HR - maximal W	9	52.19	< .001	8	19.43	< .001
Lactate - submaximal W	26	37.48	< .001	28	85	< .001
Lactate - maximal W	11	17.21	< .001	9	12.82	< .001

Neurotypicals: *n* = 31; Autism Spectrum Disorder (ASD): *n* = 33.
HR - 100 W: Stop of physical challenge at 7 minutes with 100 W. HR - submaximal W: Stop of physical challenge at submaximal wattage. HR - maximal W: Stop of physical challenge at maximal wattage. Lactate - submaximal W: Stop of physical challenge at submaximal wattage. Lactate - maximal W: Stop of physical challenge at maximal wattage.

Table S4a

Descriptives for CORT concentrations (repeated measures over time)

Timepoint	Sex	Group	Mean	SD	N
Baseline	Male	Neurotypicals	153.73	26.69	11
		ASD Patients	141.12	46.04	19
		Total	145.74	39.99	30
	Female	Neurotypicals	117.32	31.65	20
		ASD Patients	117.60	38.85	14
		Total	117.43	34.22	34
	Total	Neurotypicals	130.24	34.43	31
		ASD Patients	131.14	44.10	33
		Total	130.70	39.40	64
Post-Stress 3 min	Male	Neurotypicals	135.04	28.15	11
		ASD Patients	142.95	53.03	19
		Total	140.05	45.10	30
	Female	Neurotypicals	110.57	31.41	20
		ASD Patients	117.96	38.36	14
		Total	113.61	34.08	34
	Total	Neurotypicals	119.25	32.11	31
		ASD Patients	132.35	48.34	33
		Total	126.01	41.49	64
Post-Stress 8 min	Male	Neurotypicals	142.78	38.48	11
		ASD Patients	163.76	60.65	19
		Total	156.07	53.85	30
	Female	Neurotypicals	133.12	38.35	20
		ASD Patients	141.41	47.60	14
		Total	136.54	41.91	34
	Total	Neurotypicals	136.55	38.04	31
		ASD Patients	154.28	55.81	33
		Total	145.69	48.49	64
Post-Stress 13 min	Male	Neurotypicals	141.37	42.18	11
		ASD Patients	167.26	63.90	19
		Total	157.76	57.52	30
	Female	Neurotypicals	142.78	41.84	20
		ASD Patients	155.36	51.68	14
		Total	147.96	45.82	34
	Total	Neurotypicals	142.28	41.26	31
		ASD Patients	162.21	58.46	33
		Total	152.56	51.45	64

CORT: Cortisol in ng/ml. Neurotypicals: *n* = 31; Autism Spectrum Disorder (ASD): *n* = 33.

Table S4b

CORT - Repeated measures between-subject and within subject effects (without age)

Source	df	MS	F	*p*	partial η²
Time	1.68	14235.54	11.74	.000*	0.164
Time x Sex	1.68	3156.48	2.60	.088	0.042
Time x Group	1.68	3306.02	2.73	.079	0.043
Time x Sex x Group	1.68	1028.59	0.85	.414	0.014
Sex	1	5441.06	3.67	.060	0.058
Group	1	1179.12	0.80	.376	0.013
Sex * Group	1	43.83	0.03	.864	0.000

CORT: Cortisol in ng/ml.
*denotes significance at $p < .05$.

Table S4c

CORT - Repeated measures between-subject and within subject effects (including age)

Source	df	MS	F	*p*	partial η²
Time	1.68	1368.50	1.12	.321	0.019
Time * Age	1.68	825.30	0.68	.486	0.011
Time * Sex	1.68	2597.84	2.13	.132	0.035
Time * Group	1.68	2254.44	1.85	.168	0.030
Time * Sex * Group	1.68	1053.87	0.87	.407	0.014
Age	1	96.04	0.06	.801	0.001
Sex	1	5495.83	3.65	.061	0.058
Group	1	894.71	0.59	.444	0.010
Sex * Group	1	45.95	0.03	.862	0.001

CORT: Cortisol in ng/ml.

Table S5a

Descriptives for salivary OXT concentrations (repeated measures over time)

Timepoint	Sex	Group	Mean	SD	N
Baseline	Male	Neurotypicals	1.01	0.19	11
		ASD Patients	1.09	0.36	19
		Total	1.06	0.31	30
	Female	Neurotypicals	0.97	0.23	20
		ASD Patients	0.99	0.19	14
		Total	0.98	0.21	34
	Total	Neurotypicals	0.99	0.22	31
		ASD Patients	1.05	0.30	33
		Total	1.02	0.26	64
Post-stress 1 min	Male	Neurotypicals	0.98	0.19	11
		ASD Patients	1.00	0.24	19
		Total	0.99	0.22	30
	Female	Neurotypicals	0.95	0.17	20
		ASD Patients	0.93	0.25	14
		Total	0.94	0.21	34
	Total	Neurotypicals	0.96	0.18	31
		ASD Patients	0.97	0.24	33
		Total	0.97	0.21	64
Post-stress 15 min	Male	Neurotypicals	0.90	0.22	11
		ASD Patients	1.00	0.24	19
		Total	0.96	0.24	30
	Female	Neurotypicals	0.96	0.20	20
		ASD Patients	0.92	0.22	14
		Total	0.94	0.21	34
	Total	Neurotypicals	0.94	0.21	31
		ASD Patients	0.96	0.23	33
		Total	0.95	0.22	64

OXT: Oxytocin in pg/ml. Neurotypicals: *n* = 31; Autism Spectrum Disorder (ASD): *n* = 33.

Table S5b

Salivary OXT - Repeated measures between-subject and within subject effects (without age)

CORT response	Source	df	MS	F	*p*	partial η^2
< 1.155	Time	2	0.05	1.73	.187	0.053
	Time x Sex	2	0.02	0.74	.483	0.023
	Time x Group	2	0.01	0.43	.650	0.014
	Time x Sex x Group	2	0.01	0.16	.857	0.005
	Sex	1	0.06	1.66	.207	0.051
	Group	1	0.05	1.60	.215	0.049
	Sex * Group	1	0.03	0.97	.332	0.030
≥ 1.155	Time	2	0.04	1.98	.149	0.073
	Time x Sex	2	0.01	0.27	.762	0.011
	Time x Group	2	0.01	0.37	.694	0.015
	Time x Sex x Group	2	0.01	0.46	.633	0.018
	Sex	1	0.00	0.05	.823	0.002
	Group	1	0.11	3.07	.092	0.109
	Sex * Group	1	0.03	0.73	.400	0.028

CORT response: quotient of the cortisol concentrations +13 min/ baseline. The table contains OXT concentrations transformed by natural logarithmic transformation to achieve a normal distribution.

Table S5c

Salivary OXT - Repeated measures between-subject and within subject effects (including age)

CORT response	Source	df	MS	F	*p*	partial η^2
< 1.155	Time	2	0.01	0.33	.718	0.011
	Time * Age	2	0.00	0.14	.866	0.005
	Time * Sex	2	0.02	0.61	.548	0.020
	Time * Group	2	0.01	0.27	.761	0.009
	Time * Sex * Group	2	0.01	0.16	.855	0.005
	Age	1	0.00	0.09	766	0.003
	Sex	1	0.06	1.69	.203	0.053
	Group	1	0.06	1.63	.212	0.052
	Sex * Group	1	0.03	0.96	.334	0.031
≥ 1.155	Time	2	0.01	0.32	.728	0.013
	Time * Age	2	0.00	0.18	.832	0.008
	Time * Sex	2	0.00	0.23	.796	0.009
	Time * Group	2	0.01	0.45	.643	0.018
	Time * Sex * Group	2	0.01	0.46	.635	0.019
	Age	1	0.01	0.19	.670	0.008
	Sex	1	0.00	0.10	.749	0.004
	Group	1	0.12	3.15	.088	0.116
	Sex * Group	1	0.03	0.74	.399	0.030

CORT response: quotient of the cortisol concentrations +13 min/ baseline. The table contains OXT concentrations transformed by natural logarithmic transformation to achieve a normal distribution.

Table S6a

Descriptives for plasma OXT concentrations (repeated measures over time)

Timepoints	Sex	Group	M	SD	N
Baseline	Male	Neurotypicals	2.36	1.09	11
		ASD Patients	2.81	1.20	19
		Total	2.64	1.16	30
	Female	Neurotypicals	2.96	1.23	20
		ASD Patients	3.03	0.79	14
		Total	2.99	1.06	34
	Total	Neurotypicals	2.75	1.20	31
		ASD Patients	2.90	1.04	33
		Total	2.83	1.11	64
Post-stress 3 min	Male	Neurotypicals	2.47	0.81	11
		ASD Patients	3.03	1.86	19
		Total	2.83	1.56	30
	Female	Neurotypicals	2.97	1.20	20
		ASD Patients	2.90	0.63	14
		Total	2.94	0.99	34
	Total	Neurotypicals	2.79	1.09	31
		ASD Patients	2.98	1.45	33
		Total	2.89	1.28	64
Post-stress 8 min	Male	Neurotypicals	2.15	0.89	11
		ASD Patients	3.00	1.57	19
		Total	2.69	1.40	30
	Female	Neurotypicals	3.03	1.68	20
		ASD Patients	2.83	0.86	14
		Total	2.95	1.39	34
	Total	Neurotypicals	2.72	1.49	31
		ASD Patients	2.93	1.30	33
		Total	2.83	1.39	64
Post-stress 13 min	Male	Neurotypicals	2.21	0.86	11
		ASD Patients	3.05	1.36	19
		Total	2.74	1.26	30
	Female	Neurotypicals	2.63	1.00	20
		ASD Patients	2.61	0.82	14
		Total	2.62	0.92	34
	Total	Neurotypicals	2.48	0.96	31
		ASD Patients	2.86	1.17	33
		Total	2.68	1.08	64

OXT: Oxytocin in pg/ml.

Table S6b

Plasma OXT - Repeated measures between-subject and within subject effects (without age)

CORT response	Source	df	MS	F	*p*	partial η^2
< 1.155	Time	2.80	0.15	2.11	.109	0.064
	Time x Sex	2.80	0.15	2.14	.106	0.064
	Time x Group	2.80	0.07	0.91	.433	0.029
	Time x Sex x Group	2.80	0.11	1.53	.214	0.047
	Sex	1	0.07	0.54	.470	0.017
	Group	1	0.70	5.14	.030	0.142
	Sex * Group	1	0.12	0.86	.361	0.027
≥ 1.155	Time	3	0.01	0.27	.847	0.011
	Time x Sex	3	0.01	0.28	.843	0.011
	Time x Group	3	0.05	1.24	.302	0.047
	Time x Sex x Group	3	0.03	0.83	.484	0.032
	Sex	1	0.17	1.66	.210	0.062
	Group	1	0.01	0.12	.738	0.005
	Sex * Group	1	0.00	0.02	.890	0.001

CORT response: quotient of the cortisol concentrations +13 min/ baseline. The table contains OXT concentrations transformed by natural logarithmic transformation to achieve a normal distribution.

Table S6c

Plasma OXT - Repeated measures between-subject and within subject effects (including age)

CORT response	Source	df	MS	F	*p*	partial η^2
< 1.155	Time	2.89	0.05	0.67	.571	0.022
	Time * Age	2.89	0.02	0.22	.879	0.007
	Time * Sex	2.89	0.15	2.08	.111	0.065
	Time * Group	2.89	0.05	0.65	.577	0.021
	Time * Sex * Group	2.89	0.11	1.53	.213	0.049
	Age	1	0.13	0.91	.347	0.030
	Sex	1	0.05	0.33	.568	0.011
	Group	1	0.46	3.38	.076	0.101
	Sex * Group	1	0.13	0.93	.344	0.030
≥ 1.155	Time	3	0.04	0.95	.420	0.038
	Time * Age	3	0.04	1.08	.365	0.043
	Time * Sex	3	0.02	0.47	.702	0.019
	Time * Group	3	0.04	1.02	.390	0.041
	Time * Sex * Group	3	0.03	0.82	.489	0.033
	Age	1	0.01	0.11	.746	0.004
	Sex	1	0.18	1.70	.204	0.066
	Group	1	0.01	0.06	.802	0.003
	Sex * Group	1	0.00	0.02	.883	0.001

CORT response: quotient of the cortisol concentrations +13 min/ baseline. The table contains OXT concentrations transformed by natural logarithmic transformation to achieve a normal distribution.

Table S7a

Correlations of ΔCORT and ΔOXT in neurotypical participants according to CORT response

Neurotypicals			ΔOXT-1	ΔOXT-3	ΔOXT-8	ΔOXT-13	ΔOXT-15
CORT response < 1.155	ΔCORT-3	r_s	.003	-.158	-.003	-.096	.181
		p-value	.990	.506	.990	.686	.444
		N	20	20	20	20	20
	ΔCORT-8	r_s	-.035	-.340	-.057	.026	.259
		p-value	.885	.142	.811	.915	.269
		N	20	20	20	20	20
	ΔCORT-13	r_s	.144	-.390	.048	-.069	.490
		p-value	.544	.089	.840	.772	**.028***
		N	20	20	20	20	20
CORT response ≥ 1.155	ΔCORT-3	r_s	.209	.027	-.009	.355	-.200
		p-value	.537	.937	.979	.285	.555
		N	11	11	11	11	11
	ΔCORT-8	r_s	-.218	.118	-.218	-.127	-.145
		p-value	.519	.729	.519	.709	.670
		N	11	11	11	11	11
	ΔCORT-13	r_s	-.282	.273	-.018	.045	-.200
		p-value	.401	.417	.958	.894	.555
		N	11	11	11	11	11

CORT response: quotient of the cortisol concentrations +13 min/ baseline.

ΔCORT in ng/ml; ΔOXT in pg/ml.

*****denotes *p*-value adjusted with Bonferroni correction for multiple testing with a significance at $p < .033$

ΔCORT-3: CORT concentration at 3 min post-stress – baseline CORT concentration

ΔCORT-8: CORT concentration at 8 min post-stress – baseline CORT concentration

ΔCORT-13: CORT concentration at 13 min post-stress – baseline CORT concentration

ΔOXT-1: OXT concentration at 1 min post-stress – baseline CORT concentration (saliva)

ΔOXT-3: OXT concentration at 3 min post-stress – baseline CORT concentration (plasma)

ΔOXT-8: OXT concentration at 8 min post-stress – baseline CORT concentration (plasma)

ΔOXT-13: OXT concentration at 13 min post-stress – baseline CORT concentration (plasma)

ΔOXT-15: OXT concentration at 15 min post-stress – baseline CORT concentration (saliva)

Table S7b

Correlations of ΔCORT and ΔOXT in autistic individuals according to CORT response

Autistic individuals			ΔOXT-1	ΔOXT-3	ΔOXT-8	ΔOXT-13	ΔOXT-15
CORT response < 1.155	ΔCORT-3	r_s	-.586	-.250	.082	-.264	-.121
		p-value	**.022***	.369	.771	.341	.666
		N	15	15	15	15	15
	ΔCORT-8	r_s	-.286	-.621	-.300	-.282	.071
		p-value	.302	**.013***	.277	.308	.800
		N	15	15	15	15	15
	ΔCORT-13	r_s	-.321	-.596	-.361	-.236	.021
		p-value	.243	**.019***	.187	.398	.940
		N	15	15	15	15	15
CORT response ≥ 1.155	ΔCORT-3	r_s	-.176	.100	.273	.060	-.119
		p-value	.484	.693	.272	.813	.639
		N	18	18	18	18	18
	ΔCORT-8	r_s	-.354	.121	-.123	.093	-.317
		p-value	.150	.633	.627	.714	.200
		N	18	18	18	18	18
	ΔCORT-13	r_s	-.321	-.152	-.158	.033	-.445
		p-value	.194	.548	.531	.896	.064
		N	18	18	18	18	18

CORT response: quotient of the cortisol concentrations +13 min/ baseline.

ΔCORT in ng/ml; ΔOXT in pg/ml.

*****denotes *p*-value adjusted with Bonferroni correction for multiple testing with a significance at $p < .033$

ΔCORT-3: CORT concentration at 3 min post-stress – baseline CORT concentration

ΔCORT-8: CORT concentration at 8 min post-stress – baseline CORT concentration

ΔCORT-13: CORT concentration at 13 min post-stress – baseline CORT concentration

ΔOXT-1: OXT concentration at 1 min post-stress – baseline CORT concentration (saliva)

ΔOXT-3: OXT concentration at 3 min post-stress – baseline CORT concentration (plasma)

ΔOXT-8: OXT concentration at 8 min post-stress – baseline CORT concentration (plasma)

ΔOXT-13: OXT concentration at 13 min post-stress – baseline CORT concentration (plasma)

ΔOXT-15: OXT concentration at 15 min post-stress – baseline CORT concentration (saliva)

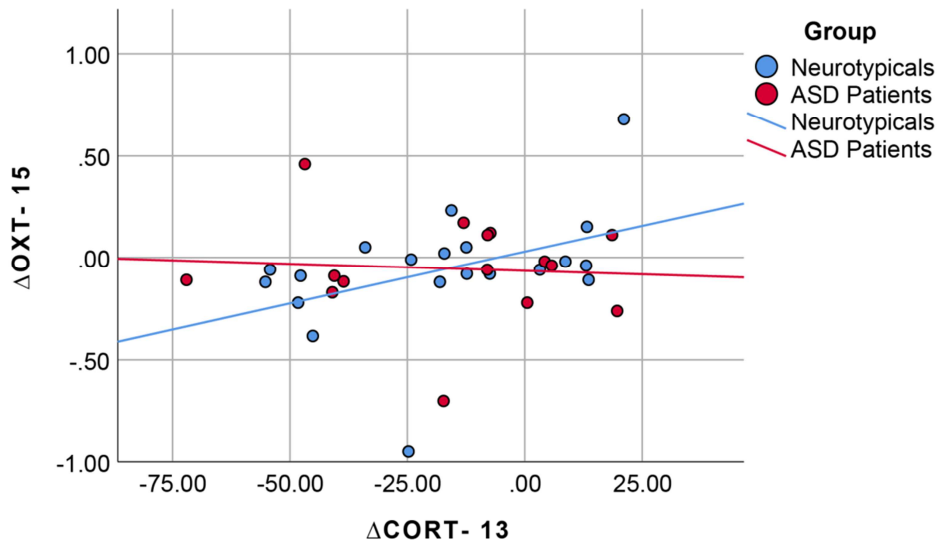

Figure S1a. *Correlations between ΔCORT and ΔOXT values among CORT non-responders*

This figure illustrates the positive correlation between ΔCORT-13 and ΔOXT-15 values in the neurotypical group (r_s = .49, p = .028). No significant correlation was found between ΔCORT-13 and ΔOXT-15 values in the group of patients with autism spectrum disorder (ASD) (r_s = .02, p = .940).

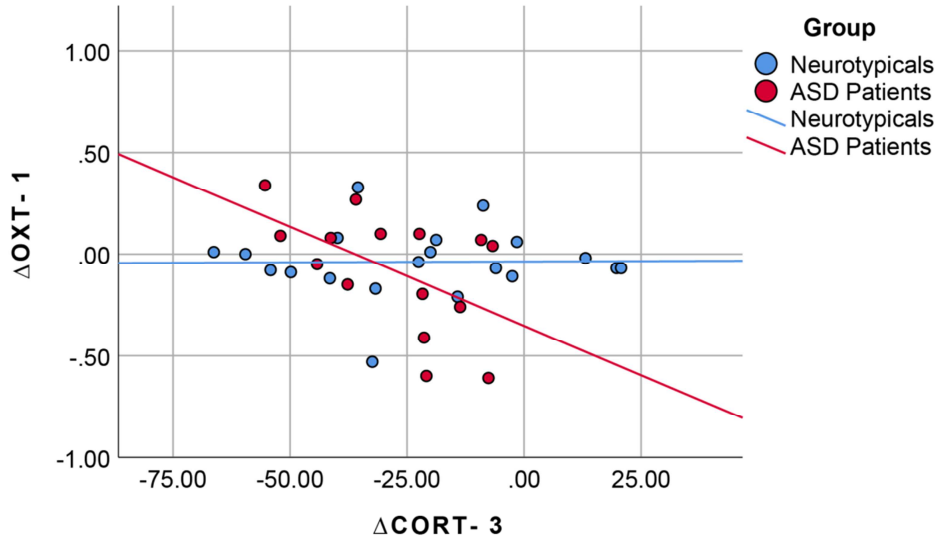

Figure S1b. *Correlations between ΔCORT and ΔOXT values among CORT non-responders*

This figure illustrates the negative correlation between ΔCORT-3 and ΔOXT-1 values in the group of patients with autism spectrum disorder (ASD) (r_s = -.59, p = .022). No significant correlation was found between ΔCORT-3 and ΔOXT-1 values in the neurotypical group (r_s = .003, p = .990).

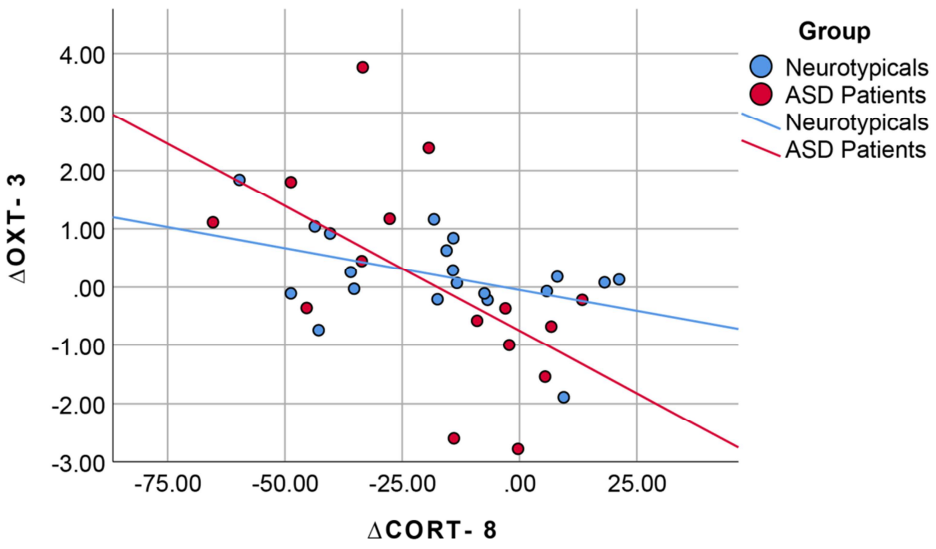

Figure S1c. *Correlations between ΔCORT and ΔOXT values among CORT non-responders*

This figure illustrates the negative correlation between ΔCORT-8 and ΔOXT-3 values in the group of patients with autism spectrum disorder (ASD) (r_s = -.62, p = .013). No significant correlation was found between ΔCORT-8 and ΔOXT-3 values in the neurotypical group (r_s = -.34, p = .142).

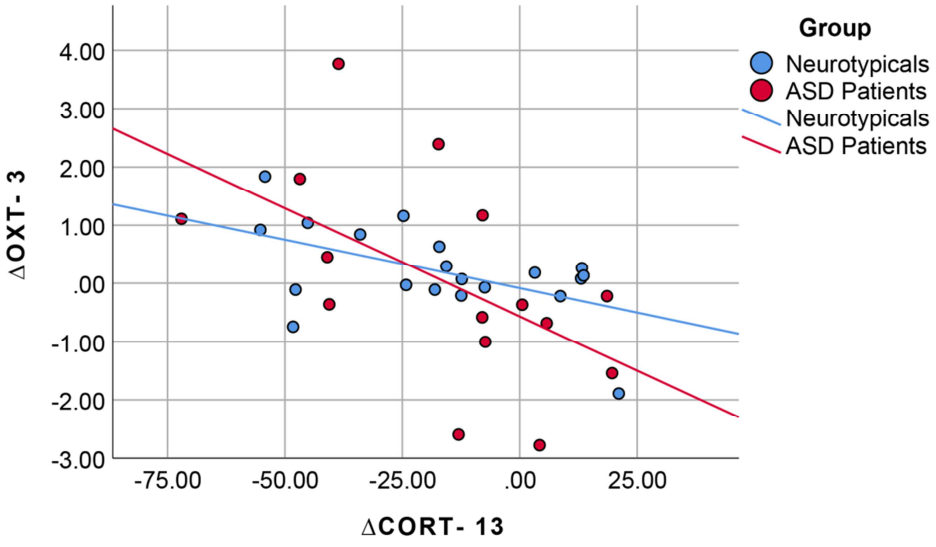

Figure S1d. *Correlations between ΔCORT and ΔOXT values among CORT non-responders*

This figure illustrates the negative correlation between ΔCORT-13 and ΔOXT-3 values in the group of patients with autism spectrum disorder (ASD) (r_s = -.60, p = .019). No significant correlation was found between ΔCORT-13 and ΔOXT-3 values in the neurotypical group (r_s = -.39, p = .089).

3. The relevance of alexithymic and autistic traits on anxiety and mood disorders in adults with and without autism

3.1 Summary

This chapter includes the second study of the thesis in which I investigated the contribution of autistic and alexithymic traits as potential risk factors for psychiatric comorbidities frequently seen in ASD such as depression and social phobia.

As has been indicated by previous work (e.g. Hemming, Haddock, Shaw, & Pratt, 2019; Leweke, Leichsenring, Kruse, & Hermes, 2012), alexithymia might act as a vulnerability factor on mental health in various psychiatric conditions. Considering the high comorbidity rates of depression and social phobia in adults with autism, the question was addressed whether alexithymic traits would increase the risk of depressive and social phobic symptoms in adults with autism (*n* = 122). Since alexithymic and autistic traits also appear in the general population (Franz et al., 2008; Ruzich et al., 2015), it was additionally examined whether these traits would increase depressive and social phobic symptoms in non-autistic patients (*n* = 62), who had presented with social interaction difficulties other than autism, as well as in typically developing adults (*n* = 261). The diversity of the study sample including autistic, non-autistic and typically developing adults also addresses the dimensional character of autism (Austin, 2005; Ingersoll & Wainer, 2014; Kamp-Becker et al., 2010; Ruzich et al., 2015).

The findings indicate that alexithymia and autistic traits incrementally increase the risk for mental disorders, which suggests that both traits should be assessed in individuals with social interaction difficulties.

The thesis study, therefore, provides important new insights into the role of alexithymia and autistic traits on common comorbid psychopathology.

3.2 Contributions

Authors:

Albantakis, L., Brandi, M.-B., Zillekens, I.C., Henco, L., Weindel, L., Thaler, H., Schliephake, L., Timmermans, B., Schilbach, L.

Contributions:

The author of this thesis is the first author of the publication. Laura Albantakis designed the research with help of Marie-Luise Brandi, Imme Christina Zillekens, Lara Henco and Hanna Thaler. Laura Albantakis provided the data from autistic and non-autistic patients. Marie-Luise Brandi, Imme Christina Zillekens, Lara Henco and Lena Schliephake provided the data from healthy participants. Leonie Weindel helped with the data collection from patients. Laura Albantakis performed the computational data analysis with help of Marie-Luise Brandi, Imme Christina Zillekens, Lara Henco, Hanna Thaler, and Bert Timmermans. Laura Albantakis wrote the manuscript. All authors reviewed and edited the manuscript. Leonhard Schilbach was the supervisor of the project and provided funding.

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3.3 Alexithymic and autistic traits - relevance for comorbid depression and social phobia in adults with and without autism spectrum disorder

Albantakis, L.[1,2], Brandi, M.-B.[1], Zillekens, I.C.[1,2], Henco, L.[1,3], Weindel, L.[1], Thaler, H.[1], Schliephake, L.[4], Timmermans, B.[5], Schilbach, L.[1,2,6,7]

[1]Independent Max Planck Research Group for Social Neuroscience, Max Planck Institute of Psychiatry, Munich, Germany

[2]International Max Planck Research School for Translational Psychiatry, Munich, Germany

[3]Graduate School for Systemic Neurosciences, Munich, Germany

[4]Biological Psychology, University of Muenster, Germany

[5]School of Psychology, University of Aberdeen, Scotland

[6]Clinic for disorders of social interaction, LVR-Klinikum Duesseldorf / Kliniken der Heinrich-Heine-Universitaet Duesseldorf, Germany

[7]Ludwig-Maximilian-University, Munich, Germany

Correspondence concerning this article should be addressed to

Laura Albantakis, Max Planck Institute of Psychiatry, Kraepelinstr. 2 – 10, 80804 Munich, Germany.

Email: laura_albantakis@psych.mpg.de

Abstract

High alexithymic traits and psychiatric comorbidities such as depression and social phobia are frequently observed among adults with autism spectrum disorder (ASD). In this study, we tested whether alexithymic and/or autistic traits are risk factors for depressive and social phobic symptoms in adults with ASD (*n* = 122), patients with social interaction difficulties other than autism (*n* = 62), and neurotypical participants (*n* = 261). Multiple regression analyses of these three groups demonstrated that both traits explained considerable variance of depressive and social phobic symptoms. In adults with ASD, alexithymic traits were predictive of depressive symptoms, while autistic traits predicted social phobic traits. In patients with social interaction difficulties other than autism, alexithymic and autistic traits were identified as predictors for social phobic symptoms, while no variable predicted depressive symptoms. In neurotypicals, both alexithymic and autistic traits were predictive of depressive and social phobic symptoms. Our results, therefore, highlight the importance of assessing both alexithymic and autistic traits in patients with and without ASD for identifying comorbid psychopathology. Depending on the underlying core symptomatology, alexithymic and/or autistic trait increase the risk of depressive and social phobic symptoms calling for therapeutic strategies to prevent or at least reduce comorbid psychopathology.

Key words: autism spectrum disorder, alexithymia, depression, social phobia, psychiatric comorbidity, psychosocial functioning, adults

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with core deficits in social communication and social interaction aside from restricted, repetitive patterns of behavior, interests or activities according to DSM-5 criteria (American Psychiatric Association, 2013). In addition to the underlying core symptoms of ASD, autistic individuals often experience comorbid mental health problems. World-wide, depression and social phobia are thought to occur in up to 50 % of cases with ASD (Albantakis et al., 2018; Hedley, Uljarević, Foley, Richdale, & Trollor, 2018; Maddox & White, 2015; Spain et al., 2016). Moreover, approximately 50 % of autistic patients display clinically significant levels of alexithymia (Hill et al., 2004; Kinnaird, Stewart, & Tchanturia, 2019; Milosavljevic et al., 2016; Morie, Jackson, Zhai, Potenza, & Dritschel, 2019). This raises the need to enhance our understanding of alexithymia in ASD and its contribution to comorbid mental health problems.

Alexithymia is a subclinical condition in which affected individuals have difficulties identifying and describing their own emotions (Taylor, 2000) as well as the emotions in others, e.g. through the interpretation of facial expressions, which is central to the diagnosis of ASD (Cook, Brewer, Shah, & Bird, 2013; Starita, Borhani, Bertini, & Scarpazza, 2018). In fact, some researchers have even suggested that emotional impairments seen in ASD are due to concurrent alexithymia rather than representing a genuine feature of autism (Bird & Cook, 2013; Trevisan et al., 2016).

Thus, it is possible that emotion recognition and regulation difficulties of comorbid psychopathology seen in patients with ASD (Aldao, Nolen-Hoeksema, & Schweizer, 2010; McLaughlin & Nolen-Hoeksema, 2011; Weissman et al., 2019) are associated with alexithymia (Bilotta, Giacomantonio, Leone, Mancini, & Coriale, 2016; Laloyaux, Fantini, Lemaire, Luminet, & Larøi, 2015). In addition, high levels of autistic traits have similarly been associated with altered emotion processing (Corden, Chilvers, & Skuse, 2008; Samson, Huber, & Gross, 2012).

Indeed, maladaptive emotion regulation strategies like suppression and avoidance are typical for people with alexithymic, but also with autistic traits (e.g. Bilotta et al., 2016; Jahromi, Meek, & Ober-Reynolds, 2012; Laloyaux et al., 2015; Samson, Wells, Phillips, Hardan, & Gross, 2015).

They can negatively affect social interactions resulting in a lack of social support and potentially mood and anxiety disorders (Figure 1) (Hofmann, 2014; Marroquín, 2011; Williams, Morelli, Ong, & Zaki, 2018). Importantly, previous studies have shown that alexithymic traits (Hemming et al., 2019; Leweke et al., 2012; Pandey, Saxena, & Dubey, 2011) and autistic traits (Fietz et al., 2018; Lundström et al., 2011; Morie et al., 2019) may both act as a vulnerability factor for mental illness, notably depressive and anxiety disorders. This is highly relevant because (comorbid) mental health problems, in particular depressive disorders, have been identified as a major risk factor for suicidal ideation and suicide attempts in autistic children (Mayes et al., 2013) and suicide represents the second leading cause of death in adult individuals with ASD (Hirvikoski et al., 2016). These dramatic findings highlight the need to improve our understanding of alexithymic and autistic traits in comorbid psychopathology of ASD.

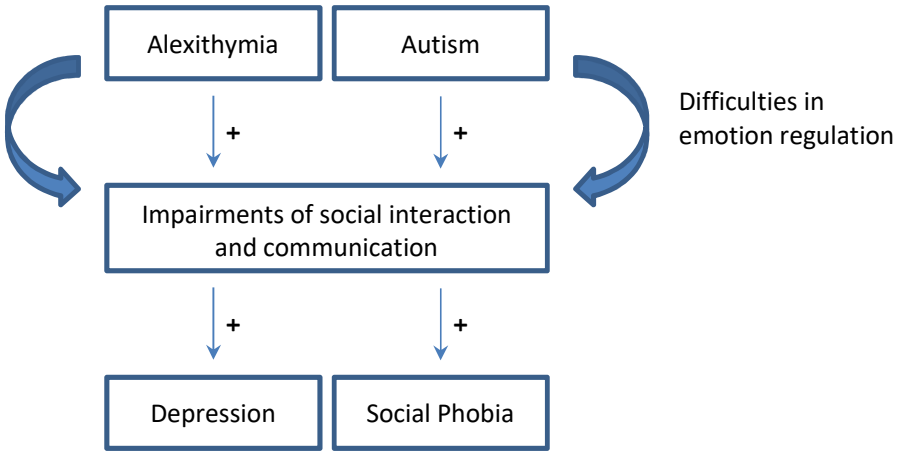

Figure 1. *Model depicting the positive associations of alexithymic and autistic traits on depression and social phobia through difficulties in emotion regulation*

Study aims

Our study aimed to investigate whether the degree of autistic and alexithymic traits can explain the co-occurrence of depressive and social phobic symptoms. Since autistic and alexithymic traits are dimensional constructs and present in both clinical and non-clinical populations (Austin, 2005; Fietz, Valencia, & Silani, 2018; Franz et al., 2008; Ingersoll & Wainer, 2014; Kamp-Becker et al., 2010; Ruzich et al., 2015; Salminen, Saarijärvi, Äärelä, Toikka, & Kauhanen, 1999), we extended the investigation beyond ASD to include other patients with social interaction difficulties other than autism and the general population. This approach was chosen in concordance with a dimensional and transdiagnostic approach to mental health, as for instance set out in the NIMH RDoC framework (Insel et al., 2010), which had been implemented in a specialized "Outpatient and Day Clinic for Disorders of Social Interaction" at the Max Planck Institute of Psychiatry. Consequently, we included patients with a confirmed diagnosis of ASD, patients who presented with social interaction difficulties, but did not receive a formal diagnosis of ASD as well as neurotypicals. In light of the dimensional character of alexithymic and autistic traits and their existence in both clinical and non-clinical populations, we investigated the degree to which both traits contribute to depressive and social phobic symptoms irrespective of the underlying core condition.

Methods

Participants

The study included three groups of participants: participants with a confirmed diagnosis of ASD, participants with social interaction difficulties, but no diagnosis of ASD and neurotypicals without any social-communicative impairments. Participants with a confirmed or an excluded diagnosis of ASD were all patients admitted to the "Outpatient and Day Clinic for Disorders of Social Interaction" at the Max Planck Institute of Psychiatry in Munich, Germany, from April 2015 to January 2018 (Table 1). They had been referred to the clinic for ASD evaluation. All patients received a diagnostic assessment of ASD according to the autism guidelines (AWMF, 2015) (Figure 2). Depending on the results of the diagnostic evaluation, patients were divided into two groups:

Individuals of the first group fully met the DSM-5-criteria of ASD (*n* = 122) and received the diagnosis of ASD. They are referred to as "ASD group". Since patients of the ASD group did not present with any intellectual impairment, they were regarded as patients with high-functioning autism. Individuals of the second group showed significant impairments of their social communicative skills, but did not fulfill the diagnostic criteria for ASD according to DSM-5 (*n* = 62). For example, patients presented with social interaction difficulties but did not give any indication for repetitive and restricted patterns of behavior, interests or activities. They are referred to as "non-ASD group". We also included a third group of neurotypical participants (*n* = 261) defined as adults without any history of psychiatric or neurological impairments. Subjects of this group had taken part in research projects within the independent Max Planck Research Group for "Social Neuroscience" at the Max Planck Institute of Psychiatry in the past. All study participants (*N* = 445) provided written informed consent. Ethical approval was granted by the Ethics Committee of the Ludwig-Maximilian-University, Munich. All procedures were performed in accordance with the Declaration of Helsinki.

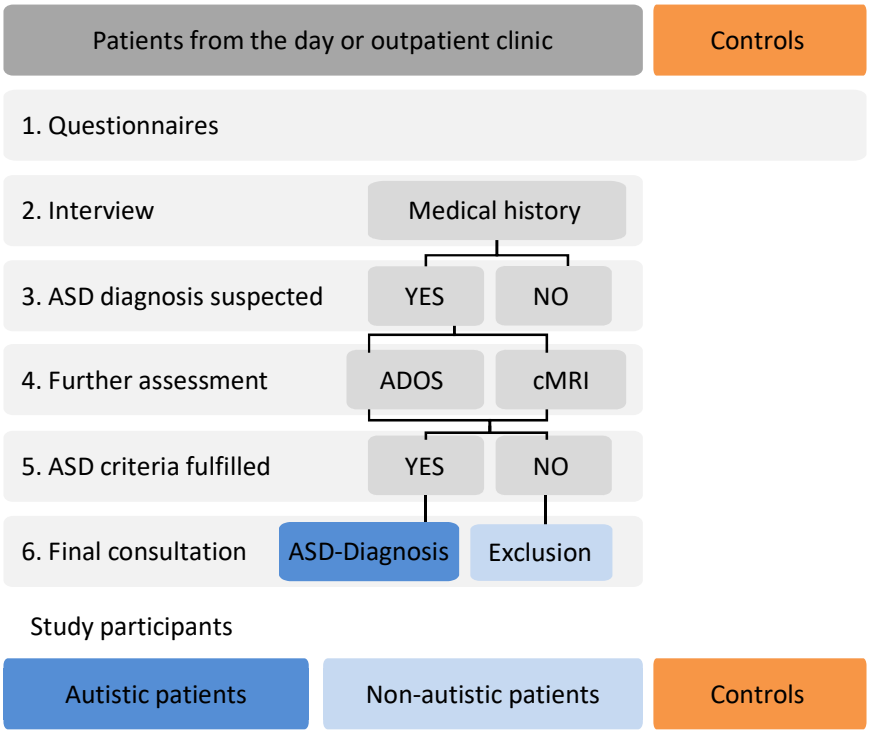

Figure 2. *Diagnostic procedure for study participants*

ADOS: Autism Diagnostic Observation Schedule
cMRI: cranial magnetic resonance imaging

Clinical data

Medical and psychosocial histories from all patients (ASD and non-ASD group) were assessed in interviews conducted by a psychologist or psychiatrist experienced in diagnosing ASD (Supplementary Table S1 for psychiatric comorbidities). As part of the regular diagnostic process for ASD, patients (ASD and non-ASD group) were tested using the "Autism Diagnostic Observation Schedule-2" (ADOS-2) (Hus & Lord, 2014) (Table 1).

Measures

Participants of all three groups (ASD, non-ASD, neurotypicals) were asked to fill out the same set of psychometric questionnaires. To evaluate autistic traits, the "Autism-Spectrum Quotient (AQ)" (Baron-Cohen, Wheelwright, Skinner, et al., 2001) was used. The "Toronto Alexithymia Scale" with 20 Items („TAS-20") (Bagby et al., 1994) reflected the level of alexithymia in individuals, whereas the "Liebowitz Social Anxiety Scale (LSAS)" (Fresco et al., 2001) and "Beck Depression Inventory-II (BDI-II)" (Beck, Steer, & Brown, 1996) provided information about social phobic and depressive symptoms, respectively. Only data sets with less than 10% of missing data per instrument were included (Table 1).

Table 1

Characteristics of participants

Variables	ASD	non-ASD	NT	*F*	*p*	Difference
N	122	62	261	-	-	-
Sex (m/f)	83/39	37/25	120/141	-	-	-
Alexithymia (yes/no)	68/54	30/32	11/250	-	-	-
Mean ADOS (SD)	7.01 (3.17)[1]	3.95 (2.97)[2]	-	-	<.001	ASD > non-ASD[3]
Mean Age in years (SD)	33.46 (10.40)	35.15 (12.62)	26.41 (7.80)	36.47	<.001	non-ASD > ASD> NT
Mean AQ (SD)	36.25 (8.16)	32.29 (9.39)	15.08 (5.60)	441.18	<.001	ASD > non-ASD > NT
Mean TAS-20 (SD)	62.18 (10.90)	59.36 (10.72)	44.36 (9.71)	149.45	<.001	ASD > non-ASD > NT
Mean BDI-II (SD)	17.30 (11.59)	21.92 (10.54)	5.40 (5.33)	148.41	<.001	non-ASD > ASD > NT
Mean LSAS (SD)	77.28 (26.81)	70.55 (29.17)	31.26 (18.36)	203.37	<.001	ASD > non-ASD > NT

ASD: patients with autism spectrum disorder; non-ASD: patients with social interaction difficulties, but no diagnosis of ASD; NT: typically developing group; Alexithymia: TAS-20 scores ≥ 61. AQ: Autism Quotient (scale: 0-50); TAS-20: Toronto Alexithymia Scale-20 (scale: 20-100); BDI-II: Beck Depression Inventory (scale: 0-63); LSAS: Liebowitz Social Anxiety Scale (scale: 0-144), (SD): Standard Deviation. [1]: available information for n=102; [2]: available information for n=41. [3]Unpaired t-test: $t(141) = -5.31$, $p < .001$.

Note. ANOVAs with contrasts were calculated to determine group differences. Results are based on 1,000 bootstrap samples.

Analyses

Data processing and statistical analyses were performed in Matlab (R2010a, The MathWorks, Inc., Natick, MA, USA) and IBM SPSS 25.0 including the bootstrapping tool (IBM Corp., 2017). Tests of normality revealed that the relevant measures (age, AQ, BDI-II, TAS-20, LSAS) were not normally distributed neither in the total sample (including all three groups) nor in each subgroup (Kolmogorov-Smirnov tests, all *p*-values < .05). Data transformation failed to improve skewness. Therefore, correlational, logistic and multinomial regression analyses were performed with 1,000 resamples bootstrapping to provide more robust statistics (Field, 2018).

Models

We generated two models for testing our hypotheses and performed the analyses for each group separately. In the first model (Figure 3), we tested whether autistic, alexithymic or both traits explained variance of depressive symptoms. In the second model (Figure 4), we tested whether autistic, alexithymic or both traits explained variance of social phobic symptoms. For each model, we performed a three-step, forced entry hierarchical regression analysis according to the procedures established by Cook and colleagues (Cook, Brewer, Shah, & Bird, 2013), with depressive symptoms as dependent variable in model 1 and social phobic symptoms in model 2. To explain the approach in short: In a first step, predictors of no interest (in our case age and sex) were included in the model. In the following step, predictors of interest (in our case alexithymic and autistic traits) were added to the model, first alexithymic, then autistic traits. By doing this, we could observe how much additional variance was explained by each predictor of interest. Multicollinearity of predictor variables was checked for by computing the variance inflation factor (VIF) and the tolerance statistic for each analysis. Values of VIF and of tolerance were below cut-off criteria in all analyses, suggesting that multicollinearity was negligible. Although tests did not indicate significant multicollinearity, moderate correlations between TAS-20 and AQ scores were found in each group (Supplementary Table S2). Since this might bias the estimated roles of predictors in the model, we computed two further regressions changing the order of entries of alexithymic and autistic traits in

the analyses. Thus, our complete computational pathway can be summarized as follows: In the first step (1), age and sex were entered in the model. Second (2 A), alexithymic traits were added. Last (3 A), autistic traits were included. Then the order of entries was changed. So autistic traits were added second (2 B), and alexithymic traits last (3 B).

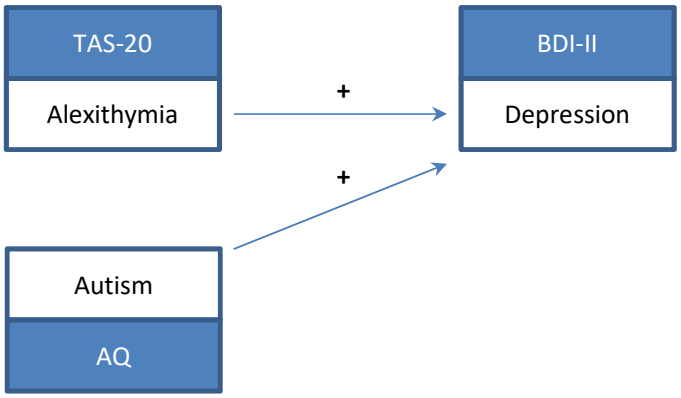

Figure 3. *Model depicting the positive associations of alexithymic and autistic traits on depression*

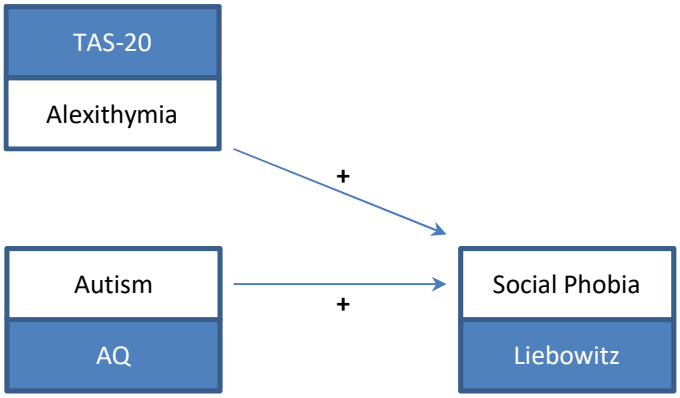

Figure 4. *Model depicting the positive associations of alexithymic and autistic traits on social phobia*

Correlations between alexithymic and autistic traits

In order to identify associations among the variables, simple uncorrected correlation analyses were run for each group (Supplementary Table S2).

Results

Characteristics of participants

Patients with a confirmed diagnosis of ASD had significantly higher ADOS scores than patients with no ASD diagnosis (Table 1). Alexithymia, defined as TAS-20 scores ≥ 61 according to Bagby and colleagues (1994), was found in 55.7 % of autistic and 48.4 % of non-autistic patients, while only 4.2 % of neurotypicals presented with alexithymia. Patients with ASD and non-ASD showed similar rates of psychiatric comorbidities (Supplementary Table S1).

Alexithymic and autistic traits predicting depressive symptoms

To address our hypothesis that variance in depressive symptoms can be explained by both autistic and alexithymic traits, we observed for each group separately the stepwise changes of variance induced by entering alexithymic and autistic traits as predictors in the models (Table 2). The results are described in detail for the ASD group, while the results for the non-ASD and neurotypical groups are summarized in the text (Table 2 and Supplementary Tables S3 a and b for further details).

In the ASD group, entering alexithymic traits into the model (step 2 A) increased R^2 by 13.2 % with alexithymic traits as significant predictor of depressive symptoms (β = .40, p = .001). Including autistic traits last (step 3 A) increased R^2 by 0 %. The final model, however, remained significant [F(4, 117) = 5.74, p < .001] with alexithymic traits as the only significant predictor of depressive symptoms (β = .38, p = .003). AQ and TAS-20 scores were moderately correlated, r = .61, p < .001. Thus, for reasons mentioned above, we changed the order of entries and re-ran the analyses. Entering autistic before alexithymic traits into the model (step 2 B), increased R^2 by 5.1 % with autistic traits as significant predictor of depressive symptoms (β = .34, p = .012). Including alexithymic traits last (step 3 B) increased R^2 by additional 8.1 % with alexithymic traits as the only significant predictor of depressive symptoms (β = .38, p = .001). These results indicate that autistic traits only explained variance in depressive symptoms in the absence of alexithymic traits (step 2 B), while alexithymic traits predicted depressive symptoms irrespective of the inclusion of autistic traits in the models (step 2 A and 3 B).

In the non-ASD patient group, none of the models produced a statistically significant effect. Neither alexithymic nor autistic traits were significant predictors of depressive symptoms.

In the neurotypical group, both alexithymic and autistic traits explained additional variance in depressive symptoms. Alexithymic (β = .14, p = .001) and autistic traits (β = .27, p = .001) were both significant predictors of depressive symptoms.

Taken together, analyses in the ASD group revealed that autistic traits only predicted depressive symptoms in the absence of alexithymic traits, while alexithymic traits predicted depressive symptoms irrespective of autistic traits in the models. In the non-ASD group, neither alexithymic nor autistic traits were a significant predictor of depressive symptoms, while in the neurotypical group, both alexithymic and autistic traits were significant predictors of depressive symptoms irrespective of the other variable.

Table 2

Three-step hierarchical regression models for depression

Groups	Steps	Predictors	R^2	Δ R^2	*F* change	Sig. *F* change
ASD	1	Age, Sex	3.2 %	3.2 %	$F(2, 119) = 1.96$	.142
	2 A	Age, Sex, TAS-20	16.4 %	13.2 %	$F(1, 118) = 18.55$	< .001***
	3 A	Age, Sex, TAS-20, AQ	16.4 %	0 %	$F(1, 117) = .05$	.820
	2 B	Age, Sex, AQ	8.3 %	5.1 %	$F(1, 118) = 6.47$	.012*
	3 B	Age, Sex, AQ, TAS-20	16.4 %	8.1 %	$F(1, 117) = 11.41$	.001**
non-ASD	1	Age, Sex	0.2 %	0.2 %	$F(2, 59) = 0.06$	.945
	2 A	Age, Sex, TAS-20	4.3 %	4.1 %	$F(1, 58) = 2.51$	.119
	3 A	Age, Sex, TAS-20, AQ	4.6 %	0.3 %	$F(1, 57) = .16$	.689
	2 B	Age, Sex, AQ	2.1 %	1.9 %	$F(1, 58) = 1.14$	.291
	3 B	Age, Sex, AQ, TAS-20	4.6 %	2.5 %	$F(1, 57) = 1.49$	.228
NT	1	Age, Sex	1.3 %	1.3 %	$F(2, 258) = 1.71$	.182
	2 A	Age, Sex, TAS-20	14.5 %	13.2 %	$F(1, 257) = 39.5$	< .001***
	3 A	Age, Sex, TAS-20, AQ	21.1 %	6.6 %	$F(1, 256) = 21.47$	< .001***
	2 B	Age, Sex, AQ	15.8 %	14.5 %	$F(1, 257) = 44.13$	< .001***
	3 B	Age, Sex, AQ, TAS-20	21.1 %	5.3 %	$F(1, 256) = 17.23$	< .001***

ASD: patients with autism spectrum disorder; non-ASD: patients with social interaction difficulties, but no diagnosis of ASD; NT: typically developing group; AQ: Autism Quotient (scale: 0-50) measuring autistic traits; TAS-20: Toronto Alexithymia Scale-20 (scale: 20-100) measuring alexithymic traits.

Note. Results are based on 1,000 bootstrap samples.

*$p < .05$, **$p < .01$, ***$p < .001$.

Alexithymic and autistic traits predicting social phobic symptoms

To investigate the relationship of autistic and alexithymic traits on social phobic symptoms, we observed for each group separately the stepwise changes of variance induced by entering alexithymic and autistic traits as predictors in the models (Table 3). The results are described in detail for the ASD group, while the results for the non-ASD and neurotypical groups are summarized in the text (Table 3 and Supplementary Tables S4 a and b for further details).

In the ASD group, entering alexithymic traits into the model (step 2 A) increased R^2 by 11.8 % with sex (β = 11.40, p = .011) and alexithymic traits (β = .87, p = .001) as significant predictors of social phobic symptoms. Including AQ last (step 3 A) increased R^2 by additional 10.3 % with autistic traits (β = 1.39, p = .001) as the only significant predictor of social phobic symptoms in the final model. AQ and TAS-20 scores moderately correlated, r = .61, p < .001. Thus, for reasons mentioned above, we changed the order of entries and re-ran the analyses. Entering autistic before alexithymic traits into the model (step 2 B), increased R^2 by 21.1 % with autistic traits (β = 1.63, p = .001) as significant predictor of social phobic symptoms (β = 1.63, p = .001). Including alexithymic traits last (step 3 B) increased R^2 by additional 1.0 % with autistic traits (β = 1.39, p = .001) as the only significant predictor of social phobic symptoms in the final model, F(4, 117) = 13.80, p < .001. These results indicate that alexithymic traits only explained variance in social phobic symptoms in the absence of autistic traits (step 2 A), while autistic traits predicted social phobic symptoms irrespective of the inclusion of alexithymic traits in the models (step 2 B and 3 A).

In the non-ASD patient and in the neurotypical group, both alexithymic and autistic traits explained additional variance in social phobic symptoms. Alexithymic (non-ASD: β = 1.24, p = .001, Neurotypical: β = .59, p = .001) and autistic (non-ASD: β = .68, p = .032; Neurotypical: β = .90, p = .001) traits were significant predictors of social phobic symptoms in the final model.

Taken together, analyses in the ASD group revealed that alexithymic traits only predicted social phobic symptoms in the absence of autistic traits, while autistic traits predicted social phobic symptoms irrespective of alexithymic traits in the models. In the non-ASD and neurotypical group,

both alexithymic and autistic traits were significant predictors of social phobic symptoms irrespective of the other variable.

Table 3

Three-step hierarchical regression models for social phobia

Groups	Steps	Predictors	R^2	Δ R^2	*F* change	Sig. *F* change
ASD	1	Age, Sex	10 %	10 %	$F(2, 119) = 6.60$	.002**
	2 A	Age, Sex, TAS-20	21.8 %	11.8 %	$F(1, 118) = 17.78$	< .001***
	3 A	Age, Sex, TAS-20, AQ	32.1 %	10.3 %	$F(1, 117) = 17.72$	< .001***
	2 B	Age, Sex, AQ	31.1 %	21.1 %	$F(1, 118) = 36.23$	< .001***
	3 B	Age, Sex, AQ, TAS-20	32.1 %	1.0 %	$F(1, 117) = 1.60$	.208
non-ASD	1	Age, Sex	9.6 %	9.6 %	$F(2, 59) = 3.12$	.052
	2 A	Age, Sex, TAS-20	39.6 %	30.1 %	$F(1, 58) = 28.89$	< .001***
	3 A	Age, Sex, TAS-20, AQ	43.2 %	3.6 %	$F(1, 57) = 3.62$	.062
	2 B	Age, Sex, AQ	27.0 %	17.4 %	$F(1, 58) = 13.87$	< .001***
	3 B	Age, Sex, AQ, TAS-20	43.2 %	16.2 %	$F(1, 57) = 16.30$	< .001***
NT	1	Age, Sex	2.5 %	2.5 %	$F(2, 258) = 3.30$	.039*
	2 A	Age, Sex, TAS-20	19.7 %	17.2 %	$F(1, 257) = 55.17$	< .001***
	3 A	Age, Sex, TAS-20, AQ	25.9 %	6.2 %	$F(1, 256) = 21.45$	< .001***
	2 B	Age, Sex, AQ	18.0 %	15.5 %	$F(1, 257) = 48.57$	< .001***
	3 B	Age, Sex, AQ, TAS-20	25.9 %	7.9 %	$F(1, 256) = 27.45$	< .001***

ASD: patients with autism spectrum disorder; non-ASD: patients with social interaction difficulties, but no diagnosis of ASD; NT: typically developing group; AQ: Autism Quotient (scale: 0-50) measuring autistic traits; TAS-20: Toronto Alexithymia Scale-20 (scale: 20-100) measuring alexithymic traits.

Note. Results are based on 1,000 bootstrap samples.

*$p < .05$, **$p < .01$, ***$p < .001$.

Discussion

The present study examined the association of autistic and alexithymic traits with depressive and social phobic symptoms in adults with a confirmed diagnosis of ASD, patients with social interaction difficulties but no diagnosis of ASD and neurotypical participants. Analyses were performed in these three groups separately in order to investigate the impact of the underlying core condition on the contribution of alexithymic and autistic traits on depressive and social phobic symptoms.

We observed a high prevalence of alexithymia in the ASD group, which is in line with previous reports of alexithymic traits in autism (Berthoz & Hill, 2005; Kinnaird, Stewart, & Tchanturia, 2019; Milosavljevic et al., 2016; Morie et al., 2019). Furthermore, the prevalence of depression and social phobia in this group are consistent with other studies about autism in adulthood (Albantakis et al., 2018; Hedley, Uljarević, Foley, Richdale, & Trollor, 2018; Maddox & White, 2015; Spain et al., 2016). Thus, our ASD group realistically meets the characteristics of autistic adults including comorbid psychopathology. The prevalence of alexithymia in the non-ASD patient group is also consistent with previous findings in non-autistic patients with depressive and anxiety disorders (Cox, Swinson, Shulman, & Bourdeau, 1995; Leweke et al., 2012). The prevalence of alexithymia in the neurotypical group was in line with a recent finding for the general population (Fietz et al., 2018). Importantly, patients from the ASD and non-ASD group in our study presented with similar rates of comorbidities, leaving the underlying core condition as the main difference.

The model-based analyses that used depressive symptomatology as the dependent variable revealed that in autistic patients, depression scores were predicted by alexithymic traits, but not by autistic traits. This is in line with results of a study with 68 autistic individuals, in which depression was associated with alexithymia, but not autistic symptoms (Morie et al., 2019). Our study, importantly, replicates this previous finding in a substantially bigger group of patients (122 autistic adults). Additionally, autism diagnoses in our study were confirmed using the highest possible assessment standards, whereas Morie et al. (2019) relied on self-reported diagnoses. Furthermore,

we found that autistic traits were predictors of depressive symptoms before alexithymic traits were entered in the model. Once alexithymic traits were added, the effect of autistic traits on depressive symptoms did not reach significance anymore. This observation is relevant for future studies highlighting the importance of including alexithymia as a control variable to avoid misinterpretation and a potentially false attribution to ASD. Since most current research on alexithymia suggests that it is a stable personality trait rather than a state-related condition (Hemming et al., 2019), our findings are in favor of an assessment of alexithymic traits in patients with ASD in order to identify and prevent the risk of a subsequent depressive disorder.

Contrary to our expectations, the analysis of the non-ASD patient group showed that neither alexithymic nor autistic traits were identified as significant predictors of depressive symptoms. This is surprising given that the non-autistic patients presented with social interaction difficulties and scored highest on mean BDI-II values. Also, previous studies have shown that alexithymia tends to co-occur with depression (Hemming et al., 2019; Leweke et al., 2012). A possible explanation for not having found a link between alexithymia and depression in the non-ASD patient group may be attributed to a large heterogeneity of psychopathology in this group, which also constitutes an important limitation of our characterization of this subgroup. Also, the non-ASD group was the smallest in number of the three subgroups and therefore underpowered to demonstrate significant effects with any of the variables included.

In the neurotypical group, alexithymic and autistic traits independently accounted for a significant amount of variance in depressive symptoms. These findings are again similar to results by Fietz and colleagues (Fietz et al., 2018) who found a small-to-moderate effect for alexithymic and a moderate effect for autistic traits in predicting depression in the general population.

Regarding social phobic symptoms, we conversely found autistic traits to be significant predictors of social phobic symptoms in the ASD patient group. Our findings thus indicate that in contrast to depressive symptoms, autistic rather than alexithymic traits were predictive of social phobic symptoms in patients with ASD. Again, our results are consistent with results by Morie et al.

(2019) who did not observe an association of anxiety and alexithymia. In the non-ASD patient and neurotypical groups, we found that alexithymic and autistic traits were both significant predictors of social phobic symptoms. Results in the neurotypical group stand in contrast to findings by Fietz and colleagues (2018) who only found alexithymic, but not autistic traits to be significantly correlated with anxiety-related symptoms. Despite similar sample sizes the comparability to our study is limited due to the use of different psychometric instruments. Fietz and colleagues (2018) focused on general aspects of anxiety rather than social phobia when examining the interaction of autistic and alexithymic traits.

Taken together, both alexithymic and autistic traits accounted for depressive and social phobic symptoms in the neurotypical group. Furthermore, both traits predicted social phobic symptoms in the non-ASD patient group. Importantly, in the ASD group, only alexithymia but not autistic traits predicted levels of depression, while conversely autism severity explained variance in social phobia. Therefore, our findings extend previous research which has suggested that alexithymia and not levels of autism may play a particularly important role in emotion processing (e.g. emotion recognition and expression) that may lead to the development of affective disorders (Bird et al., 2010; Cook, Brewer, Shah, & Bird, 2013; Shah, Hall, Catmur, & Bird, 2016; Trevisan, Bowering, & Birmingham, 2016). A key element in this discussion could be emotion regulation, briefly summarized as a process of identifying emotions, selecting a reaction to the emotion and applying strategies to regulate the reaction to the identified emotion (Gross, 2015; Morie et al., 2019). High alexithymic traits were found in depression and social phobia, suggesting that alexithymia might be the link to the psychopathology due to maladaptive emotion regulation strategies that have also been observed in these disorders (Panayiotou et al., 2015; Spokas, Luterek, & Heimberg, 2009). However, in patients with ASD, patterns of these maladaptive strategies remained after controlling for alexithymia (Samson, Huber, & Gross, 2012), indicating that autistic traits may modulate emotion regulation in addition to alexithymia.

Furthermore, individuals with ASD tend to use cognitive reappraisal, e.g. taking another mental perspective on a situation in order to reinterpret its meaning, less often as an emotion regulation strategy (Samson et al., 2012). This could be due to an impaired ability of perspective taking or theory of mind, commonly found in ASD (Boucher, 2012). This hypothesis is supported by findings from an fMRI study, which showed that ASD was associated with atypicalities in brain networks associated with theory of mind functions (Bernhardt et al., 2014). In contrast, alexithymia was associated with brain networks subserving affective processes, e.g. emotions and empathy, but not with activation of the theory of mind networks. This dissociation between deficits in sociocognitive and socioaffective networks in ASD and alexithymia could also be relevant for comorbid psychopathology. Given that depression is an affective or emotional disorder, it can be assumed that alexithymia is involved in the pathological process of depression. This was supported by our findings in the ASD and neurotypical group but not in the non-ASD group.

Contrary to our results in depression, autistic traits (including deficits in theory of mind) instead of alexithymic traits seem to be more relevant for social phobia in ASD. While patients with social phobia unlike autistic individuals tend to hyper-mentalize (Ballespí, Vives, Sharp, Tobar, & Barrantes-Vidal, 2019; Hezel & McNally, 2014), deficits of perspective taking could indirectly increase the risk of social phobia in ASD due to negative experiences in social interactions. In other words, due to an impaired theory of mind and other deficits in social interactional skills, autistic individuals are at greater risk of receiving negative social feedback or even of being mocked or bullied by others. Thus, while autistic individuals like social phobic patients may tend to avoid these situations, the underlying mechanisms and reasons may differ.

Importantly, our findings may have direct implications for therapeutic interventions and can help to direct future research. For example, reducing alexithymic traits through psychotherapy could indirectly lead to a differential decrease of depressive and social phobic symptoms across the different patient groups. Beneficial therapeutic strategies for treating alexithymia could be, for example, a group-based setting (Ford & Long, 1977; Swiller, 1988), supportive and educational

approaches rather than interpretive approaches (Cameron, Ogrodniczuk, & Hadjipavlou, 2014; Freyberger, 1977; Sifneos, 1975) with a focus on increasing emotional intelligence by teaching emotional components (Amani, Goodarzi, & Ahamadian, 2013). Such techniques are also part of group-based psychotherapies for adults with high-functioning autism that are currently being developed (Parpart et al., 2018).

Strengths and limitations

A strength of our study lies in the relatively large number of study participants (ASD: *n* = 122, non-ASD: *n* = 62, neurotypicals: *n* = 261), which increases the statistical power of the analysis and stands out in comparison to previous research done in this field (e.g. Morie et al., 2019). Furthermore, we applied a multi-sample approach to examine the impact of the underlying core condition on the variables of interest because the origin of the samples (clinical or non-clinical data) matter when investigating psychopathology (Aldao et al., 2010). The statistical analyses chosen for this study are, however, limited with regard to identifying the exact directions or order of events underlying the complex interactions of autistic and alexithymic traits with comorbid psychopathology.

As expected, we found high correlations among our variables of interest (Supplementary Table 2). However, tests performed indicated that multicollinearity was negligible. In addition, we tackled this issue by applying multiple hierarchical regression analyses with separate entries of TAS-20 and AQ scores including changed orders to control for an effect of order of entry in concordance with previous approaches (Cook et al., 2013; Shah, Hall, Catmur, & Bird, 2016; Trevisan et al., 2016).

Conclusion

Our study demonstrates that alexithymic and autistic traits are associated with an increased risk of depressive and social phobic symptoms, but that the extent of these associations varies based on the diagnostic group. In the ASD group, only alexithymia but not autistic traits predicted levels of depression, while conversely autism severity explained variance in social phobia. Consequently, the assessment of alexithymia during the diagnostic procedure for autism seems well-warranted, as it

may facilitate identifying and reducing the risk for a subsequent depressive disorder including suicidality. In this regard, we support the statement by Trevisan and colleagues (2016) that alexithymia is an important, but too often ignored trait associated with ASD. Future research should aim for an investigation of the behavioral and neural mechanisms of social interaction difficulties associated with autistic and alexithymic traits as this might help to further refine current treatment approaches.

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Supplementary material

Table S1

Common psychiatric comorbidities in both patient groups

Comorbidities*	ASD	non-ASD
Depression	70 (57.4)	29 (46.8)
Social Phobia	33 (27.0)	16 (25.8)
AD(H)D	12 (9.8)	6 (9.7)
Obsessive compulsive disorder (OCD)	5 (4.1)	5 (8.1)
No comorbidities	34 (27.9)	17 (27.4)

Note. *According to ICD-10 criteria in N (%); N (%) are not cumulating to 100 % due to multi-comorbidity.
ASD: patients with autism spectrum disorder; non-ASD: patients with social interaction difficulties, but no diagnosis of ASD.

Table S2

Correlations among variables of interest

			Age	Sex	AQ	BDI-II	LSAS	TAS-20
ASD	AQ	*r*	.32	.24	1	.28	.54	.61
		p-value	<.001***	.008**		.002**	<.001***	<.001***
		95 % CI	[0.15, 0.48]	[0.08, 0.39]	[1, 1]	[0.11, 0.42]	[0.43, 0.65]	[0.49, 0.72]
	TAS-20	*r*	.22	.11	.61	.39	.40	1
		p-value	.016	.217	<.001***	<.001***	<.001***	
		95 % CI	[0.05, 0.39]	[-0.06, 0.27]	[0.49, 0.72]	[0.24, 0.54]	[0.25, 0.54]	[1, 1]
non-ASD	AQ	*r*	-.08	.21	1	.14	.48	.46
		p-value	.518	.101		.284	<.001***	<.001***
		95 % CI	[-0.36, 0.16]	[-0.05,-0.46]	[1, 1]	[-0.17, 0.41]	[0.31, 0.63]	[0.25, 0.62]
	TAS-20	*r*	.03	.08	.46	.20	.57	1
		p-value	.813	.550	<.001***	.117	<.001***	
		95 % CI	[-0.22, 0.27]	[-0.17, 0.29]	[0.25, 0.62]	[-0.09, 0.46]	[0.39, 0.71]	[1, 1]
NT	AQ	*r*	.05	-.17	1	.36	.36	.39
		p-value	.423	.006		<.001***	<.001***	<.001***
		95 % CI	[-0.07, 0.16]	[-0.29, -0.5]	[1, 1]	[0.23, 0.46]	[0.26, 0.47]	[0.29, 0.49]
	TAS-20	*r*	-.12	-.05	.39	.38	.40	1
		p-value	.061	.394	<.001***	<.001***	<.001***	
		95 % CI	[-0.24, 0.01]	[-0.17, 0.07]	[0.29, 0.49]	[0.26, 0.46]	[0.28, 0.50]	[1, 1]

ASD: patients with autism spectrum disorder; non-ASD: patients with social interaction difficulties, but no diagnosis of ASD; NT: typically developing group; AQ: Autism Quotient (scale: 0-50) measuring autistic traits; TAS-20: Toronto Alexithymia Scale-20 (scale: 20-100) measuring alexithymic traits.

Note. Results are based on 1,000 bootstrap samples.

*$p < .05$. **$p < .01$. ***$p < .001$.

Table S3a

Predictors of depressive symptoms

Group	Model	Predictor	*b*	Bias	Std. Error	*p*	BCa 95% CI	
							Lower	Upper
ASD	1	Age	.158	0.000	0.101	.124	-0.037	0.360
		Sex	2.364	-0.019	2.267	.295	-1.903	6.783
	2	Age	.072	-0.003	0.097	.471	-0.125	0.259
		Sex	1.540	0.014	2.132	.474	-2.672	5.837
		TAS-20	.397	-0.001	0.096	.001**	0.203	0.591
	3	Age	.066	-0.003	0.100	.514	-0.140	0.261
		Sex	1.441	0.030	2.113	.501	-2.652	5.695
		TAS-20	.382	-0.001	0.113	.003**	0.163	0.611
		AQ	.036	-0.002	0.144	.807	-0.245	0.310
non-ASD	1	Age	-.037	-0.001	0.105	.715	-0.231	0.179
		Sex	-.064	-0.003	2.891	.982	-5.748	5.543
	2	Age	-.044	0.001	0.099	.654	-0.226	0.156
		Sex	-.427	0.143	2.813	.869	-6.018	4.871
		TAS-20	.201	0.006	0.145	.193	-0.069	0.484
	3	Age	-.040	-0.006	0.102	.702	-0.240	0.164
		Sex	-.637	0.274	2.947	.827	-6.341	5.340
		TAS-20	.175	0.009	0.159	.288	-0.110	0.503
		AQ	.067	-0.023	0.191	.719	-0.367	0.386
NT	1	Age	-.018	-0.001	0.036	.591	-0.090	0.054
		Sex	1.169	0.007	0.649	.073	-0.036	2.466
	2	Age	.012	-0.001	0.032	.684	-0.057	0.071
		Sex	1.411	-0.005	0.603	.026*	0.155	2.555
		TAS-20	.201	0.001	0.041	.001**	0.130	0.287
	3	Age	-.005	-0.001	0.030	.881	-0.067	0.051
		Sex	1.843	-0.013	0.652	.008**	0.494	3.078
		TAS-20	.139	0.001	0.038	.001**	0.072	0.216
		AQ	.271	-0.002	0.076	.001**	0.131	0.425

ASD: patients with autism spectrum disorder; non-ASD: patients with social interaction difficulties, but no diagnosis of ASD; NT: typically developing group; AQ: Autism Quotient (scale: 0-50) measuring autistic traits; TAS-20: Toronto Alexithymia Scale-20 (scale: 20-100) measuring alexithymic traits.

Note. Results are based on 1,000 bootstrap samples. *$p < .05$. **$p < .01$.

Table S3b

Predictors of depressive symptoms – changed entry order

Group	Model	Predictor	*b*	Bias	Std. Error	*p*	BCa 95% CI	
							Lower	Upper
ASD	1	Age	.158	0.002	0.105	.134	-0.049	0.365
		Sex	2.364	-0.028	2.305	.314	-2.540	6.831
	2	Age	.078	0.002	0.105	.456	-0.119	0.287
		Sex	1.131	-0.038	2.182	.590	-3.281	5.397
		AQ	.344	0.001	0.129	.012*	0.087	0.593
	3	Age	.066	0.001	0.101	.517	-0.129	0.266
		Sex	1.441	-0.016	2.075	.495	-2.795	5.715
		AQ	.036	0.008	0.147	.810	-0.236	0.336
		TAS-20	.382	-0.008	0.118	.001**	0.144	0.617
non-ASD	1	Age	-.037	0.000	0.102	.731	-0.245	0.163
		Sex	-.064	-0.109	2.872	.975	-5.852	5.579
	2	Age	-.030	-0.006	0.103	.771	-0.240	0.169
		Sex	-.676	0.071	2.969	.828	-6.450	5.214
		AQ	.159	-0.022	0.174	.357	-0.244	0.436
	3	Age	-.040	-0.005	0.099	.688	-0.240	0.149
		Sex	-.637	0.220	2.933	.829	-6.051	5.341
		AQ	.067	-0.023	0.195	.720	-0.365	0.410
		TAS-20	.175	-0.001	0.159	.272	-0.130	0.524
NT	1	Age	-.018	-0.002	0.036	.602	-0.090	0.049
		Sex	1.169	0.024	0.662	.071	-0.059	2.544
	2	Age	-.028	-0.001	0.031	.379	-0.089	0.028
		Sex	1.856	0.015	0.682	.005**	0.528	3.227
		AQ	.368	-0.002	0.078	.001**	0.225	0.525
	3	Age	-.005	-0.001	0.030	.864	-0.064	0.054
		Sex	1.843	0.018	0.672	.003**	0.513	3.193
		AQ	.271	-0.003	0.076	.001**	0.130	0.424
		TAS-20	.139	0.001	0.038	.001**	0.067	0.217

ASD: patients with autism spectrum disorder; non-ASD: patients with social interaction difficulties, but no diagnosis of ASD; NT: typically developing group; AQ: Autism Quotient (scale: 0-50) measuring autistic traits; TAS-20: Toronto Alexithymia Scale-20 (scale: 20-100) measuring alexithymic traits.

Note. Results are based on 1,000 bootstrap samples. *$p < .05$. **$p < .01$.

Table S4a

Predictors of social phobic symptoms

Group	Model	Predictor	*b*	Bias	Std. Error	*p*	BCa 95% CI	
							Lower	Upper
ASD	1	Age	.494	0.001	0.197	.015*	0.105	0.877
		Sex	13.202	-0.007	4.481	.003**	4.616	22.337
	2	Age	.305	-0.004	0.194	.127	-0.085	0.670
		Sex	11.396	0.028	4.334	.011*	3.357	20.007
		TAS-20	.869	0.000	0.185	.001**	0.492	1.245
	3	Age	.107	-0.005	0.188	.553	-0.290	0.455
		Sex	7.595	0.056	4.059	.073	-0.365	15.625
		TAS-20	.298	9.305E-05	0.243	.227	-0.179	0.782
		AQ	1.392	-0.006	0.313	.001**	0.805	2.017
non-ASD	1	Age	-.218	0.001	0.281	.433	-0.753	0.323
		Sex	16.603	-0.273	7.425	.032*	1.039	30.885
	2	Age	-.272	0.001	0.245	.256	-0.749	0.223
		Sex	13.895	-0.297	6.201	.028*	1.192	24.933
		TAS-20	1.499	-0.006	0.232	.001**	1.049	1.994
	3	Age	-.235	0.004	0.233	.311	-0.702	0.237
		Sex	11.767	-0.341	6.286	.065	-1.331	23.070
		TAS-20	1.235	0.004	0.262	.001**	0.714	1.780
		AQ	.678	0.001	0.301	.030*	0.080	1.255
NT	1	Age	.099	-0.002	0.150	.516	-0.201	0.392
		Sex	5.702	0.073	2.193	.015*	1.551	9.859
	2	Age	.218	0.001	0.137	.108	-0.056	0.490
		Sex	6.653	-0.006	1.983	.001**	2.796	10.403
		TAS-20	.791	0.002	0.119	.001**	0.559	1.046
	3	Age	.163	3.704E-05	0.131	.208	-0.086	0.420
		Sex	8.094	0.041	1.955	.001**	4.170	11.941
		TAS-20	.586	0.001	0.122	.001**	0.354	0.832
		AQ	.903	0.005	0.204	.001**	0.509	1.304

ASD: patients with autism spectrum disorder; non-ASD: patients with social interaction difficulties, but no diagnosis of ASD; NT: typically developing group; AQ: Autism Quotient (scale: 0-50) measuring autistic traits; TAS-20: Toronto Alexithymia Scale-20 (scale: 20-100) measuring alexithymic traits.

Note. Results are based on 1,000 bootstrap samples. *$p < .05$. **$p < .01$.

Table S4b

Predictors of social phobic symptoms - changed entry order

Group	Model	Predictor	*b*	Bias	Std. Error	*p*	BCa 95% CI	
							Lower	Upper
ASD	1	Age	0.494	-0.006	0.184	.013*	0.112	0.856
		Sex	13.202	0.079	4.572	.005**	4.204	21.758
	2	Age	0.116	-0.005	0.178	.506	-0.264	0.442
		Sex	7.353	0.157	4.157	.081	-0.878	15.291
		AQ	1.632	0.006	0.228	.001**	1.211	2.105
	3	Age	0.107	-0.006	0.182	.544	-0.277	0.450
		Sex	7.595	0.149	4.235	.068	-0.937	15.417
		AQ	1.392	0.002	0.306	.001**	0.791	1.984
		TAS-20	0.298	0.002	0.232	.207	-0.164	0.780
non-ASD	1	Age	-0.218	-0.003	0.291	.446	-0.780	0.370
		Sex	16.603	0.104	7.411	.031*	2.724	31.811
	2	Age	-0.163	-0.003	0.252	.526	-0.662	0.345
		Sex	11.495	-0.054	6.880	.094	-1.928	25.665
		AQ	1.330	0.026	0.300	.001**	0.807	1.991
	3	Age	-0.235	-0.003	0.234	.319	-0.677	0.252
		Sex	11.767	-0.201	6.409	.081	-0.873	24.801
		AQ	0.678	0.017	0.301	.032*	0.151	1.331
		TAS-20	1.235	-0.009	0.262	.001**	0.676	1.718
NT	1	Age	0.099	-0.004	0.152	.529	-0.197	0.381
		Sex	5.702	0.033	2.216	.009**	1.382	10.225
	2	Age	0.064	-0.001	0.140	.661	-0.211	0.346
		Sex	8.150	-0.013	2.141	.001**	3.648	12.180
		AQ	1.309	0.000	0.203	.001**	0.926	1.745
	3	Age	0.163	0.000	0.136	.240	-0.094	0.427
		Sex	8.094	-0.037	2.020	.001**	4.116	11.837
		AQ	0.903	-0.002	0.198	.001**	0.515	1.319
		TAS-20	0.586	-0.001	0.115	.001**	0.374	0.819

ASD: patients with autism spectrum disorder; non-ASD: patients with social interaction difficulties, but no diagnosis of ASD; NT: typically developing group; AQ: Autism Quotient (scale: 0-50) measuring autistic traits; TAS-20: Toronto Alexithymia Scale-20 (scale: 20-100) measuring alexithymic traits.

Note. Results are based on 1,000 bootstrap samples. *$p < .05$. **$p < .01$.

4. Discussion

In this thesis, I investigated potential causes of stress vulnerability in adults with HFA, focusing on peripheral OXT and alexithymia as potential factors to increase stress and thus, mental comorbidities.

In the first study (see Section 2.3), I examined the responsiveness of the OXT system in autistic adults during a physiological stress task under consideration of methodological aspects and common characteristics of adults with ASD in comparison to neurotypical peers. The main aim of the study was to examine whether OXT release would be impaired under stress between participants with and without ASD which would be in favour of the hypothesis that OXT dysregulation contributes to stress vulnerability in autism. Neither salivary nor plasma OXT concentrations significantly differed between groups at baseline. After physical exercise, increased plasma OXT concentrations were observed in patients with ASD compared to neurotypicals, but only when a physiological stress reaction as measured by CORT was absent in patients. When age was added to the statistical model, the group effect did not remain significant. In contrast to plasma OXT, saliva OXT remained unchanged both in neurotypicals and in patients with ASD. Correlations between changes of peripheral OXT and CORT concentrations were positive in neurotypicals, while they were negative in autistic individuals indicating a potential dysregulation of the interaction between the OXT and stress system in ASD. In the following chapter, the most relevant aspects of the assessment of peripheral OXT concentrations and its relevance for ASD will be discussed (see Section 4.1).

In the second study (see Section 3.3), I investigated the contribution of autistic as well as alexithymic traits as potential risk factors for depression and social phobia. Data of patients with ASD, patients with disorders of social interaction other than ASD, and healthy individuals were analysed. The aim of the study was to reveal which traits would predict depression and social phobia depending on the underlying core condition. Analyses of the three study groups demonstrated that both traits explained considerable variance of depressive and social phobic symptoms. In adults with ASD, alexithymic traits were predictive of depressive symptoms, while autistic traits predicted social phobic traits. In patients with social interaction difficulties other than autism, alexithymic and

autistic traits were identified as predictors for social phobic symptoms, while no variable predicted depressive symptoms. In neurotypicals, both alexithymic and autistic traits were predictive of depressive and social phobic symptoms. In the following chapter, emotion regulation in context of mental illness, alexithymia, and autism will be discussed (see Section 4.2).

4.1. Peripheral OXT: an indicator for ASD?

In line with previous studies (see Table 2) no significant group related differences were found between autistic and neurotypical individuals at baseline in the thesis study. Thus, the hypothesis of an OXT deficiency in ASD was not confirmed by comparing basal OXT concentrations between neurotypical controls and patients with ASD. However, the reliability of basal OXT concentrations as indicator of central OXT processes remains to be proven (Valstad et al., 2017). Positive correlations between peripheral and central OXT concentrations have only been found after stimulation (Landgraf & Neumann, 2004; Neumann & Landgraf, 2012; Valstad et al., 2017). An important aspect most studies in ASD have not considered so far (see Tables 2 and 3). In this regard, the thesis study has extended previous research of OXT in ASD in adulthood by implementing a stimulus in form of rapid cycling in the experimental set-up. By measuring pre- and post-exercise OXT levels in both study groups, the responsiveness of the OXT system was compared between autistic and neurotypical participants. With this approach, it was more likely to reveal a central dysregulation of the OXT system than by using baseline concentrations only.

In fact, plasma OXT concentrations of autistic patients were significantly higher after the physical challenge relative to those measured in neurotypical controls. The only other study so far, which has assessed peripheral OXT levels in autistic adults and included a stimulus in form of a public speaking task, was done by Jansen et al. (2006) (see Table 3). The authors also observed higher plasma OXT concentrations in autistic adults compared to healthy controls. However, OXT concentrations were already higher at baseline in their study and did not show any change in response to the stress induction (Jansen et al., 2006).

Aside from group-related differences of plasma OXT levels post-exercise, divergent correlations between the temporal dynamics of peripheral OXT and CORT were found between the groups in the thesis study. While *positive* correlations between peripheral OXT and CORT concentrations were observed in neurotypicals, *negative* correlations were found in autistic individuals. These counter-correlations between peripheral OXT and CORT levels further support the hypothesis of an OXT dysregulation in ASD. While the positive correlations found in the control group are in line with results from other studies (Bernhard et al., 2018; Engert et al., 2016; Jong et al., 2015), no prior findings have been reported in autistic adults as Jansen et al. (2006) did not test for correlations between peripheral OXT and CORT levels.

Aside from autism, a dysfunction of the OXT system has been suggested for multiple psychiatric disorders e.g. depression, social phobia, schizophrenia, personality disorders, and others (Cochran, Fallon, Hill, & Frazier, 2013). Similar to ASD, equivocal results have been found in studies investigating peripheral OXT concentrations in various psychiatric conditions (Cochran, Fallon, Hill, & Frazier, 2013; Erdozain & Peñagarikano, 2020). Thus, it is unlikely that a dysregulation of the OXT system – if at all – is only involved in the pathomechanism of ASD. Since most psychiatric disorders (see Section 1.3) entail difficulties in social interaction and communication, impairments in social functioning are distinct but not exclusive features of ASD (Schilbach, 2016). In this regard, it seems more reasonable to investigate OXT differences not in disorder related categories (e.g. ASD, depression, social phobia etc.) but – as suggested by the Research Criteria Domain Initiative (RDoC) of the National Institute of Mental Health (Insel et al., 2010) – in a dimensional approach. This concept is further supported by the fact that at least 50 % of adults with HFA suffer from concomitant psychiatric conditions (Albantakis et al., 2018; Lai & Baron-Cohen, 2015; Lehnhardt et al., 2013). Thus, the comorbid psychopathology frequently seen in ASD can be understood as an important aspect pertaining to ASD and should, therefore, be included in the dimensional construct of ASD in adulthood (Insel et al., 2010). Future studies should, therefore, aim to investigate OXT

dysregulations in a dimensional approach including various disorders of social interaction which share phenotype features such as social-communicative deficits.

4.1.1 Peripheral OXT under basal conditions

In the thesis study, neither salivary nor plasma OXT concentrations significantly differed between neurotypical and autistic participants at baseline. This was in line with results of several previous studies including children and adolescents with ASD (Miller et al., 2013; Parker et al., 2014; Taurines et al., 2014) but contrary to results involving autistic adults (see Table 2) (Andari et al., 2010; Jansen et al., 2006). While Andari et al. (2010) found significantly lower OXT concentrations in 13 adults with ASD compared to neurotypical controls, Jansen et al. (2006) observed increased levels of peripheral OXT in 10 autistic individuals. Compared to both previous studies focusing on basal OXT levels of patients with ASD in adulthood, the thesis study provided greater power given its bigger sample size (33 autistic and 31 neurotypical study participants).

However, the equivocal study results from the three studies including autistic adults confirm conflicting findings of basal OXT levels in autistic children and adolescents (see Table 2). Although a comparison between studies is limited due to the heterogeneity of study designs including methodological and biological aspects which are discussed later in more detail (see Sections 4.1.5 - 4.1.6.4), measuring OXT concentrations under baseline conditions does not seem to be a reliable indicator of ASD. Furthermore, significant associations between central and peripheral OXT levels may only be present in response to physiological or stressful stimuli but not under baseline conditions (Valstad et al., 2017). Thus, an assessment of peripheral OXT concentrations solely at baseline should be avoided in future studies.

Table 2: Overview of studies investigating peripheral OXT concentrations in ASD under baseline conditions

First author	Andari	Husarova	Modahl	Jacobson	Jansen	Taurines	Miller	Parker
Publication year	2010	2016	1998	2014	2006	2014	2013	2014
Characterization of participants								
Total sample size (*N*)	26	63	59	78	24	55	75	193
Cases with ASD (*n*)	13	19	29	37	10	19	40	79
IQ ≥ 70 (yes/no/unclear)	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Not all
Males (*n*)	11	19	29	25	9	19	21	62
Mean age in years ± SD of cases with ASD; Controls	26.0; 26.0	4.7 ± 2.1; 4.9 ± 1.9	8.1 ± 1.7; 8.8 ± 1.8	4.8 ± 0.7[1]; 4.9 ± 0.6[1]	21.8 ± 2.0; 21.0 ± 3.4	10.7 ± 3.8; 13.6 ± 2.1	12.0 ± 3.5; 12.3 ± 2.8	8.4 ± 0.4; 7.1 ± 0.4
ASD cases with psychiatric comorbidities (*n*)	Unclear	No	Unclear	Unclear	1[2]	17[3]	No	No
ASD cases on psychiatric medication (*n*)	-	-	10	-	1[4]	13[5]	12	-
Methods								
OXT analysis method	EIA	EIA	RIA	EIA	RIA	RIA	EIA	EIA
Extraction prior to analysis	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes
OXT compared to controls	↓	↓	↓	↑ (males)	↑	=	=	=
Baseline OXT concentrations (pg/ml) ± SD in ASD cases	1.1 ± 1.0	124.1 ±90.6	0.6 ± 0.6	24.2 (males)	9 ± 1.5*	19.6 ± 7.1	Girls: 525.2 ± 325.8 Boys: 357.1 ± 184.1	3.8 ± 1.5*
OXT biomaterial	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma
Time of sample collection	8.30 am	8.00 - 9.00 am	12.00 - 2.00 pm	10.00 - 12.00 am	09.40 am - 2.00 pm	7.30 - 10.00 am	9.45 am - 5.00 pm	10.00 am - 2.00 pm

OXT: Oxytocin; ASD: Autism spectrum disorder; SD: Standard deviation; [1]only males; [2]diagnosis of dysthymia; [3]68 % of ASD cases had a comorbid ADHD diagnosis and 3 cases had a mood or anxiety disorder; [4]antidepressant; [5]psychostimulants, antidepressants and antipsychotics. ↑: increased; ↓: decreased; =: no difference; *Values were extracted from a figure and do not represent exact values.

4.1.2 Peripheral OXT after stimulation

In the thesis study, physical exercise in form of rapid cycling (ergometry) was chosen as OXT inducing stimulus. The motivation for this approach was to implement an unbiased stimulus for neurotypicals and autistic patients in order to focus on the neurobiological OXT responses between these two groups, and ideally to reveal stress-related differences. Successful OXT stimulation has previously been reported in response to running (Hew-Butler et al., 2008; De Jong et al., 2015) and rapid cycling (Gebert et al., 2018). Other studies used social tasks (e.g. Trier Social Stress Task [TSST]) to stimulate the OXT system (Bernhard et al., 2018; De Jong et al., 2015; Engert et al., 2016) (see Table 3). However, these tasks were mostly tested in neurotypicals (Allen et al., 2017), and those who included autistic patients either failed to induce a stress (Levine et al., 2012) or OXT response (Jansen et al., 2006). Therefore, to increase the chances of a successful OXT stimulation in autistic individuals, a physical exercise was applied in the thesis study, based on former study designs.

In the thesis study, heart rate, lactate levels and CORT concentrations increased in autistic patients and neurotypicals during the physical exercise, reflecting the physiological stress response. There was no difference in the performance of the physical exercise between autistic participants and neurotypical controls (see Section 2.3). However, time did not have a significant effect on OXT concentrations pre- to post-exercise neither in neurotypicals nor in autistic patients.

Taking a closer look at previous studies (summarized in Table 3), Hew-Butler et al. (2008) only observed statistically significant pre- to post-run increases of plasma OXT levels in well trained participants following an ultramarathon of 56 km considered as “prolonged endurance exercise”. No changes of peripheral OXT were observed after 60-min treadmill run or a high intensity work-out. In contrast, de Jong et al. (2015) reported significant increases of salivary OXT concentrations after 10 minutes of “moderate running”, which was not further specified in the study. Clearly, the intensities of the physical exercise applied in both studies strongly diverge. However, it could be possible that the physiological processes activated by the prolonged endurance exercise in well-trained athletes (Hew-Butler et al., 2008) are similar to those induced by the moderate running exercise in untrained

individuals (De Jong et al., 2015). Thus, the OXT response might depend on the intensity of the experimental challenge and the bodily fitness of the participants. In a study by Gebert et al. (2018) the experimental set-up was similar to the one presented in the thesis study. Healthy controls showed a significant increase of salivary OXT concentrations after rapid cycling. Healthy controls and patients with craniopharyngeoma performed equally well regarding duration of exercise and physical stress measured by wattage and lactate levels. No group related differences of salivary OXT concentrations were found at baseline or after the physical exercise (Gebert et al., 2018).

Consequently, various previous studies reported a peripheral OXT increase in response to running and rapid cycling in participants with varying bodily fitness levels. However, results indicate that a successful OXT induction depends on the kind of experimental challenge and the individual training state. As an example, a prolonged endurance exercise was more successful than a high-intensity work in well-trained athletes (Hew-Butler et al., 2008). These findings may lead to conclude that a secondary stress marker (e.g. CORT) is necessary to evaluate the physiological stress level.

Table 3: Overview of studies investigating peripheral OXT concentrations in response to stimuli

First author	**De Jong**	**Gebert**	**Hew-Butler**	**Bernhard**	**De Jong**	**Engert**	**Jansen**
Publication year	2015	2018	2008	2018	2015	2016	2006
Characterization of participants							
Total sample size (*N*)	17	52	7	57	30	114	24
Cases with any illness or psychiatric disorder (*n*)	No	Yes, CP (26)	No	No	No	No	Yes, ASD (10)
Males (*n*)	10	26	5	27	15	49	9
Mean age in years ± SD	Males: 29.1 Females: 32.2	Patients: 39.7 ± 12.1 Controls: 36.7 ± 12.8	44 ± 4	TSST: 14.8 ± 2.1 Controls: 15.4 ± 1.9	Males: 24.8 Females: 22.5	40.18 ± 8.7	21.8
Cases with psychiatric comorbidities (*n*)	No	Not stated	No	No	No	No	Yes (1)
Cases on psychiatric medication (*n*)	No	No	No	No	No	No	Yes (1)
Cases using oral contraceptives (*n*)	Not stated	No	No	Yes (7)	Yes (11)	Yes (14)	Not stated
Methods							
Stimulus	Moderate running	Rapid cycling	Running	TSST	TSST	TSST	TSST
OXT analysis method	RIA	RIA	RIA	RIA	RIA	RIA	RIA
Extraction prior to analysis	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dynamic change of OXT	↑	↑ (controls)	↑	↑	↑	↑	=
Assessment of CORT	No	No	Yes	Yes	Yes	Yes	Yes
CORT biomaterial	-	-	Plasma	Saliva	Saliva	Saliva	Plasma
OXT biomaterial	Saliva	Saliva	Plasma	Saliva	Saliva	Plasma	Plasma
Time of sample collection	6 pm - 12 am	8.30 - 10 am	morning	3 - 4 pm	1 - 3.30 pm	12 - 6 pm	9.40 am - 4 pm

CP: Craniopharyngeoma; ASD: Autism spectrum disorder; SD: Standard deviation; TSST: Trier Social Stress Task; OXT: Oxytocin; CORT: Cortisol; RIA: Radioimmunoassay. ↑: increased; =: no difference.

4.1.3 OXT and CORT interaction

Since CORT is a well-established marker to measure physiological stress in human beings (Kozlov & Kozlova, 2014), CORT levels were assessed at the same time points as OXT in the thesis study (see Section 2.3). Furthermore, previous findings in healthy participants support the idea that CORT increase is required to stimulate OXT (Bernhard et al., 2018; Brown, Cardoso, & Ellenbogen, 2016; De Jong et al., 2015; Engert et al., 2016). Thus, this aspect has been considered in the thesis study. To ensure that the chosen physical exercise successfully induced stress, a cut-off of ≥ 15.5 % CORT baseline-to-peak increase was defined (Miller, Plessow, Kirschbaum, & Stalder, 2013), which has been used as stress indicator in an OXT related study before (Bernhard et al., 2018). Accordingly, participants with a CORT post-stress-to-baseline quotient of at least 1.155 were defined as CORT responders, while others below this quotient were defined as CORT non-responders to the physical challenge.

Irrespective of group affiliation and CORT response, no dynamic changes of OXT concentrations were found in saliva samples in response to the physical exercise. Increased plasma OXT levels were observed in adults with ASD, however, only in the subsample of *CORT non responders* after the challenge. In this regard, it seems as if stimulation below the CORT cut-off for a physiological stress response may be beneficial to reveal group-related differences between autistic individuals and neurotypical peers. Furthermore, associations between dynamic changes of peripheral CORT and OXT showed opposing directions indicating a dysregulation of the CORT and OXT systems in ASD (see Section 4.1).

Positive correlations between endogenous OXT and CORT have been described in various studies with healthy participants (Bernhard et al., 2018; De Jong et al., 2015; Engert et al., 2016). These findings were further supported by results from a recent meta-analysis including various experimental stimuli e.g. TSST, pharmacological challenge, and physical exercise (Brown et al., 2016). Given the dampening effect of exogenous OXT on peripheral CORT levels (Cardoso, Ellenbogen, Orlando, Bacon, & Joober, 2013; Ditzen et al., 2009; Heinrichs, Baumgartner, Kirschbaum, & Ehlert,

2003; Quirin, Kuhl, & Düsing Rainer, 2011), the positive correlations found between endogenous OXT and CORT concentrations seem counter-intuitive. However, the observations of multiple studies investigating effects of exogenous and endogenous OXT on peripheral CORT might be time-dependent, and associations between these hormones might consequently differ from each other (Engert et al., 2016). In order to attenuate the provoked stress reaction, endogenous OXT has to be secreted first to exert its dampening effect (Engert et al., 2016).

The hypothesis of a time-dependent release is supported by results from the thesis study. In neurotypicals, positive correlations between peripheral OXT and CORT concentrations were observed at similar time points of sample collection, indicating that dynamic changes took place simultaneously or with a minor delay of time. These observations are in line with findings from de Jong et al. (2015) who proposed that OXT and CORT were co-released in response to a stimulus given a similar pattern of peripheral OXT and CORT increase during the TSST.

Taken together, the evidence available suggests that CORT should be assessed in OXT studies since both hormones seem to interact with each other in a time-dependent manner.

4.1.4 OXT and alexithymia

Alexithymic traits were found to explain variance of plasma OXT concentrations in autistic adults in the thesis study (see Section 2.3), indicating the involvement of alexithymia in the OXT system. This assumption is supported by findings from Baskaran et al. (2017) who found an inverse correlation between OXT pulse height and pulse mass, and alexithymic traits in healthy men. Participants with lower OXT pulse height and pulse mass reported to have greater difficulty in describing their feelings, presented a more avoidant style of attachment, and felt less supported by others (Baskaran et al., 2017).

Furthermore, comparing the effect of exogenous OXT on social cognition between people with high and low alexithymic traits, Luminet et al. (2011) demonstrated that participants with higher alexithymic traits performed better under OXT treatment, while those with low alexithymic traits had no observable benefit from OXT. The authors concluded that the effects of OXT are not

only context- but also personality-related (Luminet, Grynberg, Ruzette, & Mikolajczak, 2011; Olff et al., 2013). Unfortunately, this aspect has been largely ignored in OXT research. Consequently, over the last 20 years, numerous OXT studies have been produced with conflicting results, toning down the original enthusiasm for OXT as potential treatment for psychiatric disorders (Erdozain & Peñagarikano, 2020). Similar to the equivocal results found in emotion recognition studies in ASD (see Section 1.7), the inconsistent findings in the OXT studies might be due to varying levels of alexithymia in study participants.

Despite the limited number of existing studies considering alexithymia as relevant factor in OXT related processes, preliminary results support the importance of integrating alexithymia in future OXT studies.

4.1.5 Methodological aspects

In the thesis study, no correlations were found between saliva and plasma OXT concentrations (see Section 3.3). Peripheral OXT concentrations were assessed using radioimmunoassay (RIA) with an extraction process prior to analysis. This method was applied for both saliva and plasma samples.

RIA has been the method of choice for analyzing OXT (McCullough, Churchland, & Mendez, 2013), especially in studies relating peripheral OXT to peripheral CORT levels (Brown, Cardoso, & Ellenbogen, 2016). Alternative methods for OXT analysis are enzyme immunoassay (EIA) and more recently, liquid chromatography with mass-spectrometry (LC-MS) has been tested (McCullough et al., 2013; Zhang, Zhang, Fast, Lin, & Steenwyk, 2011). In this context, the extraction process prior to sample analysis seems to be a critical step for quantification accuracy, especially when using EIA or RIA. The extraction procedure aims to remove all molecules in the sample, which may interfere with the assay itself and lead to false OXT quantification (Christensen, Shiyanov, Estepp, & Schlager, 2014; McCullough et al., 2013). Skipping the extraction process can lead to OXT values 100-fold higher than measures where extraction has been applied (McCullough et al., 2013). Christensen et al. (2014) evaluated the coefficients of variance and the recovery values of unextracted samples as critical and

unreliable. The authors, therefore, strongly recommended an extraction procedure for both EIA and RIA prior to analysis (Christensen et al., 2014). Since these methodological aspects are important and have great impact on OXT concentrations, a comparison between study results is only useful when the same methods have been applied.

Contradicting the results from the thesis study are findings of positive correlations between saliva and plasma OXT levels, where unextracted (Feldman et al., 2010) and extracted samples were analyzed with EIA (Grewen et al., 2010). Although Martin et al. (2018) also found positive correlations between saliva and plasma OXT concentrations using RIA and an extraction process, samples derived from critically ill patients with neurological and neurosurgical illnesses. Thus, the validity of these finding should be treated with caution. These results highlight, however, that methodological aspects need to be considered when assessing peripheral OXT concentrations.

4.1.6 Biological confounding factors

Several factors such as age, sex, medication, hormonal status, and others have been suggested as confounding factors of peripheral OXT concentrations. In the following paragraphs the most relevant biological factors and their potential relevance to the findings of this thesis will be discussed.

4.1.6.1 Age

Age did not have an effect on peripheral OXT concentrations in the thesis study. This was in line with other studies including children (Taurines et al., 2014) and adults with ASD (Andari et al., 2010). But it was contrary to findings from Modahl et al. (1998) who observed age-related differences in their sample with autistic children.

Only a limited number of studies have investigated age-related differences in the OXT system. Those who considered age as potential confounding factor primarily focused on non-human species with limited applicability to humans (Ebner, Maura, MacDonald, Westberg, & Fischer, 2013). Interestingly, age-related differences were mostly observed in studies using central OXT concentrations (Fliers & Swaab, 1983; Melis et al., 1992; Arsenijevic et al., 1995; Parker et al., 2010),

while comparable levels through different ages were observed analysing peripheral levels (Fliers & Swaab, 1983; Zbuzek et al., 1988; Melis et al., 1992). Thus, it was suggested that aging might modulate central OXT processes but does not affect the peripheral system (Melis et al., 1999; Ebner et al., 2013). Therefore, the effect of age on peripheral OXT concentrations needs to be further evaluated.

4.1.6.2 Sex

In the thesis study, sex-related differences of peripheral OXT were found neither at baseline nor under experimental conditions in any group. This is in line with former studies reporting no differences of peripheral OXT levels between healthy male and female participants at baseline (e.g. Engert et al., 2016; Graugaard-Jensen, Hvistendahl, Frøkiaer, Bie, & Djurhuus, 2014; De Jong et al., 2015; Marazziti et al., 2012) but in contrast to other findings showing increased plasma levels in healthy men (Floyd, Pauley, & Hesse, 2010) or women (Marazziti et al., 2019).

Under experimental conditions, equivocal results have been found with higher (Pierrehumbert et al., 2010) and lower levels of peripheral OXT in healthy women (Floyd et al., 2010) and no differences between the sexes (Engert et al., 2016; De Jong et al., 2015). In context of experimental set-ups including OXT stimulation, no sex-related effects on the interaction of peripheral OXT and CORT concentrations have been identified (Brown et al., 2016). A meta-analysis of sex-related differences of peripheral OXT concentrations with focus on ASD would be very limited because most studies have only included male participants (see Tables 2 and 3). This decision has been justified by most authors referring to former male-to-female ratios of five boys to one girl in ASD or higher (Baxter et al., 2015). These prevalence rates are not considered as representative numbers nowadays with recent estimates suggesting a sex ratio of two or three males to one female (Constantino, Zhang, Frazier, Abbacchi, & Law, 2010; Kim et al., 2011; Zwaigenbaum, Bryson, & Garon, 2013). Given the lack of ASD research in female participants, future OXT studies should further include a representative number of females.

4.1.6.3 Sexual hormones

To control for potential confounding effects, the intake of hormonal contraceptive was an exclusion criterion in the thesis study. Gonadal steroids especially estrogen have been suggested to modulate the OXT system (Jurek & Neumann, 2018; Lim & Young, 2006; Patisaul, Scordalakes, Young, & Rissman, 2003). In humans, the intake of oral contraceptives including estrogen has resulted in equivocal effects on peripheral OXT concentrations. While some studies have reported increased levels of peripheral OXT in participants using oral contraceptives with estrogen (Engert et al., 2016; Stock, Silber, & Uvnas-moberg, 1989), others have found decreased peripheral OXT concentrations (De Jong et al., 2015).

Hormonal changes due to the menstrual cycle have been discussed as relevant factor for peripheral OXT levels with controversial results. While findings from a meta-analysis have suggested an increase of OXT concentrations from the early follicular phase to ovulation and a decrease from ovulation to the mid-luteal phase (Engel, Klusmann, Ditzen, Knaevelsrud, & Schumacher, 2019), another study including 65 healthy women has found no cycle dependent changes of plasma OXT levels (Engert et al., 2016). Changes related to the menstrual cycle have not been examined in the thesis study but should be addressed in future studies.

4.1.6.4 Medication

Psychiatric medication frequently prescribed in patients with ASD includes antidepressants, antipsychotics, and stimulants (Esbensen, Greenberg, Seltzer, & Aman, 2009). Intended effects of the medication are the relief of autistic symptoms or those of comorbid psychiatric conditions. In the thesis study, approximately half of the patient sample was on psychiatric medication on a regular basis (see Section 2.3). A reduction of medication and stop of intake prior to the study participation would have caused a disruption of familiar procedures in the patients' everyday lives, causing psychological stress, and potentially confounding with the experiment's measures. Therefore, patients were merely asked not to take the medication in the morning prior to the experiment but were permitted to do so afterwards.

Although psychiatric medication usually targets different neurotransmitter systems e.g. the serotonergic, dopaminergic, or noradrenergic system, existing research on potential effects of antidepressant intake on peripheral OXT concentrations did not reveal differences in OXT levels after intake of serotonin reuptake inhibitor, selective serotonin and norepinephrine reuptake inhibitors or tricyclic antidepressants (Keating et al., 2013; Ozsoy et al., 2009). Aside from antidepressant medication antipsychotic or neuroleptic medication did not alter OXT concentrations either (Glovinsky et al., 1994). A combination of drugs including psychostimulants, antidepressants and antipsychotics did not affect plasma OXT concentrations of children with ASD and ADHD (Modahl et al., 1998; Taurines et al., 2014). In this regard, psychiatric medication might not have such an important impact on the peripheral OXT concentrations overall.

4.2 Emotion dysregulation as risk factor for poor mental health

As highlighted in the stress vulnerability model for ASD (see Section 1.5), emotion regulation (ER) can have an impact on psychosocial functioning and thus the development of mental disorders. In this regard, it is of relevance to understand whether alexithymic and/or autistic traits contribute to certain maladaptive ER strategies, and whether these traits ultimately increase the risk for mental illness. Before relating ER to alexithymic (see Section 4.2.1) and autistic traits (see Section 4.2.2), common ER strategies will be discussed and set in context to mental health.

In general, ER can be summarized as a process of identifying emotions, selecting a reaction to the emotion and applying strategies to regulate the reaction to the identified emotion (Gross, 2015; Morie et al., 2019). ER strategies are divided into:

Adaptive ER strategies which are supposed to protect against psychopathology (Aldao et al., 2010):

- *cognitive reappraisal*: the re-interpretation of a situation in a positive way to reduce stress (Lazarus and Alfert, 1964)
- *problem*-solving: a conscious approach to reduce stress by changing a situation in a solution-oriented manner either mentally or in an action (Aldao et al., 2010)
- *acceptance:* taking a situation as it is without judging it or the thoughts, emotions and behavior triggered by the situation

Maladaptive ER strategies which are considered as risk factors for psychopathology (Aldao et al., 2010):

- *rumination*: repetitive focus on negative thoughts, emotions or situations
- *avoidance*
- *suppression*: the inhibition of expressing emotions (Gross & Levenson, 1993) and unwanted thoughts (Wenzlaff & Wegner, 2000)

It is assumed that most people use a combination of different ER strategies in a flexible manner when facing (social) demands (Bonanno & Burton, 2013). The flexible use of strategies is essential for adaptation, and psychological *in*flexibility has been considered as risk factor for anxiety and mood disorders (Aldao, Sheppes, & Gross, 2015; Bonanno & Burton, 2013; Kashdan & Rottenberg, 2010).

While adaptive ER has been associated with positive effects on mental well-being and psychosocial outcome measures such as relationships, educational qualification, employment, and health (John & Gross, 2004), maladaptive ER has been observed more frequently in psychiatric disorders including depression, social phobia, anxiety disorders and personality disorders (Kashdan & Breen, 2008; Lynch, Trost, Salsman, & Linehan, 2007; McLaughlin & Nolen-Hoeksema, 2011; Mennin, Holaway, Fresco, Moore, & Heimberg, 2007; O'Toole, Hougaard, & Mennin, 2013; Rottenberg, Gross, & Gotlib, 2005).

In particular, depression and anxiety disorders commonly observed in adults with ASD have been interpreted as results of emotion dysregulation (Aldao et al., 2010; Gross & Muñoz, 1995; Mennin et al., 2007). In a meta-analytic review rumination, avoidance, and suppression have been found to be positively correlated with anxiety disorders and depression, while cognitive reappraisal and problem-solving have been shown to be negatively correlated, and acceptance has not been significantly correlated with any of these two psychopathologies (Aldao et al., 2010).

4.2.1 Emotion dysregulation and alexithymia

In the thesis study (see Section 3.3), alexithymia has been examined as predictive measure for distress disorders. Results show that it can be used to predict depressive symptoms in adults with ASD, social phobic symptoms in adults with social interaction disorder other than autism and for symptoms of both disorders in neurotypical peers. These findings are in line with previous studies but further extend on current literature (Fietz et al., 2018; Morie et al., 2019). Findings from the thesis study support the assumption that alexithymia is a risk factor for mental illness which affects autistic individuals, patients with disorders of social interaction other than autism and neurotypicals.

It also confirms the relevance for alexithymia in the vulnerability stress model for comorbid disorders in ASD (see Section 1.5).

Alexithymia has been associated with maladaptive ER strategies and emotion dysregulation (Dubey & Pandey, 2010; Garofalo, Velotti, & Zavattini, 2018; Taylor, 2000). Some authors have even used the term alexithymia as synonym for emotion dysregulation (Berthoz & Hill, 2005). Maladaptive ER strategies have been commonly observed in people with alexithymia. While suppression has been more frequently used as ER strategy by people with high alexithymic traits, cognitive reappraisal has been less likely applied (Chen, Xu, Jing, & Chan, 2011; Laloyaux et al., 2015; Swart, Kortekaas, & Aleman, 2009). Furthermore, avoidance has been a preferable coping strategy by people with increased levels of alexithymia, which was further associated with negative emotionality (Bilotta et al., 2016). These ER strategies have been shown to have a detrimental effect on social interaction, ultimately increasing the risk for anxiety and mood disorders (Hofmann, 2014; Williams, Morelli, Ong, & Zaki, 2018). Therefore, alexithymia should be assessed in the diagnostic procedure for ASD, and attention should be paid to comorbid mental illness especially in those individuals with increased levels of alexithymia.

4.2.2 Emotion dysregulation in ASD

In the thesis study (see Section 3.3), autism severity has been identified as predictor of social phobic symptoms in adults with ASD and with social interaction disorder other than autism, and of both depressive and social phobic symptoms in neurotypical peers. These findings are in line with results from previous studies and further extend on current literature (Fietz et al., 2018; Morie et al., 2019). Autism severity has been associated with emotion dysregulation before (Samson et al., 2014), but the results of the thesis study provide more evidence that autistic traits can be considered as risk factors for mental illness.

Most research of emotion dysregulation in ASD derives from studies involving children and adolescents (Cibralic, Kohlhoff, Wallace, McMahon, & Eapen, 2019; Jahromi et al., 2012; Konstantareas & Stewart, 2006; Mazefsky, Borue, Day, & Minshew, 2014; Samson, Hardan, Podell,

Phillips, & Gross, 2015). Maladaptive ER strategies frequently observed in individuals with ASD include suppression, avoidance and venting, which lead to internalizing (anxiety disorders, depression) and externalizing behavior (aggression, tantrums) (Konstantareas & Stewart, 2006; Quek, Sofronoff, Sheffield, White, & Kelly, 2012; Sofronoff, Attwood, Hinton, & Levin, 2007). Especially in children with ASD, aggressive behavior has been misinterpreted as intentional and defiant by those not familiar with autism, although it most likely arises from the lack of adaptive ER strategies (Laurent & Rubin, 2013).

In contrast to neurotypicals, individuals with ASD seem to apply more often suppression and less often cognitive reappraisal as ER strategy (Cai, Richdale, Dissanayake, Trollor, & Uljarević, 2018; Samson, Hardan, Lee, Phillips, & Gross, 2015), which has been associated with increased levels of depression (Cai et al., 2018). Furthermore, it has been suggested that individuals with ASD do not provide sufficient social-cognitive abilities to use adaptive ER (Samson et al., 2012). In fact, autistic individuals have shown difficulty in applying goal-directed behavior or seeking social support in comparison to neurotypical peers (Jahromi, Meek, & Ober-Reynolds, 2012). This would support the assumption of an impaired "tend and befriend" behavior in ASD in response to stress (see Section 1.5). After controlling for alexithymia, maladaptive ER patterns persisted in autistic individuals (Samson et al., 2012), indicating that the underlying core condition of ASD contributes to emotion dysregulation.

4.2.3 Treatment

Since both alexithymic and autistis traits have been identified as risk factors for comorbid mental illness in ASD, it is of utmost importance to develop specifically tailored psychotherapeutic treatments for autistic patients. Ideally, these should include elements addressing the core condition of ASD and – if co-existent – also impairments due to alexithymia.

Psychoeducation about autism and ER has been suggested as important element of psychotherapeutic treatment for adults with ASD (Mazefsky et al., 2013). Like dialectical behavioral therapy (DBT), this approach might help to create a validating environment in which individual

difficulties and strengths will be addressed. This could help autistic patients to recognize personal abilities and skills related to ASD e.g. broad knowledge in specific fields, paying attention to detail, focusing on facts, being reliable and honest among others. Being aware of these strengths can increase self-confidence and resilience, reducing the risk of distress disorders (Padesky & Mooney, 2012).

Furthermore, increased awareness towards internal states experienced in distinct situations can help to identify triggers of maladaptive ER strategies and replace them with healthier coping strategies (Mazefsky et al., 2013). Similar to DBT, these therapeutic interventions might reduce the application of psychiatric medication (e.g. antipsychotic drugs) often prescribed in ASD to reduce irritability and aggression (Esbensen et al., 2009; Mazefsky et al., 2013).

Moreover, cognitive reappraisal has been shown to be beneficial for psychosocial well-being in individuals with ASD and should, therefore, be included as element of psychotherapeutic treatments for autistic patients (Cai et al., 2018). Cognitive reframing of situations and emotions have been an effective method for treating patients with anxiety and mood disorders (Mennin, Fresco, Ritter, & Heimberg, 2015), commonly found in autistic individuals (Albantakis et al., 2018; Lai & Baron-Cohen, 2015; Lehnhardt et al., 2013).

In addition to cognitive techniques, an improvement of emotional competence has proven to increase psychosocial functioning with positive effects on relationships and employability (Nelis et al., 2011). This could be relevant for individuals with ASD, who show difficulties in socially engaging with others despite interest in friendships and romantic relationships (Strunz et al., 2017). Furthermore, the majority of people with HFA are either unemployed despite good education and professional skills or are overqualified for the job they do (Frank, Jablotschkin, Arthen, Riedel, Fangmeier, Hölzel, & Elst, 2018; Vogeley et al., 2013). Preliminary results from a schema therapy-informed social interaction training in adults with HFA have indicated that autistic patients benefit from learning and identifying schema in the non-autistic interaction partner in order to respond

adequately (Parpart et al., 2018). Thus, a multimodal therapy concept including cognitive strategies with focus on emotional processes would be helpful for patients with ASD.

Importantly, not every autistic person has difficulties with emotion regulation (Cai et al., 2018), similar to the fact that not every autistic person suffers from alexithymia (approximately 50 % do not). Thus, it is essential to identify those who show impairments in ER and could potentially benefit from a specific psychotherapeutic treatment tailored for ER dysregulation in ASD. This would not only improve the mental well-being and thus the psychosocial outcomes of autistic patients, but could also reduce societal costs and the financial burden on the health care system (Croen, Najjar, Ray, Lotspeich, & Bernal, 2006; Ganz, 2007; Järbrink, Fombonne, & Knapp, 2003; Leslie & Martin, 2007).

4.3 Outlook

Despite conflicting results from various studies investigating peripheral OXT concentrations and applying exogenous OXT as treatment strategy in psychiatric disorders, the hypothesis of an OXT dysregulation as underlying mechanism of psychopathology remains of interest. Results from the thesis study further support the assumption of a dysregulation of the OXT system in relation to stress (see Section 2.3). However, future studies should apply a dimensional and not disorder related approach in order to gain more information about the exact processes involving OXT, stress and mental illness. This approach considers the observation that various psychiatric disorders e.g. autism, depression, social phobia, schizophrenia and personality disorders share impairments in social interaction and communication (Schilbach, 2016), and equivocal results of peripheral OXT concentrations have been found in all these disorders (see Section 4.1). Moreover, it is possible that alexithymia plays a central role in the dysregulation of OXT in these psychopathologies (see Section 4.1.4) and should, therefore, be included as relevant confounding factor in future studies.

Since alexithymic and autistic traits have been found to predict depressive and social phobic symptoms in adults with and without ASD in the thesis study (see Section 3.3), both traits should be considered as relevant risk factors for mental illness. In this regard, more attention should be paid to alexithymia in the diagnostic assessment of psychiatric disorders but also in the psychotherapeutic treatment. Future psychotherapy studies could compare established treatment options which have been shown to improve emotion regulation and adjust them for autistic individuals.

4.4 Summary and conclusion

The phenotype of adults with HFA is very heterogeneous. This includes the severity of ASD, the comorbid psychopathology, varying levels of psychosocial functioning, and the degree of concomitant alexithymia. This thesis addressed the vulnerability to stress and mental disorders in adults with HFA in comparison to neurotypical peers by investigating peripheral OXT concentrations in response to a stress inducing task. Furthermore, the contribution of alexithymic and autistic traits on comorbid distress disorders was examined.

An inverse correlation between peripheral CORT and OXT levels has been found in adults with HFA in contrast to neurotypical peers, indicating a dysregulation of the HPA-axis and the OXT system in ASD and thus, supporting the assumption of stress vulnerability in ASD. Furthermore, concomitant alexithymia has been shown to increase the risk for depression in adults with HFA, while autism severity has been associated with social phobia. Thus, alexithymic and autistic traits should be assessed in the diagnostic process of ASD. Furthermore, alexithymia should be considered as relevant concomitant trait in the psychotherapeutic treatment for adults with ASD in order to prevent subsequent depressive disorders.

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Publications

Journal Articles

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05/2018 **Albantakis, L.**, Parpart, H., Thaler, H., Krankenhagen, M., Böhm, J., Zillekens, I. C., & Schilbach, L. (2018). Depression bei Erwachsenen mit Autismus-Spektrum-Störung. Nervenheilkunde, 37(09): 587–593.

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05/2020 **Albantakis, L.**, Brandi, M.-L., Brückl, T., Gebert, D., Auer, M.K., Kopczak, A., Stalla, G.K., Neumann, I.D., & Schilbach, L. Physical exercise elicits

differential oxytocin and cortisol responses in adults with and without autism.

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2020 Westenberg, E., **Albantakis, L.**, Henco, L., Lahnakoski, J. M., Schilbach, L., & Brandi, M. L. Increased cognitive effort during explicit mentalizing in autism – A pupillometry study.

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Book chapters

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Medical doctoral thesis

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Affidavit

I hereby declare, that the submitted thesis entitled

The role of peripheral oxytocin levels and alexithymia in relation to stress and comorbid mental illness in adults with and without autism spectrum disorder

is my own work. I have only used the sources indicated and have not made unauthorized use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

I further declare that the submitted thesis or parts thereof have not been presented as part of an examination degree to any other university.

Munich, 13.05.2021	Dr. Laura Irena Teresa Albantakis
Place, date	Signature doctoral candidate