THE MANY FACES OF AUTISM

Implications for assessment and association with anxiety

Jorieke Duvekot

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De vele gezichten van autisme:
Implicaties voor assessment en associatie met angst

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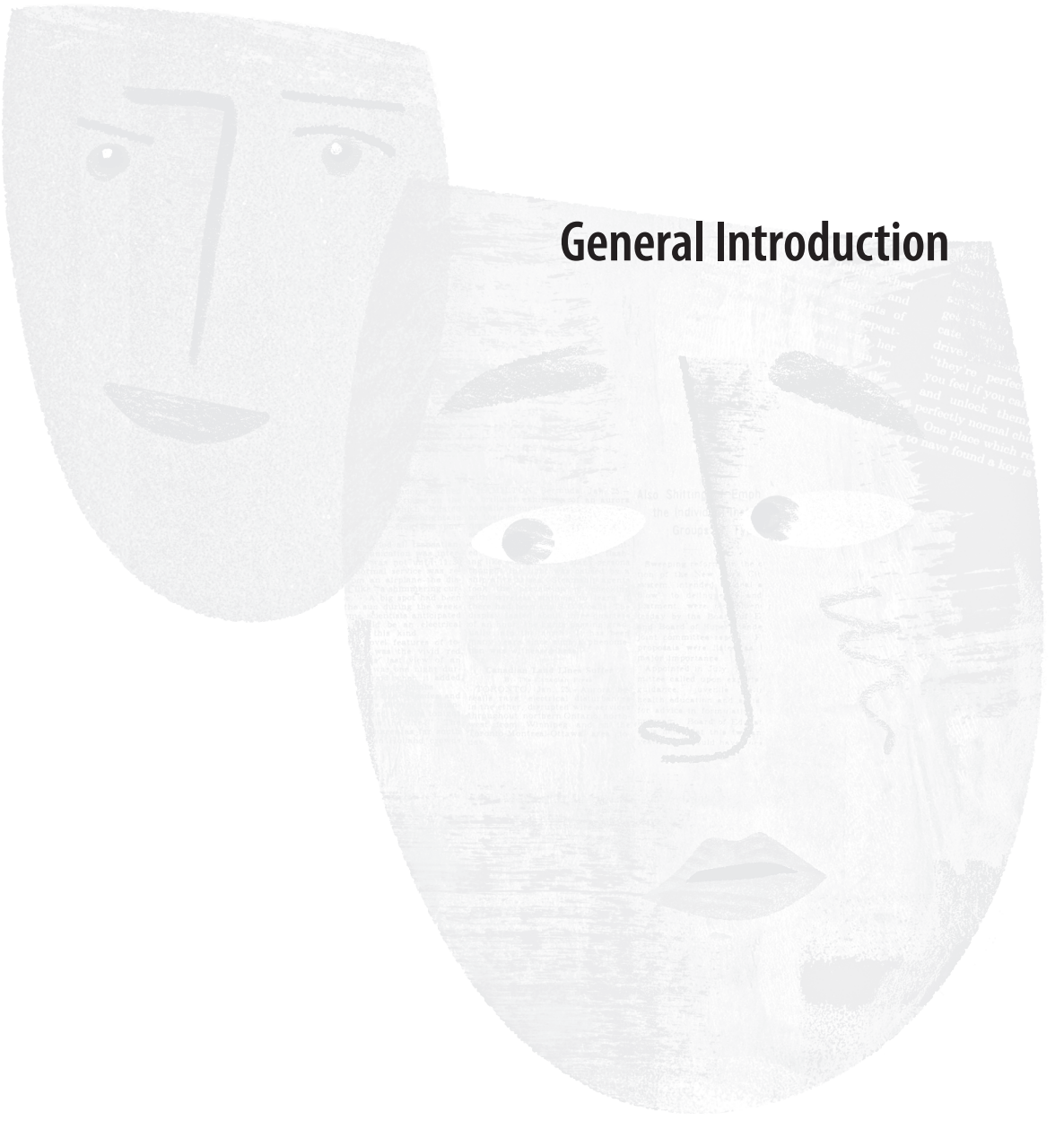
Chapter 1



General Introduction

Autism spectrum disorder (ASD) is a complex and heterogeneous neurodevelopmental disorder characterized by social communication difficulties and restricted, repetitive patterns of behavior and interests. However, individuals with ASD vary widely in the type, frequency, and severity of symptoms within these domains. This greatly complicates the process of identifying and diagnosing ASD as well as forms a major obstacle to research into the etiology of ASD (Constantino & Charman, 2016; Waterhouse, 2008). In addition to the variability in core ASD symptoms, individuals with ASD also show high levels of comorbid psychiatric problems, of which anxiety symptoms are commonly reported (Joshi et al., 2010; Simonoff et al., 2008). These comorbid problems further contribute to the phenotypic heterogeneity in ASD and may have important implications for the prognosis and treatment planning of individuals with ASD. To advance our understanding of this heterogeneity and its implications, this thesis focuses on several important issues concerning the identification of ASD in school-aged children and the interrelationships between ASD and anxiety problems. Before describing the specific aims of this thesis at the end of this chapter in more detail, I will first provide some background information.

Development of the autism spectrum concept

The first cases of autism were described, independently from one another, by the psychiatrists Leo Kanner and Hans Asperger. The 11 children Kanner described were severely affected and characterized by "an inability to relate themselves in the ordinary way to people and situations from the beginning of life" (Kanner, 1943). He also observed that the children showed unusual and repetitive patterns of behavior (stereotypies), had difficulties with dealing with change in the nonsocial world ("resistance to change"), and that their language, if they learned to speak at all, showed unusual qualities such as echolalia. Almost at the same time, Hans Asperger reported about four boys with similar characteristics as those described by Kanner, but their language development was less delayed, the onset seemed later, and they also showed motor deficits (Asperger, 1944).

The concept of classical or infantile autism, as described by Kanner, did not appear as a distinct diagnostic category in the Diagnostic and Statistical Manual of Mental Disorders (DSM) until 1980, in the third edition of the DSM (DSM-III; American Psychiatric Association, 1980). Subsequently, the concept

of autism has been revised and broadened over the years. The fourth edition of the DSM (DSM-IV-TR; American Psychiatric Association, 2000) included not only a narrowly defined classification of classical autism (Autistic Disorder) with strict criteria, but also the broader classifications of Asperger's Disorder (following the descriptions by Hans Asperger) and the rest category Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) for which fewer symptoms were required. Together, these disorders were labelled using the overarching term Pervasive Developmental Disorders. In the current "spectrum" conceptualization of ASD, these disorders represent the extreme end of a continuous distribution of autistic traits in the general population (Constantino, 2011). Consistent with this conceptualization and because evidence lacked for a reliable and valid differentiation between the different classifications in the DSM-IV-TR (Lord et al., 2012; Miller & Ozonoff, 2000), in the latest version of the DSM, the DSM-5, the prior classifications are replaced by a single category (Autism Spectrum Disorder) with varying levels of symptom severity (American Psychiatric Association, 2013).

In order to receive a diagnosis of ASD according to the DSM-5, criteria in two symptom domains need to be met: A) social interaction and communication deficits and B) restricted, repetitive patterns of behavior and interests (American Psychiatric Association, 2013). A symptom added to the domain of restricted and repetitive behavior in the DSM-5 is the presence of sensory abnormalities, such as over- or undersensitivity to sensory stimuli and an unusual interest in sensory stimuli. In order to receive a diagnosis, an individual needs to fulfill the symptom requirements in domain A and B, and show functional impairments in everyday life (criterion C). The prior criterion of an onset before 3 years of age (in the DSM-IV-TR) is changed into the presence of difficulties in early development including the recognition that for some individuals these difficulties are not fully manifested until their social communications skills are no longer sufficient to keep up with the increasing complexity of environmental demands and expectations (criterion D). In addition, other disorders have to be ruled out (criterion E).

Currently, the field is moving from a categorical approach, focusing on categorical diagnoses (yes or no), to a more dimensional approach, focusing on behavioral and neurobiological dimensions that cut across diagnostic categories with the aim of advancing the scientific quest of the etiological underpinnings of normal and abnormal behavior (the RDOC research domain

criteria; Insel, 2014). For clinical practice, diagnostic categories are important to provide a common language for researchers and clinicians and help translating research findings to clinical practice. In addition, diagnostic categories currently guide decisions regarding the provision of interventions, special education, and other care facilities (Lord et al., 2012). However, as I have outlined above, diagnostic categories are constantly evolving. Serious concerns have been expressed about the validity of diagnostic categories (Gillberg, 2010; Rutter & Pickles, 2016). It is commonly recognized that there is substantial heterogeneity within diagnostic categories as well as great overlap between individuals from different diagnostic categories, both on a behavioral and on an etiological level (Jeste & Geschwind, 2014; Waterhouse, 2008). Because of this heterogeneity and overlap, attempts to map specific causes to distinct diagnostic categories have been largely unsuccessful so far (Coghill & Sonuga-Barke, 2012). In the case of ASD, research has shown that autistic characteristics or traits form a continuum in the general population (Constantino, 2011; Hoekstra, Bartels, Verweij, & Boomsma, 2007; Skuse et al., 2009). In addition, higher rates of elevated but subclinical levels of these symptoms, referred to as the "Broader Autism Phenotype", are found in family members of individuals with ASD (Sucksmith, Roth, & Hoekstra, 2011; Virkud, Todd, Abbacchi, Zhang, & Constantino, 2009) and in children with other psychiatric diagnosis, for example attention-deficit/hyperactivity disorder (ADHD; Reiersen, Constantino, & Todd, 2008) and anxiety disorders (Pine, Guyer, Goldwin, Towbin, & Leibenluft, 2008; Towbin, Pradella, Gorrindo, Pine, & Leibenluft, 2005). Evidence is accumulating that the continuously assessed autistic traits in the general population show similar genetic influences as the discrete diagnostic category of ASD (Colvert et al., 2015; Robinson et al., 2011). This means that ASD can been seen as the extreme expression of normal variation and that the cut-off for what we consider "ASD" is rather arbitrarily (Constantino, 2011). Using a dimensional approach avoids the potential loss of important information associated with using a dichotomous classification, improves the power to detect associations, and is not restricted to small clinical samples (Coghill & Sonuga-Barke, 2012). In addition, dimensional measures are more suitable to account for the fact that the level of symptoms within individuals is not static, but continues to evolve over time (Louwerse et al., 2015; Visser et al., 2017) and can be expressed differently in different contexts (Kanne, Abbacchi, & Constantino, 2009). Therefore, investigating ASD symptoms and their relations to co-occurring

emotional and behavioral problems in broader populations may increase our understanding of the heterogeneity of ASD and advance assessment, prognosis, individualized treatment, and etiological research of ASD. Because both the categorical and dimensional approach have their unique strengths and can be considered as each serving different goals, in the current study, we used the categorical diagnosis of ASD as well as dimensional measures of ASD and associated symptoms.

Epidemiology

Although classical autism was once a rare disorder, the prevalence of the broader category of ASD has recently been estimated to be around 1,5% among children in developed countries (Christensen et al., 2016; Lyall et al., 2016). Factors that are considered to contribute to the increasing prevalence are the broadening of the concept, changing diagnostic practices, increased awareness of parents, teachers and clinicians, and a better identification of children with ASD without co-occurring intellectual disability, though a real increase in prevalence cannot be excluded (Lyall et al., 2016; Verhulst, 2010; Waterhouse, 2008). ASD is more prevalent in boys than in girls, with an overall gender ratio of 4:1, but estimates vary greatly with higher male-to-female ratios reported in samples with a higher IQ level and lower male-to-female ratios reported in recent epidemiological samples using active case-ascertainment methods (Loomes, Hull, & Mandy, 2017). Recent research suggests caution that girls may be at risk of being underidentified (Lai, Lombardo, Auyeung, Chakrabarti, & Baron-Cohen, 2015), as I will discuss more thoroughly later. Most individuals with ASD face problems during all developmental stages of life, from first going to day care or school and building up social relationships, to getting and maintaining a job. As a result, individuals with ASD are often in need of various mental health and special educational services, even those with 'milder' forms of ASD (Louwerse et al., 2015). Thus, ASD places a great burden on children, families, and the society as a whole (Buescher, Cidav, Knapp, & Mandell, 2014).

Etiology

The etiology of ASD is complex and still largely understood, though progress is being made in the identification of the genetic, neurobiological, and environmental factors involved (Chen, Penagarikano, Belgard, Swarup, & Geschwind, 2015). There is evidence that ASD is substantially heritable with

heritability estimates ranging between 64 and 91% (Tick, Bolton, Happe, Rutter, & Rijsdijk, 2016). The genetic contribution to ASD is also supported by evidence of a recurrence rate of 20% in siblings of children with ASD (Ozonoff et al., 2011) and a heightened prevalence of elevated autistic characteristics in family members of individuals with ASD (Sucksmith et al., 2011). Risk factors for ASD are likely to be shared with those for other psychiatric disorders. For example, twins and family members of individuals with ASD have also been found to be at risk for other psychiatric disorders, such as ADHD, language disorders, depression and anxiety (Sucksmith et al., 2011; Tick, Colvert, et al., 2016). Moreover, twin studies have provided evidence that there is a considerable overlap in the genetic liability of ASD and other psychiatric disorders (Lichtenstein, Carlstrom, Rastam, Gillberg, & Anckarsater, 2010; Tick, Colvert, et al., 2016). While genetic factors are assumed to play an important role in the etiology of ASD, involving de novo mutations and rare inherited variations as well as common genetic variants, relatively few genes involved in the pathophysiology of ASD have yet been consistently identified (Chen et al., 2015). In addition, several environmental factors, such as parental age, interpregnancy interval, and prenatal air pollution, have also been implicated (Lyall et al., 2016). These genetic and environmental factors are thought to give rise to a deviant neurobiological development, such as early brain overgrowth (Sacco, Gabriele, & Persico, 2015), anatomic differences in brain structures (Chen et al., 2015; Lefebvre, Beggiato, Bourgeron, & Toro, 2015), and differences in the functional connectivity and hypoconnectivity across brain structures (Di Martino et al., 2014), though much has yet to be learned about these potential pathophysiological pathways.

Screening and diagnostic assessment of autism

Since there are yet no biological markers to determine whether a child has ASD, a clinical diagnosis is based on behavioral characteristics of the child. It is generally agreed on that this evaluation should minimally include a parental interview to assess the developmental history of the child and the child's current functioning and an observation of the child by a clinician to directly observe the presence of social-communication difficulties and restricted/repetitive behavior and interests, as well as measures of the language ability, cognitive ability, adaptive functioning, and comorbid problems of the child (Charman & Gotham, 2013; Volkmar et al., 2014). Several standardized diagnostic instruments have been

developed to aid professionals in this complex diagnostic process. Currently, well-established standardized instruments for the diagnosis of ASD are the Autism Diagnostic Interview-Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003), the Diagnostic Interview for Social Communication Disorders (DISCO; Wing, Leekam, Libby, Gould, & Larcombe, 2002), and the Developmental, Dimensional and Diagnostic Interview (3Di; Skuse et al., 2004), which are all semi-structured parental interviews, combined with the Autism Diagnostic Observation Scale (ADOS; Lord, Rutter, DiLavore, & Risi, 1999), which is a standardized and semi-structured observation by a professional. However, the implementation of these instruments in clinical practice is hampered by the extensive time investment, costs and specialized training requirements associated with the use of these instruments. The ADI-R and DISCO, for example, take approximately 2-3 hours to administer by highly trained professionals and have been originally developed to provide a categorical classification. The 3Di is a computer-based interview that was developed within a dimensional framework and is easier and shorter to administer, taking approximately 90 minutes for the full interview and 45-60 minutes for the short version. Therefore, the current study used the short version of the 3Di in combination with the ADOS. In line with the recommendations, we used expert clinical judgement to integrate the information from these instruments to establish a best-estimate consensus diagnosis of ASD (Falkmer, Anderson, Falkmer, & Horlin, 2013; Volkmar et al., 2014), which is described in more detail in Chapter 2.

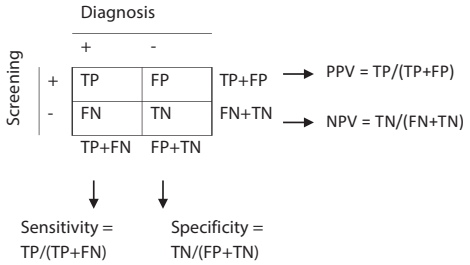
In order to support clinicians and researchers in the decision to whom this extensive and costly diagnostic evaluation should be provided, several screening questionnaires have been developed, such as the Social Responsiveness Scale (SRS; Constantino & Gruber, 2005) or the Autism Quotient (AQ; Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). In addition to being short and easy to administer, these questionnaires also provide a quantitative assessment of the level of ASD symptom severity in line with the view of ASD as a continuum. Moreover, these questionnaires can be used to follow changes in the symptom level of an individual over time, evaluate treatment effects, and collect information from different sources of the functioning of an individual in different contexts (Constantino & Gruber, 2012). The present study used the SRS to screen for ASD and as a dimensional measure of ASD symptoms. The SRS is 65-item questionnaire that has been specifically designed to capture the full range of autistic social impairment

in children, including those with 'milder' forms of ASD or subclinical levels (Constantino & Gruber, 2012). Previous international studies have shown that the SRS shows strong relations to diagnostic instruments for ASD (Bölte, Poustka, & Constantino, 2008; Constantino et al., 2003) and discriminates well between children with and without ASD (Bölte et al., 2008; Charman et al., 2007; Kamio et al., 2013). However, previous studies were conducted in samples of children with prior diagnoses of ASD of whom many were from specialized ASD clinics. Because these studies did not use a prospective design, children who obtained a negative screen were not followed up. It is therefore yet not clear what the utility is of the SRS in identifying children who need to be evaluated further using standardized diagnostic assessment in a diverse and representative sample of clinically referred, which more closely represents the population in which ASD screening instruments are commonly used. In addition, it is important to collect information from multiple sources to gain a comprehensive understanding of a child's problems (Achenbach, 2006; De Los Reyes & Kazdin, 2005). In our study, both parents and teachers completed the SRS. Information from the teacher could provide valuable information in addition to parent report, since teachers observe the child in a different setting, the classroom, in the presence of numerous other children. Despite the potential additional value of information obtained from teachers in the assessment of ASD, little is known about the added contribution of the teacher report to the parent report when screening for ASD.

Thus, the SRS may be a cost-efficient tool to identify children with a high probability of having ASD. This is important to help making decisions in clinical practice regarding whether a child requires further in-depth diagnostic assessment and qualifies for mental health or special education services. International research shows that the SRS is a promising instrument, but more research is needed to investigate the utility of the SRS in a sample that is more representative of children who are referred to mental health care for various reasons, in which also children with a negative screen receive further assessment for ASD, and to evaluate the added value of the teacher report in addition to the parent report when screening for ASD. These issues are addressed in Chapter 3. For the evaluation of the utility of the SRS, we used several parameters, or indices of diagnostic accuracy. An explanation of these parameters and how they are calculated is provided in Box 1.

Box 1. A description of the standard indices of diagnostic accuracy.

Sensitivity: the proportion of children with the disorder who are correctly identified by the screening test
Specificity: the proportion of children without the disorder who are correctly identified as not having the disorder by the screening test
Positive predictive value (PPV): the proportion of children with a positive screening result who have the disorder (and are therefore correctly classified)
Negative predictive value (NPV): the proportion of children with a negative screening result who do not have the disorder (and are therefore correctly classified)
These values for standard indices can be calculated using a 2 x 2 table:



The clinical significance of these parameters is indicated by Cicchetti, Volkmar, Klin, and Showalter (1995) as: <0.70 = poor; 0.70-0.79 = fair; 0.80-0.89 = good; 0.90-1.00 = excellent

The values for standard indices of diagnostic accuracy vary if the threshold on the screening instrument is raised or lowered. The receiver operating characteristic (ROC) curve depicts the varying values of the sensitivity and (1 minus) specificity for every possible threshold on a screening instrument. The area under the curve (AUC) of the ROC curve provides a summary index of the overall discriminatory ability of a test irrespective of the threshold used.

Identification of ASD in girls

Although the increased use of standardized screening and diagnostic instruments is assumed to improve the identification of ASD, there are some subgroups that may have a higher risk of being missed or misdiagnosed, such as girls with ASD. It is well-known that ASD is more common in males than in females, with approximately four males affected with ASD for every female (Loomes et al., 2017). There is yet no satisfactory explanation for this sex discrepancy. Since the presence of a sex discrepancy is consistent across samples, though the size varies, and has also been reported for other neurobiological disorders (Lyall et al., 2016), neurobiological factors are thought to be implicated. For example, a female protective effect has been hypothesized, suggesting that a higher etiological load is needed for ASD to come to expression in girls, such as more genetic mutations or a higher familial burden (e.g., Jacquemont et al., 2014; Robinson, Lichtenstein, Anckarsater, Happe, & Ronald, 2013). However, the finding that girls are less likely to be diagnosed with ASD even if they show

similarly elevated levels of ASD symptoms as boys suggests that girls are also at risk of being under-identified (Dworzynski, Ronald, Bolton, & Happe, 2012; Russell, Steer, & Golding, 2011). Moreover, girls who were diagnosed were more likely to have co-occurring cognitive and behavioral problems (Dworzynski et al., 2012). It is possible that girls without co-occurring difficulties are better able to mask or camouflage their autistic difficulties (Bargiela, Steward, & Mandy, 2016). In addition, there may be subtle phenotypic differences between boys and girls with ASD, making it harder to identify ASD in girls than in boys (Frazier, Georgiades, Bishop, & Hardan, 2014; Mandy et al., 2012). To contribute to our understanding of which factors may be involved in the assumed under-identification of ASD in girls, we examined in Chapter 4 which behavioral characteristics were differently related to the probability of an ASD diagnosis in girls versus boys.

The co-occurrence of ASD and anxiety

High rates of comorbid psychiatric disorders have been found in samples of individuals with ASD (de Bruin, Ferdinand, Meester, de Nijs, & Verheij, 2007; Leyfer et al., 2006; Simonoff et al., 2008). One of the most frequently reported comorbid psychiatric problems are anxiety problems, which have been estimated to be present in around 40% of the children and adolescents with ASD (van Steensel, Bogels, & Perrin, 2011). This prevalence is much higher than that in the general population (4.7-9.1%; Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). Co-occurring anxiety problems in ASD require attention, as these may negatively affect the child's functioning in various domains (White et al., 2010) and are related to higher levels of parental stress (Kerns et al., 2015). Recognition of anxiety problems/disorders in children with ASD is complicated by an overlap in symptoms between ASD and anxiety (White, Oswald, Ollendick, & Scahill, 2009). Other obstacles are diagnostic overshadowing, meaning that symptoms of anxiety may be falsely attributed to be part of ASD instead of a separate comorbid disorder that requires attention (Kerns et al., 2015; Mason & Scior, 2004), and the difficulty individuals with ASD often have with recognizing and expressing their emotions (Lecavalier et al., 2014). Despite increased attention to the frequent co-occurrence of ASD and anxiety, the reasons for this co-occurrence are still poorly understood.

One possible explanation is that ASD and anxiety share a common vulnerability or risk factors that promote their co-occurrence. Family studies

show an increased prevalence of anxiety disorders in the relatives of individuals with ASD (Bolton, Pickles, Murphy, & Rutter, 1998; Mazefsky, Folstein, & Lainhart, 2008; Micali, Chakrabarti, & Fombonne, 2004; Piven & Palmer, 1999). Despite evidence of familial aggregation of ASD and anxiety, it remains unclear whether ASD and anxiety are transmitted independently within families or whether they have a shared familial transmission. To date, the familial transmission of symptoms of ASD (e.g., De la Marche et al., 2015; Lyall et al., 2014) and anxiety (Beidel & Turner, 1997; Last, Hersen, Kazdin, Orvaschel, & Perrin, 1991) have been studied independently from each other. It is not known whether ASD in parents also increases the risk for anxiety problems in children or vice versa. Alternatively, children may also be at risk for both ASD and anxiety because of (cross-)assortative mating. This is the tendency to (not randomly) choose a partner that is either similar and dissimilar from oneself in a variety of traits. Some evidence exists for assortative mating for ASD (Constantino & Todd, 2005; Lyall et al., 2014) and anxiety (Maes et al., 1998). Only one study examined the possibility of cross-assortative mating for ASD and anxiety, thus whether a parent with autistic traits is more likely to have a partner with anxiety problems or vice versa (Lau, Gau, Chiu, & Wu, 2014). This study did not confirm the presence of cross-assortative mating, but was limited by the use of only self-report data. The role of these family factors in the co-occurrence of ASD and anxiety is investigated in Chapter 5.

Another possible explanation for the co-occurrence of ASD and anxiety is phenotypic causality, which means that one disorder affects the development of the other. It has been hypothesized that individuals with ASD are more vulnerable for experiencing anxiety because the core ASD symptoms increase the amount of stress they experience (Wood & Gadow, 2010). For example, individuals with ASD often find social interactions less predictable and are at risk for experiences of social exclusion and isolation and peers because of their social communication difficulties. Other contributors to stress are the need for sameness, which conflicts with the unpredictability of daily life, and an oversensitivity for sensory stimuli. Vice versa, anxiety problems could also exacerbate the social difficulties of individuals with ASD, by leading the individual to avoid social situations, limiting their social learning opportunities, and by interfering with social information processes and an adequate execution of social skills (White et al., 2010). Although a bidirectional influence between ASD and anxiety problems is assumed (White et al., 2014; Wood & Gadow, 2010),

there is currently little evidence regarding the direction of this relationship, as there have been few longitudinal studies (Kerns & Kendall, 2012). Even though ASD and anxiety are reported to co-occur, it does not necessarily mean that they affect each other's developmental course. For example, early social competence and language ability were found to develop largely independently from each other in preschoolers with ASD despite their concurrent associations (Bennett et al., 2014). In addition, co-occurring disorders may not influence each other in the same way. Two studies conducted in general population samples suggest a larger influence of ASD on the development of anxiety problems than vice versa (Hallett, Ronald, Rijsdijk, & Happe, 2010; Pickard, Rijsdijk, Happe, & Mandy, 2017). However, these studies were conducted in the general population with only modest effects, so it remains uncertain whether these results can be generalized to clinically referred children with ASD. A better understanding is needed of how ASD and anxiety problems influence each other over time to identify targets for prevention and intervention in children with ASD (see Chapter 6).

Sample and study design

This thesis was embedded in the larger context of the Social Spectrum Study, a prospective multicenter study of clinically referred children enriched for children with ASD. The study used a two-phase sampling design to identify children at risk for ASD. In the first phase, 1,281 children aged 2.5-10 years, who had been consecutively referred to six participating mental health care centers for a variety of problems, were all screened for ASD using the Social Responsiveness Scale (SRS). In the second phase, all children with a positive screen ($n = 428$) and a random selection of screen negatives ($n = 240$) were invited to participate in a comprehensive diagnostic assessment. In addition, parents were asked to complete various questionnaires to obtain information regarding characteristics of the child, themselves, and the family. Families of 335 children participated in at least assessment (diagnostic/questionnaires). Of the 231 children who participated in the complete diagnostic assessments, 130 children received a best-estimate consensus diagnosis of ASD according to the DSM-IV-TR criteria. After approximately a year, 168 families participated in a follow-up assessment. Please see chapter 2 for a more detailed description of the study and flow chart.

Aims and outline of this thesis

The general aims of this thesis are twofold and therefore the thesis is divided into two parts:

The first aim of this thesis is to contribute to an improved identification of ASD in children by investigating the influence of diagnostic criteria, instruments, informants and gender of the child on the screening and diagnostic assessment of ASD. In Part 1 of this thesis the following studies are discussed that address this aim. Chapter 2 provides an overview of the design of the Social Spectrum Study, sample characteristics, and attrition, as well as the impact of DSM-5 criteria on the diagnosis of ASD in children. In Chapter 3, we investigated the screening accuracy of the SRS in our multicenter study of clinically referred children and the added value of the teacher report in addition to the parent report. In Chapter 4, we investigated possible explanations for the assumed under-identification of girls by investigating whether behavioral characteristics were differently related to the likelihood of an ASD diagnosis in girls versus boys.

The second aim of this thesis is to gain more insight into the co-occurrence of ASD and anxiety by investigating the relationship between ASD and anxiety symptoms within families as well as within children with ASD over time. In Part 2 of this thesis the following studies are discussed that address this aim. In Chapter 5, we investigated familial relations between ASD and anxiety symptoms: a) associations between parents' symptoms in order to investigate cross-assortative mating and b) associations symptoms of parents and children in order to investigate shared familial transmission for ASD and anxiety. In Chapter 6, we investigated whether ASD and anxiety symptoms influence each other bidirectionally over time.

Finally, in Chapter 7, I discuss the main findings and conclusions of these studies in the context of recent literature and discuss some methodological considerations, as well as clinical implications and recommendations for future research that follow from these studies.

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Part I

Screening and diagnostic assessment of autism spectrum disorder

Chapter 2

Design and Cohort Characteristics of the Social Spectrum Study: A Multicenter Study of the Autism Spectrum Among Clinically Referred Children

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Abstract

This paper provides an overview of the design and cohort characteristics of the Social Spectrum Study: a clinical cohort study that used a two-phase sampling design to identify children at risk for ASD. After screening 1,281 children aged 2.5-10 years who had been consecutively referred to one of six mental health services in the Netherlands, children who screened positive for ASD (n=428) and a random selection of screen negatives (n=240) were invited to participate in diagnostic assessments and questionnaires regarding the child, family and society. A one-year follow-up was also conducted. Results from this study may contribute to knowledge about the identification and characterization of children with ASD, family processes, and the impact of ASD on the family and society.

Introduction

Autism Spectrum Disorder (ASD) is a pervasive neurodevelopmental disorder that greatly impacts the functioning of the individual in multiple domains, as well as the family and the broader society (Buescher et al. 2014). The Social Spectrum Study is a prospective clinical cohort study designed to contribute to the understanding of the relationships between ASD characteristics and various child, family and societal factors. In order to enhance generalizability of the findings from this cohort, we systematically screened all children who had been referred to six large mental health services and provided in-depth diagnostic assessments to children who screened positive for ASD as well as to a randomly selected sample who screened negative. This sampling method distinguishes our study from previous studies that usually sampled only children who have an ASD diagnosis or who are considered at risk for ASD. Research has shown that limiting sampling to children with an ASD diagnosis could risk the under-identification of certain subgroups, such as girls (Dworzynski et al. 2012), children with ASD who have normal to high levels of cognitive functioning or subtler symptoms (Kim et al. 2011; Baird et al. 2006), or children of certain ethnic origins (Mandell et al. 2009). Standardized screening and diagnostic methods could help to minimize these biases (Baird et al. 2006).

In line with the current view that ASD represents the extreme end of a continuum of autistic characteristics (Constantino 2011; Lord and Jones 2012; Volkmar and McPartland 2013), we used continuous measures of ASD symptomatology as well as categorical diagnostic assessments of ASD. Research has shown that ASD symptoms are continuously distributed in the general population (Constantino and Todd 2003; Skuse et al. 2009) and that subthreshold ASD symptoms in the general population are related to functional impairment (Skuse et al. 2009). In addition, there is evidence that subclinical levels of ASD symptoms have a similar genetic liability as clinically diagnosed ASD (Colvert et al. 2015). This is also consistent with a general shift in psychiatry from the focus on categorically defined disorders to the dimensional assessment of characteristics that cut across disorders, the Research Domain Criteria (Insel et al. 2010). These findings highlight the importance of examining ASD symptoms in a broader population than only children with a known ASD diagnosis.

The aims of this article are to provide an overview of the aims, design and methods of the Social Spectrum Study, and to present results regarding the characteristics of this cohort as well as factors that influence nonresponse/attrition (i.e., the loss of participants throughout the different phases of the study).

Aims of the Social Spectrum Study

The Social Spectrum Study investigates how ASD influences and is influenced by various factors on the level of the individual, family, and society. At the individual level, heterogeneity in the core characteristics of ASD as well as co-occurring emotional/behavioral problems greatly complicate diagnosis and treatment of ASD (Constantino and Charman 2015). In order to improve the identification of ASD and the provision of individualized treatments, a better understanding is needed of the performance of screening and diagnostic instruments as well as the relations between ASD and emotional/behavioral difficulties. At the level of the family, the impact of having a child with ASD is evidenced by higher levels of parenting stress and less adequate family functioning in families of children with ASD (Karst and Van Hecke 2012). In addition, parents of children with ASD are at risk for having elevated ASD symptoms and other types of psychopathology themselves (Sucksmith et al. 2011). Longitudinal research is needed to examine bidirectional influences of child and family factors over time. This could offer insights into how treatment can be tailored to the needs of families in order to improve treatment outcomes. At the societal level, a better understanding of the broader social and economic consequences of having a child with ASD in terms of employment, health care use, and costs (Kogan et al. 2008; Buescher et al. 2014; Leigh and Du 2015) is important for the planning of resources.

To address these important issues, the aims of the Social Spectrum were:

a) to evaluate the performance of screening and diagnostic instruments for ASD;
b) to investigate the relationships between ASD characteristics and other developmental/mental health problems;
c) to examine the relationships between ASD characteristics of the child and characteristics of the family, such as family functioning, parent-child interaction, parental psychopathology, parenting stress/behavior, and social support;

d) to estimate individual, familial and societal burden of ASD in terms of expenditures on care, lost productivity and quality of life.

In line with Bronfenbrenner's ecological systems theory (Bronfenbrenner 1994), these aims can be linked to the different environmental contexts in which the child is embedded, as depicted in Figure 1.

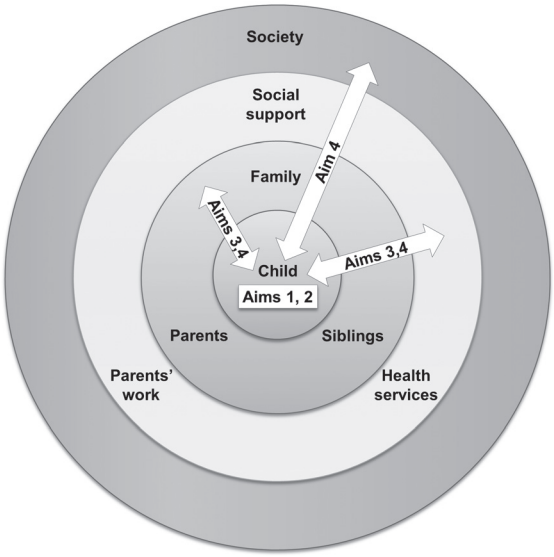

Figure 1. An illustration of how the study's aims 1 to 4 relate to the different environmental contexts in which the child develops. The figure is based on Bronfenbrenner's ecological systems theory (Bronfenbrenner 1994).

Methods

Study design

The present study used a two-phase sampling design (Dunn et al. 1999) to identify children at risk for ASD. In a first phase, all children who had been referred to six large child and adolescent mental health services (CAMHS) in the South-West of the Netherlands were systematically screened for the presence of ASD symptoms using the Social Responsiveness Scale (SRS; Constantino and Gruber 2012) at each site during a period of six months falling between

April 2011 and July 2012. Children had been referred for a variety of emotional, behavioral and developmental problems. The participating CAMHS were the six largest centers in the South-West of the Netherlands, covering both rural and urban areas. The majority of the CAMHS were secondary services, but also tertiary services participated, including specialized services for children with ASD.

In a second phase, after the completion of the sixth-month screening period at a particular site, all children with a positive screen for ASD according to the parent-reported SRS (total raw score ≥ 75) and a random sample of children with a negative screen for ASD (total raw score < 75) were selected for in-depth assessments using select cases in SPSS 20 (IBM Corporation 2011). Of the screen-negative children, we selected approximately 25% of the screen-negative children aged 4 to 10 years and—to ensure an adequate number of preschoolers—approximately 50% of the screen-negative children aged 2.5 to 4 years old. The selection was performed on coded data and selected screen-negative and screen-positive cases were mixed in one file, so the research team did not know whether a selected child had a positive or a negative screen.

The study was approved by the local medical ethics committee (MEC-2011-078) and the participating CAMHS prior to the start of the study. At the time of the in-depth assessments, written informed consent was obtained from the participating parents/caregivers and children aged ≥ 12 years.

Measures and procedures

The measures and procedure at each phase are described in more detail below. Table 1 provides an overview of the measures at different phases of the study.

T0 Screening

As part of the routine clinical procedure at the participating CAMHS, a screening package containing the ASD screening questionnaire and other questionnaires (see Table 1) was sent to the parents/caregivers prior to the first appointment. In an accompanying letter, parents/caregivers were notified about the study and that they could be invited to participate in further assessments of the study. Although families of all referred children aged 1.5 to 18 years old received the screening package, we limited further inclusion to children aged 2.5 to 10 years old to focus only on children of preschool and primary school-age, as these are the ages at which most individuals with ASD are identified.

Table 1. Overview of the measures used in the study

Topic	Instrument	Format	Informant/rater	T0	T1	T2
Child characteristics						
ASD symptoms	SRS (Constantino and Gruber 2012)	Questionnaire	Primary caregiver, teacher (only T0)	X	X	X
	3Di-sv (Santosh et al. 2009)	Parent interview	Parent (informant)/ clinician/researcher (rater)		X	
	ADOS-2 (Lord et al. 2012)	Child observation	Clinician or researcher		X	
	RBS-R (Bodfish et al. 2000)	Questionnaire	Primary caregiver		X	
	SSP (McIntosh et al. 1999)	Questionnaire	Primary caregiver		X	
Emotional/behavioral problems	CBCL (Achenbach and Rescorla 2000, 2001)	Questionnaire	Primary caregiver	X		X
Cognitive ability	Various IQ tests	Test	Clinician or researcher		X	
Daily living skills	Vineland Screener (van Duijn et al. 2009)	Questionnaire	Primary caregiver		X[a]	X
Emotion regulation	CBQ-SF (Putnam and Rothbart 2006)	Questionnaire	Primary caregiver		X[a]	X[a]
Quality of life	EQ-5D (EuroQol 1990)	Questionnaire	Primary caregiver		X	X
Health care use and expenditures on care	TiC-P (Bouwmans et al. 2012; Hakkaart-van Roijen et al. 2007)	Questionnaire	Primary caregiver	X		X
Health-related absenteeism	TiC-P (Bouwmans et al. 2012; Hakkaart-van Roijen et al. 2007)	Questionnaire	Primary caregiver		X	X
Life events in past year	List of 15 life events	Questionnaire	Primary caregiver			X
Characteristics of primary caregiver						
ASD symptoms	SRS (Constantino and Gruber 2012)	Questionnaire	Self-report & spouse-report		X	
Emotional/behavioral problems	ASR, ABCL (Achenbach and Rescorla 2003)	Questionnaire	Self-report & spouse-report		X	
Social support	VGFO (Veerman et al. 2012)	Questionnaire	Self-report		X	
Marital quality	VGFO (Veerman et al. 2012)	Questionnaire	Self-report		X	
Parenting stress	OBVL (Vermulst et al. 2012)	Questionnaire	Self-report		X	
Personal growth	PGS (Kraaij et al. 2008)	Questionnaire	Self-report		X	
Coping styles	CERQ (Garnefski and Kraaij 2007)	Questionnaire	Self-report		X	
Quality of life (generic)	EQ-5D (EuroQol 1990)	Questionnaire	Self-report		X	

Table 1. Continued

Topic	Instrument	Format	Informant/rater	T0	T1	T2
Quality of life (care-related)	CarerQol (Brouwer et al. 2006)	Questionnaire	Self-report		X	
Health care use	TiC-P (Bouwmans et al. 2012; Hakkaart-van Roijen et al. 2007)	Questionnaire	Self-report		X	
Productivity losses	SF-HLQ (van Roijen et al. 1996)	Questionnaire	Self-report		X	
Parenting behavior	PBS-A (Van Leeuwen and Noens 2013)	Questionnaire	Self-report			X
Characteristics of secondary caregiver						
Quality of life	EQ-5D (EuroQol 1990)	Questionnaire	Self-report		X	
ASD symptoms	SRS (Constantino and Gruber 2012)	Questionnaire	Self-report & spouse-report		X	
Emotional/behavioral problems	ABCL (Achenbach and Rescorla 2003)	Questionnaire	Self-report & spouse-report		X	
Characteristics of siblings						
ASD symptoms	SRS (Constantino and Gruber 2012)	Questionnaire	Primary caregiver		X	
Emotional/behavioral problems	CBCL (Achenbach and Rescorla 2000, 2001)	Questionnaire	Primary caregiver		X	
Other family characteristics						
Parent-child interaction (≤ 5 years)	DPICS (Eyberg et al. 2009)	Observation	Clinician or researcher		X	
Family functioning	FAD (Epstein et al. 1983)	Questionnaire	Primary caregiver		X	X
Family history	FTQ (Mann et al. 1985)	Interview	Primary caregiver (informant)/ researcher (rater)		X	

[a]Only for children aged ≤ 6 years.

Note. 3Di-sv = short version of the Developmental Dimensional Diagnostic interview; ADOS-2 = Autism Diagnostic Observation Schedule, second edition; ABCL = Adult Behavior Checklist; ASR = Adult Self-report; CarerQol = Care-related Quality of Life; CBCL = Child Behavior Checklist; CBQ-SF = short form of the Children's Behavior Questionnaire; CERQ = Cognitive Emotion Regulation Questionnaire; DPICS = Dyadic Parent-Child Interaction Coding System; FAD = Family Assessment Device; FTQ = Family Tree Questionnaire; OBVL = Opvoedingsbelastingsvragenlijst [Parenting stress questionnaire]; PBS-A = Parent Behavior Scale for Autism Spectrum Disorders; PGS = Personal Growth Scale; RBS-R = Repetitive Behavior Scale-Revised; SF-HLQ = short form of the Health and Labour Questionnaire; SRS = Social Responsiveness Scale; SSP = Short Sensory Profile; TiC-P = Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness; VGFO = Vragenlijst Gezinsfunctioneren voor Ouders [Questionnaire family functioning for parents]

Screening instrument. The ASD screening instrument used in the present study is the Social Responsiveness Scale (SRS), a 65-item questionnaire that assesses ASD characteristics of children in naturalistic social contexts (Constantino and Gruber 2012). We have chosen the SRS because it is a widely used screening measure for ASD that was specifically developed and validated to assess ASD symptoms across a wide a range of severity in line with the dimensional view of ASD. Therefore, the SRS is also considered useful to identify children with subtler or less severe forms of ASD, such as Pervasive Developmental Disorder Not Otherwise Specified, in addition to the more classic or severe forms, such as Autistic Disorder (Constantino and Gruber 2012). In contrast, another widely used ASD screening questionnaire, the Social Communication Questionnaire (Berument et al. 1999), was originally developed to provide an indication of the presence of an Autistic Disorder following a categorical definition, rather than to assess variations in symptoms in the broader spectrum. The present study used the school-age version for children aged 4 to 18 years and the preschool version for children aged 2.5 to 3 years. The SRS was completed by parents/caregivers as well as by teachers or day care providers. Given the stronger validation base of the parent-reported SRS, we only used the screening result of the parent-reported SRS for selection. A total raw score of 75 or higher on the parent-reported SRS has demonstrated a good sensitivity (.85) and specificity (.75) to differentiate between children with ASD and other psychiatric/developmental problems (Constantino and Gruber 2005). Additional support exists for a good reliability and convergent validity of the SRS (Constantino and Gruber 2012; Bölte et al. 2008; Charman et al. 2007; Duvekot et al. 2015). The preschool version is largely similar to the school-age version with a few items adapted to make them more appropriate for preschoolers (Constantino and Gruber 2012).

Demographic information. Information on demographic information of the selected sample was retrieved from patient files. Demographic information of the participants was also collected using online questionnaires. Ethnicity, educational level, and urbanicity were defined according to the Dutch standard classification criteria of Statistics Netherlands (2015). Ethnicity of the child was based on the country of birth of the parents and classified as Dutch, non-Dutch Western, and non-Western. The highest level of completed education of the mother was categorized into three levels: low (primary school or lower

vocational education), medium (intermediate vocational education), and high (higher vocational education or university). Because of incomplete data in patient files, maternal educational level was in 20% of the cases estimated on the basis of mapping maternal occupation to ISCED-97 educational levels (International Labour Organization 2012). Urbanicity was classified as high (≥ 1,500 addresses per square kilometer) or moderate/low (<1,500 addresses per square kilometer). Partner status was defined as cohabiting with a partner or not.

T1 In-depth assessments

Selected families for the in-depth assessments received an invitation letter accompanied by an information brochure to inform them about the study and a subsequent phone call after two weeks to invite them to participate. Parents could send back a pre-paid reply-card to indicate that they did not want to be contacted further about the study. In case of any questions concerning the study, parents were able to contact the research team and/or an independent psychiatrist. The assessment protocol was identical for the families of children with a positive or negative screen and included well-established standardized diagnostic assessments for ASD and questionnaires assessing several child, family and societal characteristics (see Table 1).

Diagnostic assessments. In line with the gold-standard procedure, a diagnosis of ASD was established based on a standardized parent interview and a standardized observational measure in combination with clinical judgment (Falkmer et al. 2013). Parents were interviewed about the child's current and past social and communicative behavior and restricted/repetitive behavior using the short version of the Developmental, Dimensional, Diagnostic Interview (3Di-sv; Santosh et al. 2009). In addition, the second edition of the Autism Diagnostic Observation Schedule (ADOS-2; De Bildt et al. 2013; Lord et al. 2012) was used as a standardized, semi-structured observation of the child's social interaction, communication and restricted/repetitive behavior. Both instruments have good criterion validity (e.g., Santosh et al. 2009; Gotham et al. 2007; Slappendel et al. 2016). The 3Di-sv and ADOS-2 were performed by two different research psychologists who were certified according to the research reliability requirements for administration and coding. They were blind for the SRS scores, the other diagnostic assessment, and any other clinical information. If parents and the child consented, the 3Di-sv was audio-taped and the ADOS-2 was video-taped. The diagnostic assessments were usually scheduled at one

of the participating centers near the participant's home address. If this was not feasible for the parents or child, we offered to administer the 3Di-sv and ADOS-2 during a home visit (12%) or administered the 3Di-sv by phone (21%). Additionally, in cases where the 3Di-sv (11%) or the ADOS-2 (35%) had already been recently conducted by a trained and certified clinician as part of the clinical evaluation at the CAMHS, the scores on these diagnostic assessments were retrieved from the patient files.

Best-estimate diagnosis. Following the diagnostic assessments, the two research psychologists who performed the 3Di-sv and the ADOS-2 indicated independently the presence (or absence) of each criterion for ASD according to the DSM-IV-TR and the DSM-5 criteria on a checklist. Subsequently, they discussed their checklists until they reached consensus about the presence of each criterion and a final ASD diagnosis on the basis of information from both the parent interview, the 3Di-sv, and the observation of the child, the ADOS-2. Thus, the consensus diagnosis was based on the information of the 3Di and ADOS, but did not always follow the classification on these instruments, as it formed an integration of information provided by both instruments. Interrater reliability between the indication of an ASD diagnosis based on the DSM-IV-TR symptom checklist that was based on information from each instrument and the consensus diagnosis was good: kappa = .81 for the checklist based on the 3Di and kappa = .70 for the checklist based on the ADOS. Children received an ASD diagnosis according to the DSM-IV-TR if they met criteria for any pervasive developmental disorder (i.e., autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified [PDD-NOS]). In addition, a diagnosis of ASD was made according to the provisional DSM-5 criteria, which were translated into Dutch and back-translated, as our data collection was ongoing during the release of the DSM-5. This procedure for establishing a best-estimate diagnosis was followed in 76% (n = 176) of the cases for which both an ADOS-2 and 3Di-sv was present (n = 231). In the other cases one or both diagnostic assessments had been performed by clinicians as part of the clinical evaluation at the CAMHS. In these cases, we used the clinical DSM-IV-TR diagnosis from the patient file established by the clinical staff, including experienced psychologists or psychiatrists, based on the standardized diagnostic assessments in combination with other information assessed during the clinical evaluation.

IQ assessment. IQ scores were obtained from the patient file if the IQ assessment had been conducted within the past two years. Frequently used IQ tests were the Wechsler Intelligence Scale for Children, third Dutch edition (WISC-III-NL; Kort 2005), the Wechsler Preschool and Primary Scale of Intelligence, third Dutch edition (WPPSI-III-NL; Hendriksen and Hurks 2009) and the Snijders-Oomen Nonverbal intelligence test (SON-R; Tellegen 1998). If no recent IQ assessment was available, an IQ assessment was conducted by the research team. For children aged six years and older, the Wechsler Abbreviated Scale of Intelligence (WASI; Axelrod 2002) was used. For children younger than six years old, the WPPSI-III-NL (in verbal children) or the SON-R (in non-verbal children) was administered.

Parent-child interaction. Parents of children aged 5 years old and younger were asked to participate in a standardized parent-child play observation. The primary caregiver and child were instructed to play together with a set of Duplo toys as they would do at home for 10 minutes, which was followed by a clean-up task and a gift-delay task. Based on video recordings of the observation, parent-child interaction was coded using a validated coding system, the third edition of the Dyadic Parent-Child Interaction Coding System (DPICS; Eyberg et al. 2009). In addition, emotional self-regulation and co-regulation strategies were coded as reported by Gulsrud, Jahromi, and Kasari (2010).

Online questionnaires. In addition to the diagnostic assessments, the primary caregiver (i.e., the parent/caregiver who spends the most time with the child) received an e-mail with a link to online questionnaires. The online questionnaires for the primary caregiver consisted of three parts: (1) questionnaires about demographic characteristics and child characteristics (i.e., ASD symptoms, daily living skills, emotion regulation, quality of life); (2) questionnaires about characteristics and well-being of the primary caregiver (i.e., mental health, ASD symptoms, social support, marital quality, parenting stress, personal growth, coping, and quality of life) and the broader social/economic impact of their child's problems (i.e., health care use and costs, productivity losses); (3) questionnaires about family functioning and characteristics of the other parent/caregiver as well as siblings of the child (see Table 1). In addition, a fourth set of questionnaires was sent to the other parent/caregiver (if present) to report on his/her own characteristics and those of the primary caregiver. In order to reduce missing data, parents had to provide an answer to each question in

order to continue. The research team was able to track online the progress of completing the questionnaires. If questionnaires were not completed after a few weeks, a researcher contacted the parent/caregiver to ask whether they had any problems filling out the questionnaires and assistance was offered if needed. A hard-copy of the questionnaires was sent if preferred.

T2 Follow-up

After approximately a year, the primary caregivers who had participated in at least the first part of the T1 questionnaires (regarding the child's characteristics) were approached for a follow-up assessment consisting of online questionnaires regarding the child's characteristics and familial/societal outcomes (e.g., family functioning, parenting behavior and health care use and costs; see Table 1). We approached only primary caregivers who had provided consent to be approached for follow-up research.

Statistical analyses

Descriptive statistics (i.e., mean, standard deviation, proportions) for the main demographic and diagnostic variables were computed for the eligible and selected sample and for the T1 and T2 participants. Descriptive statistics for the selected and participating sample were weighted by the inverse of the sampling probability.

Logistic regression analyses were used to examine predictors of attrition at T1. Participation was predicted by age and gender of the child, clinical characteristics (i.e., SRS parent and teacher total raw score, CBCL total problems score, full scale IQ, referral to secondary versus tertiary services, referral reason, and ASD diagnosis of the child before referral) and demographic characteristics (i.e., ethnicity of the child, maternal and paternal age, partner status, maternal educational level, and urbanicity). The SRS, CBCL and full-scale IQ scores were transformed to z-scores. Missing data in the predictor variables ranged from 0 to 35% (10 out of 15 variables had ≤10% missing data). Since IQ assessments were more likely to be performed as part of the clinical procedure in children who were suspected of having cognitive problems, whereas researchers performed IQ assessments in the participating children regardless of cognitive problems, we only used IQ scores derived from patient files in the analyses. To examine loss to follow-up from T1 to T2, a similar logistic regression analysis was performed predicting participation at T2 among the caregivers who completed the questionnaires at T1. In these analyses, all predictor variables had less than

10% missing data. In order to account for missing data in all attrition analyses, we used multiple imputations with 30 imputed datasets using SPSS version 20.0 (IBM, Armonk, NY).

Finally, we examined frequencies and descriptive statistics of children who were diagnosed with ASD according to the DSM-IV criteria. In addition, we examined the convergence between the DSM-IV and DSM-5 ASD diagnoses. We used multivariate analysis of variance (MANOVA) with post-hoc Games-Howell tests (because of unequal group variances) to compare core ASD symptom levels on the 3Di and ADOS of children who were diagnosed with ASD according to the DSM-IV, but not according to the DSM-5 (labelled ASD-divergent) with those of children who met criteria for ASD according to both the DSM-IV and DSM-5 (labelled ASD-convergent) and children who were classified as non-ASD according to both the DSM-IV and DSM (labelled non-ASD). There were no children who met DSM-5 criteria for ASD but not DSM-IV criteria, so this group was not included in the analysis.

Results

Sample inclusion

The flow of participants through different phases of the study is shown in Figure 2. Since it was not possible to retrieve the exact number of children in the particular age range of 2.5 to 10 years old who had been referred to the CAMHS during the screening phase, we estimated the response rate of the parent-reported SRS by dividing the total number of returned parent-reported SRS questionnaires for all children aged 1.5 to 18 years old by the total number of referrals during the six-month screening phase at each CAMHS. This resulted in a response rate of 68-81% for the parent-reported SRS among the participating CAMHS, except for one CAMHS with a response rate of 40% (see Figure 1). Because we lacked a reliable overall registry of referrals that received the screening questionnaire at this particular CAMHS, we had to estimate this response rate based on several separate registries which possibly included sites that did not sent the screening package. Therefore, this response rate should be considered with caution, probably being a conservative estimate.

In the screening phase, we received 1,281 completed parent reports of the SRS for children aged 2.5 to 10 years (*M* age = 6.9, *SD* = 2.2). Of these children,

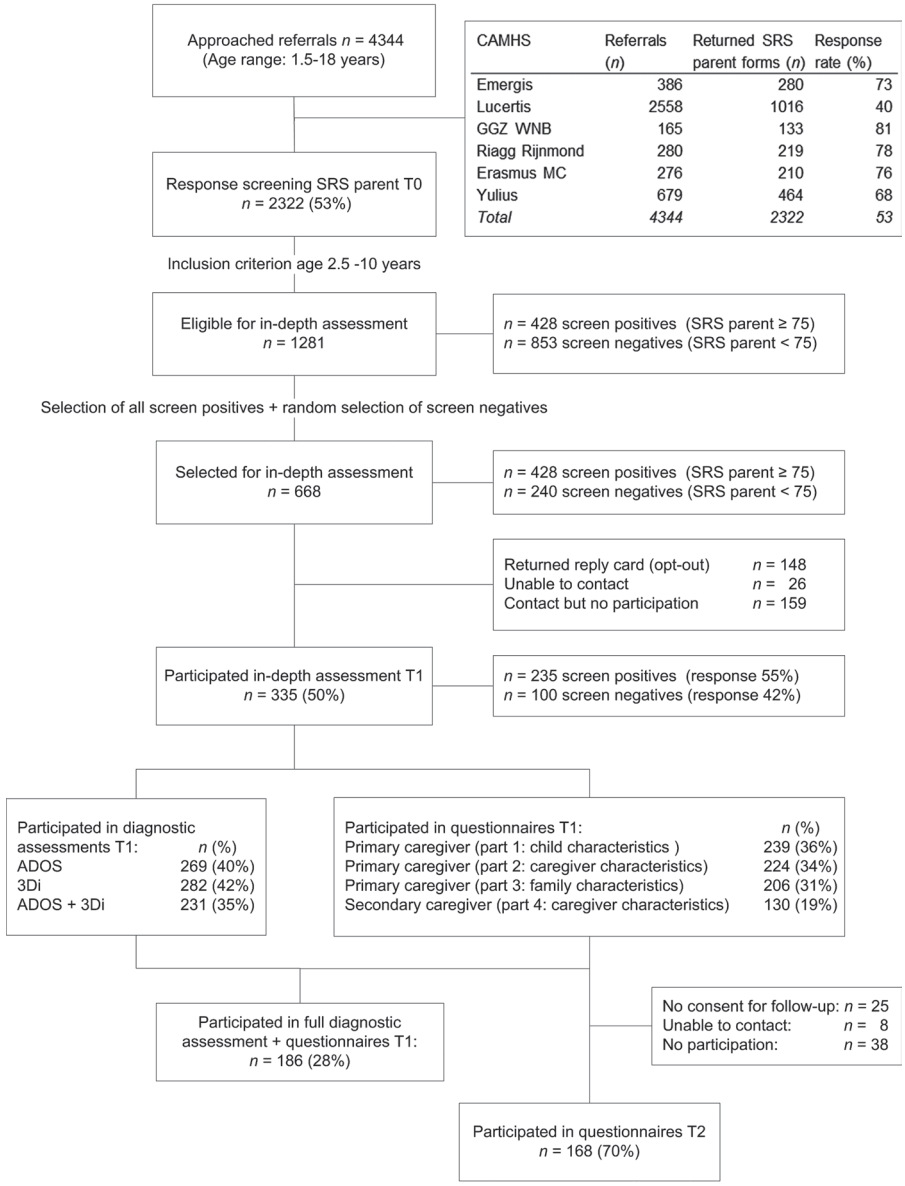

Figure 2. Flow of the participants through different phases of the study.

428 (33%) screened positive (total raw score ≥ 75) on the parent report SRS and 853 (67%) screened negative. The proportion of children with a positive screen was similar for children screened with the preschool version (35%) versus the school-age version of the SRS (33%), $\chi^2(1) = .18$, $p = .67$. The mean

age of the children who screened positive did not differ significantly from that of the children with a negative screen ($t(799.21) = -.62$, $p = .54$). A slightly higher proportion of boys had a positive screen (35%) compared with girls (30%), but this was not significant ($\chi^2(1) = 3.36$, $p = .07$). Parent reports were completed in 88% of the cases by the biological mother, in 9% by the biological father, and in 7% by another caregiver (adoptive/stepparent). For 1,089 (85%) of the children for whom a parent completed the SRS, a teacher (91%) or a day care provider/ counselor (9%) also completed the SRS.

All 428 children who scored 75 or higher on the parent-reported SRS and a random selection of 240 children who scored below this cut-off were selected for in-depth assessments. This random selection consisted of 203 out of the 789 (26%) school-age children who screened negative and 37 out of the 64 (58%) preschoolers who screened negative. Of the 668 selected children, 148 (22%) families sent back a reply card indicating that they did not want to be contacted about the study and we were unable to reach an additional 26 (4%) families. Families of 335 children participated in at least one assessment (i.e., ADOS-2, 3Di-sv or online questionnaires) at T1 (response rate 50%). For 320 children, we had at least one diagnostic assessment (ADOS-2 or 3Di-sv; response rate 48%), for the remaining 15 cases only online questionnaires were available. Full diagnostic assessment was available for 231 children (ADOS-2 and 3Di-sv; response rate 35%). Participation rates for the different parts of the online questionnaires at T1 are shown in Figure 2. For 188 cases (28%), we had full diagnostic assessments as well as questionnaire data regarding child characteristics by the primary caregiver (i.e., the first set of questionnaires). Children were on average 7.5 years old ($SD = 2.4$, range 2 to 12) at the time of the T1 diagnostic assessments and 7.9 years old ($SD = 2.4$, range 3 to 12) at the time of the T1 online questionnaires.

Of the 239 primary caregivers who completed at least the first part of the T1 questionnaires, 214 (90%) provided consent to be contacted for follow-up assessments (T2). At T2, 168 primary caregivers (70%) completed the online questionnaires. The average age of the children at the time of the T2 assessment was 8.8 years old ($SD = 2.3$, range 4 to 13).

Characteristics of the screened sample at T0 and of the participants at T1 and T2 are presented in Table 2.

Table 2. *Sample characteristics*

	Eligible T0 (*n* = 1,281)		Selected T0 (*n* = 668)		Participants T1 diagn. assessm. (*n* = 320)		Participants T1 questionnaires (*n* = 239)		Participants T2 questionnaires (*n* = 168)	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Gender, male, %	69.1%	-	69.9%	-	72.0%	-	68.9%	-	67.8%	-
Age screening (yrs)	6.9	2.2	6.9	2.3	6.8	2.3	7.0	2.3	7.0	2.2
SRS										
Parent report total	63.6	28.7	63.0	29.7	68.8	28.7	68.5	27.9	69.7	27.6
Teacher report total	63.5	30.2	62.3	31.2	66.1	30.5	64.9	30.2	66.0	30.1
CBCL										
Internalizing	61.5	10.7	61.5	9.9	63.4	9.5	63.7	9.4	63.3	9.8
Externalizing	62.4	11.4	62.4	11.0	64.0	10.4	63.9	10.7	64.2	11.0
Full scale IQ[a]	-	-	94.0	17.3	94.9	17.5	92.9	17.7	96.3	18.4
Tertiary CAMHS	15.5%	-	15.5%	-	24.3%	-	17.0%	-	20.0%	-
ASD before referral, %	-	-	8.0%	-	7.8%	-	7.3%	-	8.4%	-
Referral reason ASD, %	-	-	23.1%	-	29.5%	-	24.1%	-	28.0%	-
Child ethnicity, %										
Dutch	-	-	78.6%	-	77.7%	-	81.2%	-	89.1%	-
Non-Dutch Western	-	-	3.8%	-	4.8%	-	6.0%	-	3.2%	-
Non-Western	-	-	17.6%	-	17.5%	-	12.7%	-	7.7%	-
Maternal age	-	-	36.8	5.5	36.5	5.4	36.8	5.3	37.3	5.0
Paternal age	-	-	39.6	5.8	39.2	5.8	39.4	5.7	39.8	5.5
Maternal education, %										
Low	-	-	26.4%	-	27.9%	-	27.1%	-	26.7%	-
Medium	-	-	51.3%	-	50.5%	-	48.6%	-	47.7%	-
High	-	-	22.3%	-	21.6%	-	24.3%	-	25.6%	-
Married/cohabiting, %	-	-	75.6%	-	77.8%	-	77.9%	-	87.1%	-
High urbanicity, %	-	-	69.0%	-	67.0%	-	63.6%	-	62.8%	-

Note. Reported frequencies are unweighted; other descriptive statistics (*M*, *SD* and percentages) are weighted by the inverse of the sampling probability. diagn. assessm. = diagnostic assessment; SRS = Social Responsiveness Scale; CBCL = Child Behavioral Checklist, CAMHS = child and adolescent mental health service. [a]Only IQ scores from patient files are reported.

Attrition analyses

Since results differed for participation in the diagnostic assessments (defined as 3Di or ADOS) versus participation in the questionnaires (defined as completion of at least the first part of the online questionnaires by the primary caregiver) at T1, we present the results from these attrition analyses separately in Table 3. After accounting for other clinical and demographic characteristics, the only significant predictor of participation in diagnostic assessments at T1 was a referral to a specialized tertiary mental health service. In addition, primary caregivers were more likely to participate in the questionnaires at T1 if the child showed higher levels of internalizing problems. Participation in the online questionnaires at T2 by the primary caregivers who completed the online questionnaires at T1 was mostly determined by demographic characteristics. Caregivers who did not cohabit with a partner and caregivers who had a child of a non-Dutch ethnicity were more likely to be lost to follow-up.

ASD ascertainment

DSM-IV-TR

Within the sample of children for whom full diagnostic assessment was available (3Di-sv and ADOS-2, n = 231), 130 (56%) were assigned a best-estimate consensus diagnosis of ASD according to the DSM-IV-TR criteria (autistic disorder, n = 72; Asperger's disorder, n = 8; PDD-NOS, n = 50). Of the 130 children with a best-estimate diagnosis of ASD according to the DSM-IV-TR, 69% met criteria for an autism/ASD classification on the ADOS-2, 69% met criteria for ASD on the 3Di-sv, and 47% met ASD criteria on both instruments. For the 101 non-ASD children, these proportions were 23% for the ADOS-2, 19% for the 3Di-sv, and 5% for both. Children who did not receive an ASD diagnosis had a range of psychiatric diagnoses as reported in the patient file, with ADHD as the most common diagnosis (39%), followed by anxiety/mood disorders (11%). Of the children with ASD, 89 (69%) scored in the clinical range on at least one of the DSM-oriented subscales of the CBCL, indicating the presence of psychiatric comorbidity. Several child and family characteristics of the ASD and non-ASD sample are presented in Table 4.

Table 3. Logistic regression models predicting participation at T1 (diagnostic assessments and questionnaires) and T2 (questionnaires)

	Diagnostic assessments T1 (n = 320)			Questionnaires T1 (n = 239)			Questionnaires T2 (n = 168)		
	OR	95% CI		OR	95% CI		OR		95% CI
Child's gender (boys vs girls)	1.28	[.88,	1.87]	1.01	[.68,	1.49]	.89	[.41,	1.90]
Child's age (years)	.99	[.92,	1.08]	.98	[.91,	1.07]	.86	[.73,	1.03]
SRS parent total score	1.21	[.95,	1.55]	1.17	[.91,	1.49]	.98	[.60,	1.60]
SRS teacher total score	1.07	[.89,	1.30]	1.07	[.88,	1.30]	.95	[.64,	1.39]
CBCL internalizing	1.21	[.96,	1.53]	1.29*	[1.01,	1.64]	.89	[.56,	1.40]
CBCL externalizing	1.02	[.82,	1.27]	.96	[.77,	1.20]	1.23	[.80,	1.90]
Full Scale IQ[a]	1.05	[.86,	1.28]	1.20	[.98,	1.47]	1.04	[.73,	1.47]
CAMHS (tertiary vs secondary)	2.53***	[1.60,	3.99]	.94	[.60,	1.47]	.59	[.24,	1.41]
ASD diagnosis before referral	.64	[.36,	1.11]	.98	[.56,	1.71]	1.41	[.46,	4.31]
Referral reason (ASD vs other)	.71	[1.06,	1.06]	1.08	[.72,	1.62]	.48	[.21,	1.11]
Child's ethnicity									
Dutch	REF			REF			REF		
Western non-Dutch	1.25	[.59,	2.65]	1.96	[.92,	1.96]	.30*	[.09,	.98]
Non-Western	.93	[.57,	1.51]	.74	[.45,	.74]	.36*	[.14,	.94]
Maternal age	1.00	[.96,	1.05]	1.01	[.97,	1.01]	1.03	[.94,	1.13]
Paternal age	.99	[.95,	1.03]	1.00	[.96,	1.00]	1.06	[.98,	1.14]
Partner vs no partner	1.14	[.75,	1.72]	1.25	[.81,	1.25]	4.27***	[1.93,	9.41]
Maternal education									
Low	1.08	[.64,	1.84]	1.11	[.65,	1.11]	.44	[.17,	1.18]
Medium	1.03	[.64,	1.65]	.86	[.54,	.86]	.66	[.27,	1.59]
High	REF			REF			REF		
Urbanicity (high vs low)	.95	[.63,	1.42]	1.13	[.76,	1.13]	.96	[.47,	1.96]
Nagelkerke R^2 of model	*.12*	*[.10,*	*.15]*	*.07*	*[.05,*	*.09]*	*.24*	*[.17,*	*.31]*

Note. Non-participants are used as reference. REF = reference group, SRS = Social Responsiveness Scale; CBCL = Child Behavioral Checklist, CAMHS = child and adolescent mental health service. [a]Only Full Scale IQ scores from the patient file were used in the analyses.
* $p < .05$, ** $p < .01$, *** $p < .001$.

Table 4. Characteristics of the ASD and non-ASD sample

	ASD			Non-ASD		
	N	*M (SD) / n(%)*	Range	*N*	*M (SD) / n(%)*	Range
Child characteristics						
Gender (% boys)	130	106 (81.5%)	-	101	61 (60.4%)	-
Age at T1 (years)	130	7.6 (2.3)	2-12	101	7.7 (2.5)	3-12
Ethnicity (% Dutch)	128	104 (81.3%)	-	101	74 (73.3%)	-
Full Scale IQ	123	96.4 (17.6)	50-141	94	96.1 (17.2)	50-130
Intellectual disability[a]	127	17 (13.4%)	-	100	9 (9%)	-
SRS parent total	130	93.3 (26.0)	26-152	101	74.8 (28.3)	16-136
SRS teacher total	114	75.6 (30.6)	4-153	90	62.8 (26.1)	12-121
CBCL Internalizing problems	117	67.1 (9.8)	34-88	99	66.0 (9.4)	34-87
CBCL Externalizing problems	117	67.1 (10.6)	40-97	99	68.1 (10.3)	44-92
CBCL clinical cut-offs on DSM-scales:	117			99		
Affective Problems		53 (45.3%)	-		42 (42.4%)	-
Anxiety Problems		40 (34.2%)	-		30 (30.3%)	-
Somatic Problems[b]		11 (13.6%)	-		9 (13.4%)	-
ADHD Problems		49 (41.9%)	-		43 (43.4%)	-
Oppositional Defiant Problems		48 (41.0%)	-		50 (50.5%)	-
Conduct Problems[b]		27 (33.3%)	-		31 (45.6%)	-
ADOS Social affect CSS	130	5.3 (2.5)	1-10	101	2.5 (1.9)	1-8
ADOS Restricted/repetitive CSS	130	4.4 (2.8)	1-10	101	2.5 (2.2)	1-10
ADOS Total CSS	130	6.1 (2.4)	1-10	101	3.2 (2.3)	1-10
3Di Reciprocal social interaction	130	13.0 (5.0)	2-26	101	6.8 (5.0)	0-20
3Di Communication	130	12.5 (4.4)	1-23	101	8.0 (4.7)	0-20
3Di Repetitive/stereotyped	130	3.1 (2.3)	0-11	101	1.4 (1.6)	0-8
Family characteristics						
Maternal education (% high)	122	29 (23.8%)	-	96	21 (21.9%)	-
Two-parent household, %	128	108 (84.4%)	-	100	76 (76.0%)	-
Urbanicity (% high)	124	87 (70.2%)	-	101	66 (66.7%)	-
Parenting stress (OBVL)	97	61.5 (15.2)	34-105	79	59.9 (15.2)	35-100
Family functioning (FAD)	92	21.3 (4.8)	12-34	74	21.6 (5.6)	12-35

Note. Diagnosis of ASD was based on the DSM-IV-TR criteria. 3Di = Developmental, Dimensional and Diagnostic interview; ADOS = Autism Diagnostic Observation Schedule; CBCL = Child Behavioral Checklist; CSS = Calibrated severity scores; FAD = Family Assessment Device; OBVL = Opvoedingsbelastingsvragenlijst [Parenting stress questionnaire]; SRS = Social Responsiveness Scale; VGFO = Vragenlijst Gezinsfunctioneren voor Ouders [Questionnaire family functioning for parents].

[a]Intellectual disability was defined as an Verbal IQ, Nonverbal IQ or Full scale IQ < 70 or a DSM-IV-TR axis classification of intellectual disability (code 317, 318, 319).

[b]Only present in the CBCL/6-18 version.

DSM-5

For a subsample of 176 children for whom the research psychologists performed both diagnostic assessments, we also formed a best-estimate consensus diagnosis of ASD according to the DSM-5 criteria: 65 (37%) were diagnosed with ASD according to the DSM-5. In 81% of the cases (65 ASD and 78 non-ASD), the DSM-IV-TR and DSM-5 diagnosis agreed (Kappa = .64). However, for 33 children (19%) the DSM-IV-TR and DSM-5 disagreed: these children met ASD criteria according to the DSM-IV-TR but not according to the DSM-5. Of the children with a DSM-IV diagnosis of autistic disorder, 92% (56 out of 61) also had a diagnosis of ASD according to the DSM-5. In addition, 4 of the 5 (80%) children with a DSM-IV diagnosis of Asperger's syndrome had a DSM-5 ASD diagnosis. In contrast, of the children with a DSM-IV diagnosis of PDD-NOS, only 16% (5 out of 32) met criteria for a DSM-5 ASD diagnosis.

As would be expected, there were significant differences in ADOS and 3Di scores between children who met DSM-IV but not DSM-5 criteria for ASD (ASD-divergent), children who met both DSM-IV and DSM-5 criteria (ASD-convergent), and children who were classified as non-ASD according to both DSM-IV and DSM-5 (non-ASD), $F(10, 340) = 19.76$, $p < .001$. As shown in Figure 3, the ASD-divergent had significantly lower levels of restricted and repetitive behaviors (RRB) on the ADOS and 3Di than the ASD convergent group. The RRB scores of the ASD-divergent group were similar to those of the non-ASD group. On the ADOS, the social impairment scores of the ASD-divergent group were not different from those of the ASD-convergent group; both groups had higher scores than the non-ASD group. On the 3Di, the highest levels of social interaction and communication impairments were found in the ASD-convergent group, followed by the ASD-divergent group, and then the non-ASD group.

Discussion

The Social Spectrum Study is prospective cohort of clinically referred children enriched for children with ASD that provides the opportunity to examine a wide range of child, family, and societal factors in relation to ASD symptomatology. This paper described the aims and methods of this study and provided some details regarding attrition and characteristics of the participating children and their families.

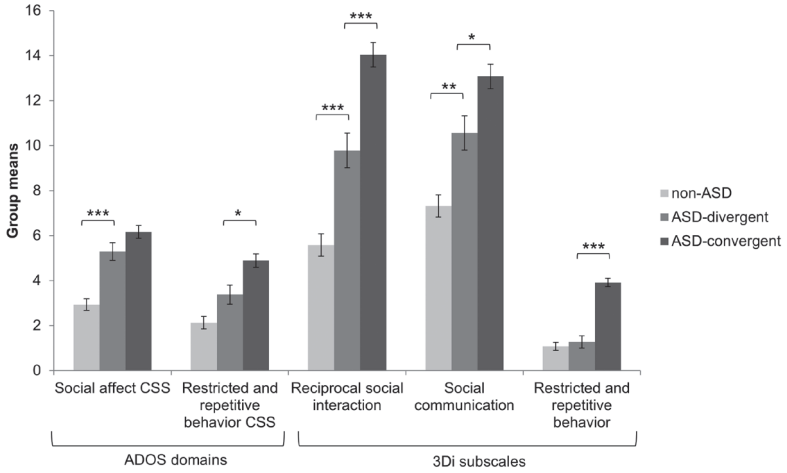

Figure 3. Mean scores on the Autism Diagnostic Observation Schedule (ADOS) and the Developmental, Dimensional and Diagnostic Interview (3Di) in children who met DSM-IV but not DSM-5 criteria for ASD (ASD-divergent) versus children who met both DSM-IV and DSM-5 criteria (ASD-convergent) and children who were classified as non-ASD according to both DSM-IV and DSM-5 (non-ASD). CSS = Calibrated Severity Score. Error bars represent standard errors. Asterisk indicate significant group differences. * p <.05, ** p <.01, *** p <.001.

Attrition

Whereas participation in the first assessments was mainly determined by clinical characteristics (i.e., referral to a tertiary service, higher levels of internalizing problems), participation in the questionnaires by primary caregivers at the one-year follow-up was mainly determined by demographic characteristics (i.e., not having a partner, non-Dutch ethnicity of child). A likely explanation for the finding that children who had been referred to tertiary mental health services were more likely to participate in the diagnostic assessments at T1, is that these assessments were more often performed as part of the clinical evaluation in tertiary than in secondary CAMHS. In addition, caregivers of children with higher levels of internalizing problems may have been more likely to complete the questionnaires at T1 because they could better relate to the relevance of the study than caregivers of children with less problems. Moreover, internalizing problems might place less burden on caregivers than other types of psychopathological problems (Davis and Carter 2008) and therefore interfere less with participation. Attrition at the one-year follow-up (T2) of caregivers who did not cohabit with a partner could reflect that these caregivers experienced greater difficulty in finding the time to complete the questionnaires in the previous assessment. In addition, caregivers of children

from other ethnicities may have been less likely to participate in the follow-up because they experienced more difficulties in completing the questionnaires due to problems with the language or topics discussed. In contrast to several general population studies (Stoltenberg et al. 2010; Jaddoe et al. 2012), we did not find that lower maternal education increased the risk of attrition during any phase of the study.

Characteristics of the sample

Our sample is relatively high-functioning in terms of intellectual ability. Only 13% of the ASD sample had an intellectual disability compared to an estimate of 32-55% in recent epidemiological studies (Baird et al. 2006; Baio 2012). Consistent with the literature (Simonoff et al. 2008), we found high rates of clinically elevated co-occurring psychiatric problems based on a parent-reported questionnaire, ranging between 33 and 45% for affective problems, anxiety problems, ADHD problems, oppositional defiant problems and conduct problems. At first sight, children with ASD seemed to have similar levels of parenting stress and family functioning as the non-ASD group. This could be explained by the fact that ASD is a very heterogeneous group showing a large variation in ASD symptom severity, intellectual functioning and co-occurring emotional and behavioral problems; characteristics that are shared with the comparison group (Hayes and Watson 2013). Moreover, some studies suggested that parenting stress and family functioning in families of children with ASD are particularly related to co-occurring emotional and behavioral problems (e.g., Herring et al. 2006; Lecavalier et al. 2006; Davis and Carter 2008). That is why it is important that we also assessed variation in ASD symptoms and emotional/behavioral problems on a dimensional scale. In addition, parent characteristics and resources, such as being a single parent, social support, and coping strategies need to be accounted for as well (Zaidman-Zait et al. 2016; Karst and Van Hecke 2012). In future papers, we will more thoroughly investigate these complex interrelations between child, parent, and family characteristics. This could help to identify families who need interventions to promote more optimal family functioning, which in turn may lead a more optimal child development. We cannot yet provide information about the societal factors we assessed (e.g., health care costs, productivity losses), as this data is still being processed.

Although this was not a specific aim of this study, in light of the discussion around the sensitivity of DSM-5 criteria for ASD (e.g., Tsai 2012), it is interesting to note that in our study a group of children with ASD according to the DSM-IV criteria did not meet DSM-5 criteria for ASD. This particularly concerned children with a DSM-IV PDD-NOS diagnosis, of which only 16% also had a DSM-5 ASD diagnosis. In contrast, almost all (92%) children with a DSM-IV diagnosis of autistic disorder had a DSM-5 ASD diagnosis. Consistently, Smith et al. (2015) reported in a systematic review that in half of the studies less than 25% of the children with PDD-NOS met DSM-5 criteria for ASD, whereas rates were much higher for children with an autistic disorder. Compared to children with an ASD diagnosis according to both the DSM-IV and DSM-5, children with a DSM-IV ASD diagnosis who did not meet DSM-5 ASD criteria were characterized by relatively low levels of RRB symptoms and milder levels of social communication impairment in our study. As they still showed significant impairments in the social domain on the ADOS and 3Di compared to the non-ASD group, these children might be eligible for a diagnosis of a Social Communication Disorder (SCD). This new and controversial diagnostic category describes social communication impairments similar to those of ASD without the RRB symptoms (American Psychiatric Association 2013). Although we did not evaluate children using the SCD criteria in our study, a previous study found that many children who did not maintain an ASD diagnosis using DSM-5 criteria met criteria for SCD (Kim et al. 2014).

Strengths and limitations

A particular strength of this study is that we systematically screened all children referred to one of six mental health services for ASD and subsequently performed standardized diagnostic assessment in both screen-positive and screen-negative children. Using this ascertainment method, we aimed to overcome certain biases that may be present when recruiting children with an established diagnosis. Besides the delineation of a well-characterized ASD sample using categorical diagnostic instruments, we also captured a wide range of ASD symptom severity in the total cohort of clinically referred children using continuous measures. Another strength is that we used various measures and informants to assess a wide range of characteristics regarding the child, family and society, allowing the investigation of a broad scope of topics. Lastly, we conducted a follow-up assessment that enables the investigation of longitudinal relations.

Findings from this study should also be interpreted in the light of some limitations. In addition to evidence of selective attrition, possible biases, which we could not investigate, may already have been present in the referral process. Thus, findings from this cohort cannot be generalized to children at risk for ASD who are not referred to mental health services (i.e., the general population). In addition, participation in full assessments was rather low (28%), limiting the number of children with a consensus diagnosis of ASD for whom we have in-depth information on a large variety of child, family, and societal factors. However, as we stated earlier, it is also of interest to investigate these factors in our larger cohort, including children with subclinical levels of ASD symptomatology. Finally, because some of the diagnostic assessments were integrated in the clinical procedure, we could not follow the same procedure for establishing a best-estimate diagnosis for all participants in the study.

Conclusion

In conclusion, we obtained a cohort of clinically referred children that includes a well-characterized sample of children with ASD as well as allows a dimensional approach of examining relationships in a broader group of clinically referred children with varying levels of ASD symptoms. Given the wide range of child, family and societal factors assessed, this study has the potential to contribute to the understanding of (1) the performance of screening and diagnostic instruments for ASD; (2) the relations between ASD symptomatology and other developmental/mental health problems; (3) the characteristics of families of children with ASD symptomatology; (4) the societal impact of ASD symptomatology. We invite all researchers interested in collaboration to contact Kirstin Greaves-Lord (k.greaves-lord@erasmusmc.nl).

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Chapter 3

The Screening Accuracy of the Parent and Teacher-Reported Social Responsiveness Scale (SRS): Comparison with the 3Di and ADOS.

Duvekot, J., van der Ende, J., Verhulst, F. C., & Greaves-Lord, K.

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Abstract

The screening accuracy of the parent and teacher-reported Social Responsiveness Scale (SRS) was compared with an autism spectrum disorder (ASD) classification according to 1) the Developmental, Dimensional and Diagnostic Interview (3Di), 2) the Autism Diagnostic Observation Schedule (ADOS), 3) both the 3Di and ADOS, in 186 children referred to six mental health centers. The parent report showed excellent correspondence to an ASD classification according to the 3Di and both the 3Di and ADOS. The teacher report added significantly to the screening accuracy over and above the parent report when compared with the ADOS classification. Findings support the screening utility of the parent-reported SRS among clinically referred children and indicate that different informants may provide unique information relevant for ASD assessment.

Introduction

Diagnosing autism spectrum disorder (ASD) is a complex process due to the variability in the clinical presentation of children with ASD, along with the symptom overlap and co-occurrence of ASD with other disorders (Lai et al. 2014). The diagnostic assessment for ASD has been advanced by the development of reliable and valid standardized diagnostic instruments (Ozonoff et al. 2005; Filipek et al. 1999). The current gold standard procedure for diagnosing ASD includes a standardized interview with parents, e.g. the Autism Diagnostic Interview-Revised (ADI-R; Lord et al. 1994) or the Developmental, Dimensional and Diagnostic Interview (3Di; Skuse et al. 2004), and a standardized clinical observation of the child, e.g. the Autism Diagnostic Observation Schedule (ADOS; Lord et al. 2012). However, the use of these instruments is time-consuming and expensive, and requires trained experts, making it necessary to carefully identify children who require in-depth diagnostic assessment using these standardized diagnostic instruments. To help clinicians make more informed decisions about which children need in-depth diagnostic assessment for ASD, several screening questionnaires for ASD have been developed that are relatively quick and easy to administer.

One ASD-specific screening questionnaire that is widely used in clinical practice as well as in research is the Social Responsiveness Scale (SRS; Constantino and Gruber 2012). The SRS consists of 65 items that can be scored in 15 minutes by a parent or teacher. One of the advantages of the SRS is that it has been designed to assess social impairment associated with ASD as rated by multiple informants on a Likert response scale. Therefore, the SRS is considered suitable to capture autistic characteristics in varying degrees and to provide a severity index of autistic social impairment (Constantino and Gruber 2012). Although the SRS has also been validated for use in the general population, it is more generally applied as a screening instrument in high-risk populations, i.e. clinically referred individuals. Several studies have supported the ability of the parent-reported SRS to discriminate between children with ASD and those with other psychiatric disorders (e.g. Kamio et al. 2013a; Bölte et al. 2011; Charman et al. 2007; Constantino and Gruber 2005).

Although using multiple informants is considered important in the assessment of ASD (Kim and Lord 2012; Ozonoff et al. 2005) and in child psychiatry in general (Kazdin 2005), little is known about the contribution of

information obtained from teachers over and above the information obtained from parents in the assessment of ASD. It is well established that different informants often do not agree in their ratings of child behavior, since parents and teachers see the child in different contexts and have different perspectives (van der Ende et al. 2012; Achenbach et al. 1987; De Los Reyes and Kazdin 2005). Therefore, parents and teachers are considered to provide unique and complementary information. Parents are generally considered important information sources of their child's behavior, as they experience how their child behaves in various circumstances and develops over time (e.g. Richters 1992). For the assessment of some childhood disorders, such as ADHD, information from teachers in addition to parents is considered a necessary component, because the symptoms, such as inattentiveness and hyperactivity, should be present in multiple settings and may be particularly visible and disrupting in the school setting (Pelham et al. 2005). For the assessment of ASD, teachers may also be a valuable source of information about the social functioning of the child as they regularly observe how the child interacts with other children in the school setting. Moreover, teachers have the expertise and opportunity to compare the behavior of the child with that of many other children, which may allow them to better distinguish between typical and atypical behavior (Constantino et al. 2007).

Despite the potential additional value of information obtained from teachers in the assessment of ASD, only few studies have examined the screening accuracy of the teacher-reported SRS. Constantino et al. (2007) found that when both a parent and a teacher rated the child as having a SRS T-score of 60 or higher, the likelihood that the child had an ASD diagnosis was very high (96.8%). Another study that contrasted children with ASD and typically developing children found that combined use of the parent and teacher report improved the screening accuracy of the SRS, but the improvement was very small compared with the use of the parent report alone (Fombonne et al. 2012). In a small sample (n = 48) of children who were referred to an ASD-specific clinic, the teacher-reported SRS corresponded better to an ASD diagnosis than did the parent report (Aldridge et al. 2012). In contrast, other studies reported that, although the teacher-reported SRS demonstrated acceptable screening accuracy, the parent report was more accurate in identifying children with ASD than the teacher report (Kamio et al. 2013b; Schanding et al. 2012). Although these studies provide some indication that combining the parent

and teacher-reported SRS may improve the identification of children with ASD, the generalizability of these results to clinical practice is limited by sample characteristics: a research sample of children who had already been diagnosed with ASD (Constantino et al. 2007; Schanding et al. 2012; Kamio et al. 2013b), a comparison group of typically developing children (Fombonne et al. 2012), and a small sample size (Aldridge et al. 2012). Therefore, more research is needed to estimate the utility of the teacher-reported SRS in addition to the parent-reported SRS in children who are consecutively referred for various mental health problems, which more closely represents the population in which ASD screening instruments are commonly used.

The present study aimed to extend previous findings by investigating the screening accuracy of the parent and teacher-reported SRS in children aged 4-10 years who had been consecutively referred for a variety of mental health problems (e.g. behavioral, emotional or developmental problems) to one of six mental health care centers, including secondary and tertiary mental health care services. We examined whether the SRS is able to identify children who have a high likelihood ('high risk') of receiving an ASD classification according to two widely used standardized diagnostic instruments: the 3Di and the ADOS. Since evaluation using these instruments is valuable, it would be useful if the SRS can assist in targeting a high-risk group who need further diagnostic evaluation and preventing unnecessary diagnostic evaluations for children with a low risk of being classified as ASD according to these instruments. Although we acknowledge that a clinical diagnosis of ASD also includes a clinical judgment, we did not take this into account given its limited objectivity and larger variability across centers and clinicians (Lord et al. 2012). The first aim of this study was to examine the screening accuracy of the parent report alone in predicting ASD classifications according to the 3Di and ADOS. Consistent with previous studies, we expected good correspondence of the parent-reported SRS scores to the ASD classifications according to *one* or *both* of these diagnostic instruments. Our second aim was to examine the additional contribution of the teacher-reported SRS over and above the parent report in the identification of children who are classified as possibly having ASD according to the 3Di, the ADOS, and *both* the 3Di *and* ADOS. As suggested in previous studies, we hypothesized that using both informants would improve the utility of the SRS to identify children with possible ASD according to these diagnostic instruments (e.g. Constantino et al. 2007).

Methods

Study design

The present study was part of the Social Spectrum Study, a prospective multicenter study investigating interrelationships between ASD and behavioral characteristics and family factors in clinically referred children at risk for ASD and their family members. The study was approved by the local medical ethics committee and the participating mental health care centers (MEC-2011-078).

The target population of the present study was children aged 4 to 10 years old who were consecutively referred to one of six participating mental health care centers in the south-west of the Netherlands during an interval of six months at each site, within a period from April 2011 to July 2012. The participating mental health care centers covered rural as well as urban areas. Of the study population, 87% of the children were referred to secondary mental health care services, 8% to tertiary ASD-specialized mental health care services, and 5% to other tertiary mental health care services. The children were referred for a variety of mental health problems, including ASD, internalizing/externalizing disorders, and more general developmental/learning difficulties. Thus, the target population was representative of children who are referred to mental health care, which we consider a good reflection of the population in which the SRS is used to help to determine which children are in need for ASD-specific diagnostic assessment.

We used a two-phase sampling design in which we oversampled the children who screened positive on the parent-reported SRS to participate in an ASD-specific diagnostic assessment (e.g., Dunn et al. 1999). First, as part of the routine procedure for clinical evaluation, the SRS was completed by parents and teachers before the first intake appointment at the mental health care center. Second, we selected all children with a positive screen based on the parent-reported SRS (cut-off: total raw score ≥75) and a random selection of children with a negative screen result (total raw score < 75 on the parent-reported SRS) and invited these children and their families to participate in further assessments. The assessments included a standardized parent interview (3Di), a standardized observation of the child (ADOS), and a standardized test to assess intelligence quotient (IQ). During this phase, written consent was obtained for all of these assessments.

Sample

SRS parent response rate by center:

Mental health care center	Approached	Returned SRS forms	Response rate (%)
Emergis	386	280	73%
Lucertis	2558	1016	40%
GGZ WNB	165	133	81%
Riagg Rijnmond	280	219	78%
Erasmus MC-Sophia	276	210	76%
Yulius	679	464	68%
Total	4344	2322	53%

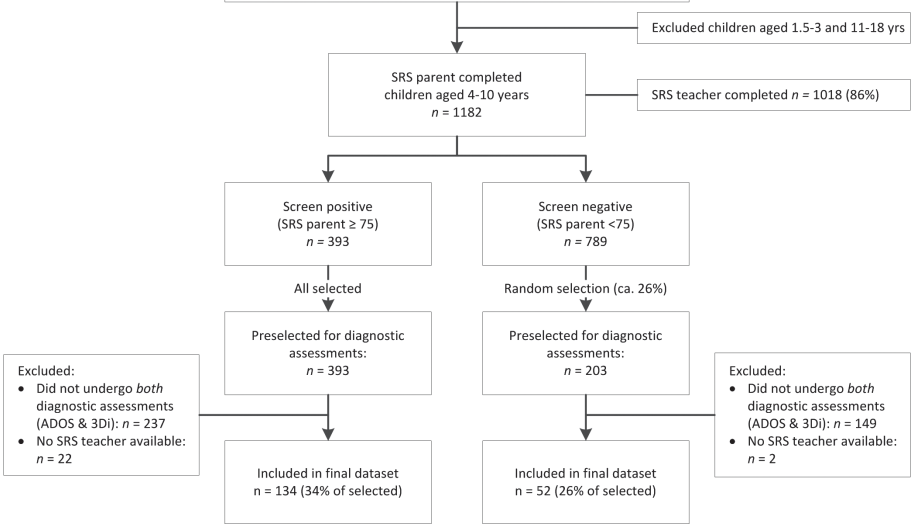

Figure 1. Participant flow chart

Figure 1 shows the flow of the participants through the different phases of the study. The SRS was sent out to 4,344 children in total. The response rate for the parent-reported SRS ranged from 40% to 81% across centers, with an overall response rate of 53 % (n = 2,322). Only children aged 4 to 10 years old were eligible for the present study. Of these children, we received 1,182 completed parent reports (mean age 7.2, SD = 1.9; 68% male). Of 1,018 (86%) of the children for whom a parent completed the SRS, a teacher also completed the SRS. Of the 1,182 children with a completed parent-reported SRS, 393 (33%) screened positive (total raw score ≥75 on the parent report) and 789 (67%) screened negative (total raw score < 75 on parent report). The mean age of the children who screened positive did not differ significantly from that of the children with a negative screen (t(730.64) = -1.06, p = .29), nor did the gender proportion (χ^2(1) = 2.55, p = .11).

Based on the scores on the parent-reported SRS, we selected 596 children aged 4-10 years for further assessments, including the 3Di, ADOS, and IQ assessment: all 393 children who screened positive and a random selection of 203 children who screened negative (26%). The assessments took place at an average of 10 months (*SD* = 4) after the SRS was completed. The final sample contained 186 children (134 screen-positives and 52 screen-negatives on the parent-reported SRS) for whom a teacher-reported SRS, the 3Di, and the ADOS were available. The final sample (*n* = 186) was weighted in order to represent the total eligible sample (*n* = 1,182; see the Statistical Analysis section for a description of the weighing procedure).

To examine possible selective attrition between the screening phase and follow-up assessment phase, we compared the selected children who were included in the final sample (*n* = 186) with the selected children who were not (*n* = 410). A larger proportion of the screen-positive children was included in the final sample (134/393 = 34%) than the proportion of screen-negative children (52/203: 26%; $\chi^2(1) = 4.49$, $p = .03$). The screen-positive children who were included were younger (7.0 vs 7.5, $t(391) = 2.2$, $p = .03$), but did not significantly differ with respect to gender ($\chi^2(1) = 1.88$, $p = .17$), parent-reported SRS scores ($t(391) = -1.67$, $p = .10$), and teacher-reported SRS scores ($t(344) = -1.04$, $p = .30$). There were no significant differences between the screen-negative children who were included and those who were not included with regard to gender ($\chi^2(1) = 1.38$, $p = .24$), age ($t(201) = -1.66$, $p = .10$), parent-reported SRS scores ($t(201) = -.22$, $p = .83$), and teacher-reported SRS scores ($t(179) = -.83$, $p = .41$).

Measures

Screening

The Social Responsiveness Scale (SRS) is a questionnaire that assesses the severity of social impairment related to ASD (Constantino and Gruber 2012, 2005). The child version for children aged 4 to 18 years old contains 65 items that are scored on 4-point scale from 0 (not true) to 3 (almost always true) by parents or teachers who have experience with the child in everyday social settings. The total sum score of 65 items, which can range from 0 to 195, is used for screening purposes (Constantino and Gruber 2005). A higher total score reflects more social impairment. The total score can be converted to a T-score, based on norms for gender and rater type, but to increase comparability

between research studies it is recommended to use the raw total score for research (Constantino and Gruber 2005). Moreover, T-scores for the Dutch version of the teacher report of the SRS do not yet exist. Therefore, in the present study we used total raw scores for both the parent-reported and the teacher-reported SRS. Since we used total raw scores and the questions of the child version are the same for both the original SRS (Constantino and Gruber, 2005) and the SRS-2 (Constantino and Gruber, 2012), the findings of our study are applicable to both the original SRS and the SRS-2. In the present study, the total raw cut-off score of 75 on the parent-reported SRS was chosen to screen for ASD, which was found to differentiate between children with ASD and children with other psychiatric disorders with a sensitivity of .85 and a specificity of .75 (Constantino and Gruber 2005).

Consistent with validation studies in other countries, the Dutch version of the parent-reported SRS demonstrated high internal consistency (Cronbach's alphas ranged from .92-.95), good convergent validity (r = .63 with the ADI-R) and was able to differentiate between children with ASD and children from the general population (Roeyers et al. 2011). Previous studies have shown moderate to good agreement between the parent and the teacher-reported SRS scores (r = .24-.82; Constantino et al. 2003; Schanding et al. 2012; Constantino et al. 2007; Kamio et al. 2013b; Fombonne et al. 2012; Constantino et al. 2000; Kanne et al. 2009; Reszka et al. 2014). In the current study, the correlations between the parent and teacher-reported SRS scores were r = .28 (p < .01, n = 186) in the final sample and r = .29 (p < .001, n = 1,018) in the total screened sample. The Cronbach's alphas in the total screened sample for the total scale were .95 for the parent report as well as for the teacher report.

Assessment

The *Developmental, Dimensional and Diagnostic Interview* (3Di; Skuse et al. 2004) is a standardized, computerized parent interview during which parents are asked about their child's current and past social communication and interaction, as well as about restricted, repetitive behaviors or interests that are characteristic of children with ASD. The 3Di has been designed according to the current conceptualization of ASD as a dimensional disorder that is often present in individuals with normal IQ levels. The 3Di covers the same ASD symptoms as the ADI-R and reflects the classification algorithm of the ADI-R, but the structure of the interview is different. The ADI-R requires the interviewer

to integrate information from several questions into one summary score for a particular characteristic, e.g. the range of facial expressions to communicate (Lord et al. 1994). In contrast, the 3Di uses short focused questions (e.g. separate questions for looking sad, guilty, embarrassed) that are each individually scored and combined using a computer algorithm (Skuse et al. 2004). In this way, the interview structure of the 3Di has been designed to reduce the influence of the subjectivity of the interviewer, which intends to enhance the reliability of its scoring and eases its administration (Skuse et al. 2004). While the original complete interview of the 3Di contains a 122-item ASD module, more recently a shorter 53-item ASD module became available that showed good agreement with the original ASD module (Santosh et al. 2009). Both versions demonstrated good agreement with the ADI-R (Skuse et al. 2004; Santosh et al. 2009). The short version has also demonstrated good ability to differentiate between children diagnosed with ASD and typically developing children (Chuthapisith et al. 2012). The present study used the short ASD module of the 3Di. A computer algorithm produces scores on the scales social reciprocity, verbal and non-verbal communication, and restricted/repetitive behaviors, which we summed up to a total score in the current study. In addition, the algorithm produces a DSM-IV-TR classification of autistic disorder, Asperger's syndrome, atypical autism versus non-ASD, which we collapsed into ASD versus non-ASD. Preliminary findings from our data demonstrated a fairly good sensitivity (.75) and specificity (.74) for the Dutch version of the 3Di with respect to a DSM-IV-TR clinical ASD diagnosis.

The *Autism Diagnostic Observation Schedule* (ADOS; Lord et al. 2012; Lord et al. 1999) is a semi-structured and standardized observation of the child's social interaction, play/imaginative use of materials, and restricted and repetitive behaviors that is used as part of the diagnostic assessment of ASD. The ADOS has different modules that can be used for individuals with different levels of expressive language. In the present study, we used Module 1 ($n = 2$), Module 2 ($n = 22$) and Module 3 ($n = 162$). Children were classified as having ASD (Autism + ASD combined) or not according to the ADOS using the revised algorithms as described in the second edition of the ADOS manual (ADOS-2; de Bildt et al. 2013; Lord et al. 2012). This revised algorithm has been found to increase comparability between modules and to improve diagnostic validity (Gotham et al. 2007; Gotham et al. 2008). The validity of the revised algorithms has been confirmed in Dutch samples (de Bildt et al. 2009b; Oosterling et al. 2010).

The 3Di and ADOS were always administered by two different clinicians or researchers who had met research requirements of standardized administration and scoring reliability. All researchers were blind to the SRS scores when they performed the 3Di (*n* = 170, 91%) and the ADOS (*n* = 146, 79%). In a minority of cases, a clinician had performed the 3Di (*n* = 16, 9%) or the ADOS (*n* = 40, 21%) as part of the routine clinical evaluation. In these cases, we cannot guarantee that the clinician performing the diagnostic assessment was blind to the SRS scores. However, a priori analyses showed that the agreement between the SRS and the diagnostic assessments was not higher in the cases where a clinician performed the assessment than in the cases where it was performed by a researcher (details available upon request). Therefore, we regard it unlikely that a possible lack of blinding to the SRS scores in this small subsample biased the results.

We compared the SRS with three ASD classifications according to these standardized diagnostic instruments, used separately and combined: 1) an ASD classification according to the 3Di, 2) an ASD classification according to the ADOS, and 3) an ASD classification according to *both* the 3Di *and* ADOS. Thus, the first two classifications reflect whether the child was classified as having ASD when considering a single instrument, whereas the third—more stringent—classification reflects whether a child meets the criteria for an ASD classification according to *both* instruments. As shown in Table 1, more children were classified as having ASD according to the ADOS (35%) than according to the 3Di (23%). Only 11% were classified as having ASD according to both instruments. The overall percent agreement between the 3Di and ADOS classification was 63%, with a kappa of .20 (p = .005), indicating only a slight agreement (Cicchetti 2001). In comparison, the ADI-R and ADOS have also been reported to show poor to moderate agreement (e.g. de Bildt et al. 2004; Ventola et al. 2006; Le Couteur et al. 2008; Lord & Kim, 2012).

Intelligence (IQ) was assessed using various tests: in 50% of the children with the Wechsler Intelligence Scale for Children, third Dutch edition (WISC-III-NL; Kort 2005), in 28% with the Wechsler Abbreviated Scale of Intelligence (WASI; Axelrod 2002), in 15% with the Wechsler Preschool and Primary Scale of Intelligence, third Dutch edition (WPPSI-III-NL; Hendriksen and Hurks 2009), in 5% with the Snijders-Oomen Nonverbal Intelligence test (SON-R; Tellegen 1998), and in 2% using other intelligence tests. Total IQ score was available for 174 children (94% of the final sample).

Statistical analyses

For descriptive purposes, we tested whether children classified as 'ASD' and 'non-ASD' differed in several demographic and ASD characteristics using *t*-tests for continuous variables and χ^2-tests for categorical variables. In addition, we tested whether parents and teachers rated boys and girls differently using *t*-tests.

In order to investigate our first aim, the screening accuracy of the parent-reported SRS, we calculated sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) for the parent-reported SRS using the total raw cut-off score of 75 in relation to three ASD classification groups: 1) ASD classification according to the 3Di, 2) ASD classification according to the ADOS, and 3) ASD classification according to *both* of these instruments.

In order to investigate our second aim, whether the teacher-reported SRS added to the prediction of ASD classifications over and above the parent report, firstly we performed logistic regression analyses predicting the three ASD classifications with only the parent-reported total SRS score in the model in a first step and then the teacher-reported total SRS score added to the model in a second step. Subsequently, we used the predicted probabilities that were the result from the logistic regression analyses as input in a receiver operating characteristics (ROC) analysis. The area under the curve (AUC) of the ROC analysis reflects the probability that a randomly selected individual with the disorder has a higher score than a randomly selected individual without the disorder. It provides an indication of the overall screening accuracy irrespective of a specific cut-off point and is therefore a good measure to compare different tests (Hunink and Glasziou 2001). We used the method of Hanley and McNeil (1983) to test whether the AUCs of the combined parent and teacher report were higher than those of the parent report alone, while taking into account that the AUCs were correlated because they were based on the same sample.

The estimation of the weighted AUCs of the ROC curves and accompanying standard errors were calculated using bootstrap analyses in R (R Core Team 2014). All other analyses were conducted using the complex samples module in SPSS 20 (IBM Corporation 2011). This module uses inverse probability weighting in order to compute correct population estimates and standard errors for complex designs that include unequal sampling probabilities and differential response rates. Not correcting for the differential sampling probabilities and response rates could yield biased screening accuracy estimates because of a

verification bias (Hunink et al. 1990; Begg and Greenes 1983). In order to correct for a verification bias in the present study, we weighted each case with the inverse of the probability that the case was included in the final dataset (inverse probability weighting [IPW]; Seaman and White 2013). First, we calculated the probability that a child from the total screened sample was selected *(p1)*: for the children with a positive screen this probability was 100% and for the children with a negative screen the probability was on average 26%. Then, we conducted logistic regression analysis to predict the probability that a selected child was included in the final dataset (n = 186) using the parent-reported SRS total score as predictor (age and gender were not significant predictors). The predicted probability of this analysis *(p2)* was multiplied with the selection probability (*p1)* to calculate the final inclusion probability. Finally, each case in the final sample was weighted by the inverse of this inclusion probability (1/]*p1*p2*]), so the estimates would reflect those of the total screened sample (n = 1,182).

An alpha level of .05 was used for all statistical analyses. The screening accuracy indices (sensitivity, specificity, PPV, NPV, and AUC) were interpreted according to the following guidelines: 90-100% = excellent; 80-89% = good; 70-79% = fair; and <70% = poor (Cicchetti et al. 1995).

Results

Sample characteristics

Table 1 presents the demographic and ASD characteristics of the weighted sample split into 'ASD' and 'non-ASD' groups according to 1) the 3Di, 2) the ADOS, and 3) *both* the 3Di *and* ADOS. In addition, teachers scored boys (M = 68.80) significantly higher than girls (M = 51.95, $t(185) = 3.45$, p = .001) on the SRS, whereas no significant differences were found in the parent-reported SRS scores between boys (M = 63.79) and girls (M = 59.00, $t(185) = .80$, p = .43). Similar gender differences were found in the non-ASD and ASD-groups (not presented).

Aim 1: screening accuracy of the parent-reported SRS

Table 2 shows the sensitivity, specificity, PPV, and NPV of the parent-reported SRS for the recommended cut-off total score of 75 in relation to three ASD classifications: 1) an ASD classification according to the 3Di, 2) an ASD

Table 1. Descriptive statistics of the weighted sample

	Classification according to the 3Di				Classification according to the ADOS				Classification according to both the 3Di and ADOS			
	ASD	Non-ASD	t/χ^2	*p*	ASD	Non-ASD	t/χ^2	*p*	ASD	Non-ASD	t/χ^2	*p*
n (%)	276[a] (23%)	906[a] (77%)			416[a] (35%)	766[a] (65%)			129[a] (11%)	1,053[a] (89%)		
Gender: *n* (%) male	220[a] (80%)	622[a] (69%)	1.9	.13	334[a] (80%)	508[a] (66%)	4.1	.13	101[a] (78%)	741[a] (70%)	.6	.32
Age screening (yrs)	7.2 (2.0)	7.5 (1.9)	1.0	.33	6.8 (1.8)	7.7 (1.9)	2.6	<.01	6.5 (1.9)	7.5 (1.9)	2.8	<.01
Age assessment (yrs)	8.2 (2.0)	8.4 (2.0)	.7	.47	7.7 (1.9)	8.7 (2.0)	2.7	<.01	7.5 (1.9)	8.4 (2.0)	2.8	<.01
Total IQ	97.0 (17.6)	97.8 (15.4)	.2	.81	93.0 (17.6)	99.9 (14.8)	2.1	.04	95.7 (19.5)	97.8 (15.2)	.6	.54
Parent report SRS	95.8 (19.2)	52.2 (27.3)	10.5	<.001	69.7 (29.1)	58.5 (27.4)	2.0	.05	105.1 (19.1)	57.2 (27.8)	13.3	<.001
Teacher report SRS	77.0 (28.5)	60.0 (27.1)	3.8	<.001	74.7 (29.3)	58.1 (26.0)	3.4	<.01	87.9 (28.4)	61.0 (26.5)	5.4	<.001
3Di total score	32.1 (7.0)	12.8 (7.1)	15.3	<.001	22.3 (11.4)	14.6 (10.7)	4.1	<.001	34.9 (7.4)	15.1 (10.0)	14.0	<.001
ADOS severity	4.5 (2.7)	3.0 (2.5)	3.3	<.01	6.4 (1.8)	1.7 (.9)	17.2	<.001	6.9 (1.7)	2.9 (2.2)	11.3	<.001

Note. Table presents means and standard deviations in parentheses unless otherwise noted. The total raw SRS scores are presented. The ADOS severity reflects the ADOS-2 total calibrated severity score. The 3Di total score is the sum of the scores on the scales reciprocal social interaction, communication, and repetitive and stereotyped behavior. The total weighted sample is split into ASD and non-ASD groups according to: 1) the 3Di; 2) the ADOS; 3) *both* the 3Di *and* ADOS.

[a]All frequencies shown in the table are weighted; please see the Statistical Analysis section for more information.

SRS = Social Responsiveness Scale; 3Di = Developmental, Dimensional and Diagnostic Interview; ADOS = Autism Diagnostic Observation Schedule.

classification according to the ADOS, and 3) an ASD classification according to *both* of these instruments.

In relation to the ASD classification according to the 3Di, the cut-off of 75 on the parent-reported SRS resulted in good sensitivity (.85) and specificity (.83). The NPV was very high (.95), indicating that the probability was very low that a child scoring below the cut-off of 75 was classified as having ASD according to the 3Di. The PPV, the probability that a child scoring at or above 75 was classified as having ASD, was .60.

In relation to the ASD classification according to the ADOS, the specificity was moderate (.73) and sensitivity was poor (.45). Thus, the parent-reported SRS did not capture a substantial proportion (55%) of the children who were classified as having ASD according to the ADOS and there were also a considerable proportion of children (27%) who did not meet the ADOS cut-off for ASD.

In relation to the more stringent ASD classification—an ASD classification according to *both* the 3Di *and* ADOS—the cut-off of 75 on the parent-reported SRS identified all children with an ASD classification (sensitivity 100%), but also 25% of the children who were not classified as having ASD according to both instruments (false positives). Since there were no false negatives using this classification method, i.e. no children classified as having ASD according to *both* the 3Di *and* ADOS that scored below the cut-off of 75 on the parent-reported SRS, we were not able to calculate confidence intervals for the sensitivity and the NPV. Because of the low prevalence of this stringent ASD classification (11%), the PPV was relatively low (.33).

Table 2. Screening accuracy indices for the SRS parent report (total raw cut-off score of 75)

ASD classification according to	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
3Di	.85 (.63-.95)	.83 (.76-.87)	.60 (.51-.67)	.95 (.85-.99)
ADOS	.45 (.31-.59)	.73 (.65-.80)	.48 (.39-.56)	.71 (.57-.82)
both 3Di *and* ADOS	1.00	.75 (.68-.81)	.33 (.26-.41)	1.00

Note. SRS = Social Responsiveness Scale; 3Di = Developmental, Dimensional and Diagnostic Interview; ADOS = Autism Diagnostic Observation Schedule; PPV = Positive Predictive Value; NPV = Negative Predictive Value; CI = Confidence Interval.

Aim 2: contribution of the teacher-reported SRS

The results of the logistic regressions that tested whether the teacher-reported SRS scores significantly added to the prediction of an ASD classification over and above the parent-reported SRS scores, are shown in Table 3. The teacher report

did not significantly add to prediction of an ASD classification according to the 3Di (Nagelkerke's pseudo $\Delta R^2 = 1\%$, $\Delta\chi^2(1) = 1.78$, $p = .16$). However, the teacher report showed a significant independent contribution over and above the parent report to the prediction of an ASD classification according to the ADOS (Nagelkerke's pseudo $\Delta R^2 = 8\%$, $\Delta\chi^2(1) = 6.83$, $p = .01$). In contrast to the teacher report, the parent report did not significantly predict the ADOS classification. In addition, the teacher report significantly added to the prediction of an ASD classification according to *both* the 3Di *and* ADOS over and above the parent (Nagelkerke's pseudo $\Delta R^2 = 6\%$, $\Delta\chi^2(1) = 3.70$, $p < .001$). In this model, both parent and teacher report had a significant independent contribution.

Table 3. Logistic regression of parent and teacher-reported SRS scores predicting ASD classifications

	OR	95% CI	R^2	Model χ^2	ΔR^2	$\Delta\chi^2$
ASD classification according to the 3Di						
Step 1:			.54	47.16**	–	–
Parent-reported SRS	8.0**	4.4-14.5				
Step 2:			.55	48.94**	.01	1.78
Parent-reported SRS	7.3**	4.1-13.1				
Teacher-reported SRS	1.3	0.9-2.0				
ASD classification according to the ADOS						
Step 1:			.05	3.68	–	–
Parent-reported SRS	1.5	1.0-2.2				
Step 2:			.13	10.51*	.08	6.83*
Parent-reported SRS	1.3	0.8-1.9				
Teacher-reported SRS	1.8*	1.1-2.9				
ASD classification according to *both* the 3Di *and* ADOS						
Step 1:			.47	78.27**	–	–
Parent-reported SRS	7.5**	4.8-11.7				
Step 2:			.53	81.97**	.06	3.70**
Parent-reported SRS	7.1**	4.4-11.3				
Teacher-reported SRS	2.2**	1.5 -3.1				

Note. Parent and teacher-reported SRS scores were entered as continuous predictor variables in different steps: 1) SRS parent report, 2) SRS teacher report. Odds ratios are expressed in the change of odds per standard deviation change: *SD* = 29.11 for the parent-reported SRS and *SD* = 27.07 for the teacher-reported SRS. The pseudo Nagelkerke's R^2 is reported. OR = Odds Ratio; CI = Confidence Interval; SRS = Social Responsiveness Scale; 3Di = Developmental, Dimensional and Diagnostic Interview; ADOS = Autism Diagnostic Observation Schedule.
*$p < .05$, **$p < .01$.

To determine the overall screening accuracy of the parent-reported SRS alone and in combination with the teacher report, we performed ROC analyses using the predicted probabilities of the logistic regression analyses. Figures 2a-c show

the results of the ROC analyses compared with an ASD classification according to a) the 3Di, b) the ADOS, and c) *both* the 3Di *and* ADOS. As illustrated in these figures, the parent-reported SRS was very good in discriminating between children who were classified as having an ASD and those who were not according to the 3Di (AUC parent = .91, 95% CI .85-.96). Combining parent and teacher report did not improve the screening accuracy of the SRS compared with an ASD classification according to the 3Di (AUC combined = .91, 95% CI .86-.95). The parent report did not discriminate well between children who were classified as having ASD according to the ADOS and those who were not (AUC parent = .59, 95% CI .47-.71). Combining the parent and teacher-reported SRS significantly increased the discriminative ability with regard to an ASD classification according to the ADOS compared with the parent report alone (AUC combined = .68, 95% CI .60-.76, p = .049), although the correspondence to a classification according to the ADOS was still low. The parent-reported SRS showed an excellent screening accuracy with regard to an ASD classification according to *both* the 3Di *and* ADOS (AUC parent = .92, 95% CI .86-.97). Although the combined use of parent and teacher report slightly increased the discriminative ability (1%) with regard to an ASD classification according to *both* the 3Di *and* ADOS (AUC combined = .93, 95% CI .89-.97), this increase was not significant as compared with the parent report alone (p = .30).

Because of the gender differences in teacher-reported SRS scores, we also explored whether our results regarding the added value of the teacher report would be similar when stratifying for gender. Results regarding the added value of the teacher report appeared similarly for boys and girls. However, the ability of the SRS to discriminate between children with and without an ASD classification according to the ADOS was especially poor in girls (AUC parent = .50; AUC combined = .61), compared to boys (AUC parent = .60; AUC combined = .67). These results must be interpreted with caution as our sample contained relatively few girls (unweighted n = 57).

Discussion

The present multicenter study investigated the screening accuracy of the parent-reported SRS, alone as well as in combination with the teacher-reported SRS, in comparison with an ASD classification according to commonly used

ASD diagnostic instruments: the 3Di (parent interview) and the ADOS (clinical observation). The parent-reported SRS showed an excellent screening accuracy with regard to an ASD classification according to the 3Di and according to *both* the 3Di *and* ADOS. The ability of the parent-reported SRS to identify children who were classified as having ASD according to the ADOS was poor. Combining the parent report with the teacher-reported SRS significantly improved the ability to discriminate between children who met cut-off scores indicating possible ASD according to the ADOS and those who did not.

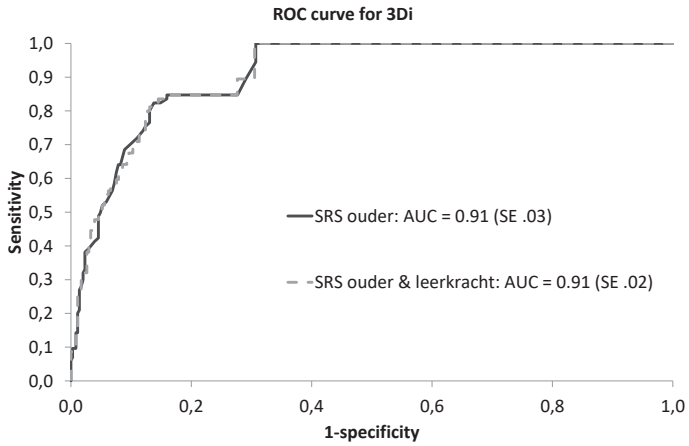

Figure 2a. ROC curve of the parent-reported SRS alone and the combined use of the parent and teacher-reported SRS compared with an ASD classification according to the 3Di.

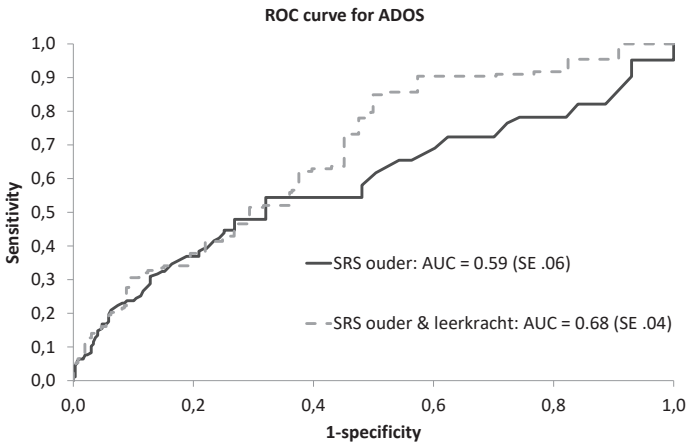

Figure 2b. ROC curve of the parent-reported SRS alone and the combined use of the parent and teacher-reported SRS compared with an ASD classification according to the ADOS.

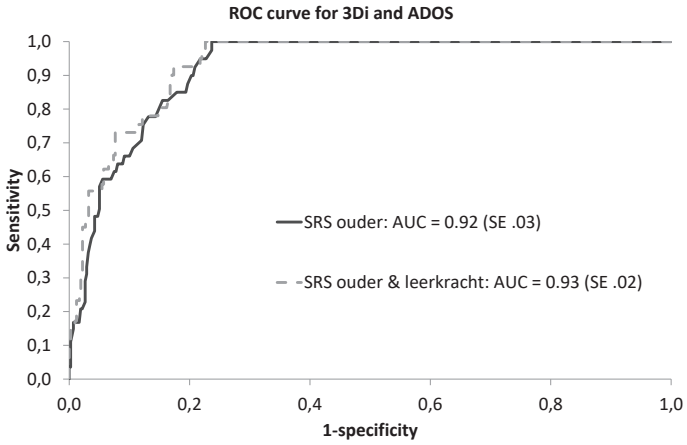

Figure 2c. ROC curve of the parent-reported SRS alone and the combined use of the parent and teacher-reported SRS compared with an ASD classification according to both the 3Di and ADOS.

The estimates of sensitivity and specificity for the parent-reported SRS with regard to an ASD classification according to the 3Di and *both* the 3Di *and* ADOS are similar to screening accuracy estimates of the original validation study conducted by Constantino and Gruber (2005) and those of other validation studies (Bölte et al. 2011; Charman et al. 2007). In line with these previous studies, we found a good to excellent sensitivity and a fair to good specificity for the total raw cut-off score of 75 on the parent report. Although this cut-off score on the parent-reported SRS may not identify all children who receive an ASD classification according to a clinical observation (i.e. ADOS), it identifies most children who are classified as having ASD according to a parent interview (i.e. 3Di) and those who meet stringent ASD classification criteria (i.e. classification according to *both* the 3Di *and* ADOS). Since in our sample more children had a non-ASD classification than an ASD classification (prevalence of ASD classifications varied from 11 to 35% dependent on the diagnostic instruments used), the NPVs were higher than the PPVs. This indicates that, in diverse clinically referred populations where the overall prevalence of ASD is relatively low, the parent-reported SRS is especially effective in correctly identifying children who do *not* need further ASD-specific diagnostic assessment.

There is no single cut-off for the SRS that can be used in all circumstances; the most optimal cut-off may vary with the population screened or the purpose of screening (Constantino and Gruber 2012). In clinical practice, the SRS is generally used to indicate children for further diagnostic evaluation, requiring high sensitivity. In our study, the total raw cut-off score of 75 served this purpose well. However, the aim to identify as much ASD cases as possible will go at the expense of the specificity, i.e. also a considerable proportion of non-ASD cases will be identified and thus selected for further diagnostic assessment with the accompanying costs and burden on the family. Choosing a higher cut-off may be preferred when it is important to further minimize the number of false positives, i.e. children with non-ASD who are incorrectly identified at risk for ASD. For instance, when selecting cases for biological studies, it is required that all cases meet stringent ASD criteria and the costs of incorrectly including non-ASD cases are relatively higher than those of missing some children with ASD. Thus, clinicians and researchers should be aware of the trade-off between maximizing the identification of children at risk (i.e. optimal sensitivity) versus minimizing the number of children targeted to receive further assessments (i.e. optimal specificity) when selecting the cut-off that best serves their particular purpose or the population screened (Charman and Gotham 2013).

We found support for the contribution of the teacher-reported SRS when screening for ASD in relation to an ASD classification according to the ADOS. When compared with an ASD classification according to the 3Di or *both* the 3Di *and* ADOS, the parent report alone already showed excellent screening accuracy, leaving little room for improvement. Thus, the screening accuracy of the parent and teacher-reported SRS differed depending on the ASD classification method used: the 3Di, the ADOS, or *both* the 3Di *and* ADOS. One factor that may be important in this respect is the source of information. It is perhaps not surprising that the parent-reported SRS showed high agreement with the 3Di classification, as for both measures the parent is the main source of information (i.e. shared method variance). However, an important difference between both measures is that during the 3Di the information from the parent is obtained, interpreted, and scored by a trained expert, while the parent-reported SRS purely reflects the parent's perspective. In addition, when an ASD classification according to both a parent interview and clinical observation was used as comparison, the parent-reported SRS also showed a high screening accuracy. Thus, despite the shared method variance, these results indicate that

the parent-reported SRS, which is relatively short and easy to administer, is able to differentiate between children who meet cut-off scores indicating possible ASD according to a more elaborate parent interview and to both a parent interview and clinical observation and those who do not.

The finding that the teacher-reported SRS improved the prediction of an ASD classification according to the ADOS over and above the parent report alone is consistent with previous studies that have shown that teacher reports corresponded better to the ADOS than parent reports to the ADOS (Schanding et al. 2012; Reszka et al. 2014; de Bildt et al. 2003). A possible explanation is that children with ASD behave more similarly in school and research or clinical contexts than at home (Schanding et al. 2012; Reszka et al. 2014; de Bildt et al. 2003). This may be attributed to the fact that teachers and clinicians observe the child in relatively structured settings, whereas parents see the child across a variety of unstructured settings (Szatmari et al. 1994; Koning and Magill-Evans 2001). The possible influence of the environmental context on the expression of behavior in children with ASD was also indicated in the study by Kanne et al. (2009). However, even when parents and teachers rated behavior problems of children with ASD in the same setting, large discrepancies were found between their ratings for individual children (Reed and Osborne 2013). Besides the role of environmental context, the better agreement between teachers and clinicians than between parents and clinicians could also reflect the perspective of the raters, i.e. teachers and clinicians may observe and rate autistic behavior more similarly than parents and clinicians (Reszka et al. 2014; Schanding et al. 2012). This could be due to the fact clinicians and teachers both observe regularly more children than parents do, and thus are expected to have more knowledge of how the child behaves in comparison with peers (Ferdinand et al. 2003).

Even when combining parent and teacher-reported SRS, the screening accuracy with regard to the ADOS classification was not that high. This finding is consistent with previous studies showing poor agreement between screening questionnaires, particularly parent-reported, and the ADOS (de Bildt et al. 2009a; Bishop and Baird 2001; Sikora et al. 2008). The lack of correspondence of parent and teacher ratings with clinical observations may also be explained by contextual factors and different perspectives. Clinicians have been trained extensively to recognize autistic behaviors and have considerable knowledge on the typical as well as atypical development of children, whereas parents and teachers may have more opportunities to observe all kinds of behaviors

in everyday life that might not always be shown during relatively short one-to-one test situations. Thus, all these different perspectives—parents, teachers, and clinicians—are needed to form a more complete understanding of the child's autistic symptoms.

We found that teachers rated girls lower than boys, although this did not seem to affect the results regarding the added value of the teacher-reported SRS. Parents also tended to rate girls lower than boys, but this difference was less pronounced and not significant. Similar gender differences in teacher-reported SRS scores have been reported for the US norm data (Constantino and Gruber, 2012) and in a Japanese study (Kamio et al. 2013b). These findings are also consistent with other studies that found that particularly teachers rated lower levels of ASD symptoms in girls than boys (Mandy et al. 2012; Posserud et al. 2006). This could reflect a better adaptation of girls in the school setting. Alternatively, it has been raised that girls with ASD may present with different or more subtle difficulties than boys with ASD, which are less easily recognized by clinicians (Dworzynski et al. 2012) and even less so by teachers (Hiller et al., 2014). Teachers also reported lower levels of behavioral problems in girls with ASD (Mandy et al. 2012), suggesting that girls with ASD may show less disruptive behavior than boys with ASD in the school environment. In addition, girls with ASD appear to be less overtly rejected by peers than boys with ASD (Dean et al. 2014). This could all contribute to girls with ASD being overlooked at school. It would be interesting for future research to study how ASD may present differently in girls versus boys across different contexts using observational measures and how the identification of ASD in girls by teachers may be improved.

A problem inherent in research regarding screening accuracy is choosing the reference standard to which the screener is compared, as a single and error-free test often does not exist (Reitsma, Rutjes, Khan, Coomarasamy, & Bossuyt, 2009). Although the commonly accepted gold standard is a diagnosis of ASD determined by a multidisciplinary team using clinical judgment and standardized diagnostic instruments (Falkmer et al. 2013), scores on standardized assessment instrument have been found to be more consistent across centers than clinical judgment (Lord et al., 2012a). Since it is important to use a reliable and replicable reference standard in diagnostic research (Reitsma et al., 2009), we evaluated the screening accuracy of the SRS against ASD classifications according to commonly used and well-validated

standardized diagnostic instruments. Certainly, from a clinical perspective, a diagnosis should not be based solely on the classification according to diagnostic instruments, but needs to incorporate a clinical judgment in which all information is taken into account. However, the SRS is mostly used as a first step in the diagnostic process to decide which children need to be further evaluated using standardized diagnostic instruments, such as the ADOS and ADI-R/3Di. Therefore, we also consider it clinically relevant to compare the results of the SRS against the outcomes on these standardized diagnostic instruments.

In the DSM-5, the new category of social (pragmatic) communication disorder (SCD) has been introduced for individuals who have significant problems in the social use of language and non-verbal communication, but who fall outside the autism spectrum. Potentially, the SRS may also be a useful instrument to identify cases with SCD. Since there are yet no gold standard procedures and instruments for the diagnosis of SCD (Gibson et al. 2013), this potential of the SRS was not investigated in the current study. However, it would be an interesting avenue for future research.

A limitation of the current study is that not all children screened participated in the diagnostic assessments. In an ideal situation, all screened children would have undergone diagnostic assessments, but this was not feasible due to time and financial constraints. Another limitation is that we only used the parent-reported SRS to select children for further assessments, which may have influenced the results regarding the teacher-reported SRS. However, we did not only select children who screened positive on the parent-reported SRS, but also an additional random sample of consecutively referred children who screened negative. Since the selected screen-negative children had a similar mean and standard deviation on the teacher report as the screen-negative children who were not selected, we were also able to estimate the screening accuracy of the teacher-reported SRS. Moreover, because the characteristics of the total screened sample from which we selected were known, we could estimate the screening accuracy of the SRS for the total screened sample using an inverse weighting procedure and thereby correcting for a possible verification bias. This methodological approach thus helped overcoming our practical design limitations.

A strength of this study is that we included a broad variety of children who had been consecutively referred for mental health care, representing the

population in which the SRS is most likely to be used. Previous studies have investigated the utility of the teacher-reported SRS in research samples of children who had already been diagnosed with ASD before the start of the study (Constantino et al. 2007; Schanding et al. 2012; Kamio et al. 2013b); in a general population sample (Fombonne et al. 2012); or in a very small and specific sample (Aldridge et al. 2012). In these case-control design studies, the size of the population from which is sampled and the predicted values for ASD by the SRS scores in the source population are often not known. Consequently, correction for a possible verification bias is not possible, which could have led to biased screening accuracy estimates in these studies (Whiting et al. 2013; Begg and Greenes 1983). To our knowledge, this is the first study to examine the contribution of the teacher-reported SRS in consecutively referred children, which is important for the external validity of our findings.

An important implication of our findings is that the choice of using parent report alone or in combination with teacher report depends on the purpose of screening. Since the parent-reported SRS already show a good screening accuracy and acquiring teacher reports can be difficult and time-consuming, it may be more cost-effective to collect only parent reports in clinical practice. In addition, in a research context, when the aim is to select only children with a stringent ASD classification (i.e. fulfilling ASD criteria according to both a parent interview and child observation), one may choose to use only the parent report to efficiently identify children who have a high likelihood of receiving an ASD classification according to both diagnostic instruments. However, using the parent report alone may not identify all children with potential ASD, specifically those who are classified as having ASD according to the ADOS. The ADOS is widely used in research as well as clinical practice and such information from clinical child observation is an important source of information in the diagnostic evaluation of ASD (Risi et al. 2006; Corsello et al. 2013). Therefore, it may be recommendable to use the parent report in combination with the teacher report in research and specialized ASD settings when identification of all potential ASD cases using a broader ASD definition is important. Furthermore, it should be kept in mind that information from parents cannot substitute the unique information from the experiences of the teacher with the child at school. It may be helpful to stress this to parents in order to increase the chances that teachers will complete and return the SRS. A model process has been developed to involve teachers in the identification

of ASD, but further research is needed to evaluate the cost-effectiveness of this approach (Noland & Gabriel, 2004).

To conclude, this multicenter study confirms the utility of the SRS as a screening tool to identify children who need ASD-specific diagnostic assessment among children who are referred for various mental health problems. Careful consideration should be given to the cut-off as well as the selection of an informant when using the SRS to screen for ASD, as the parent and teacher report show differential relationships to the different ASD diagnostic instruments. It is important to stress that an outcome on the SRS, or any instrument, does *not* equal a clinical diagnosis of ASD, which can only be made by a multidisciplinary team after an extensive diagnostic procedure, preferably including standardized diagnostic instruments such as the ADOS or ADI-R/3Di (Falkmer et al. 2013). The SRS scores can be used to provide a standardized and quantified indication of whether a child needs further diagnostic assessments. In addition, the SRS scores may be valuable as part of the entire diagnostic process by complementing other information in acquiring a comprehensive view of the ASD characteristics of the child. The limited agreement between instruments and informants—parents, teachers, and clinicians—highlights the importance of using multiple instruments that collect information from multiple informants in the overall diagnostic process, since they all contribute distinct information from unique contexts and perspectives. More research is needed before a firm conclusion can be drawn about what unique information the teacher information adds in different stages of the assessment of ASD (i.e. screening versus diagnostic assessment) and how information from different informants should be combined or integrated. More specifically, future studies could investigate whether the contributions of parents and teachers differ depending on characteristics of the child or rater.

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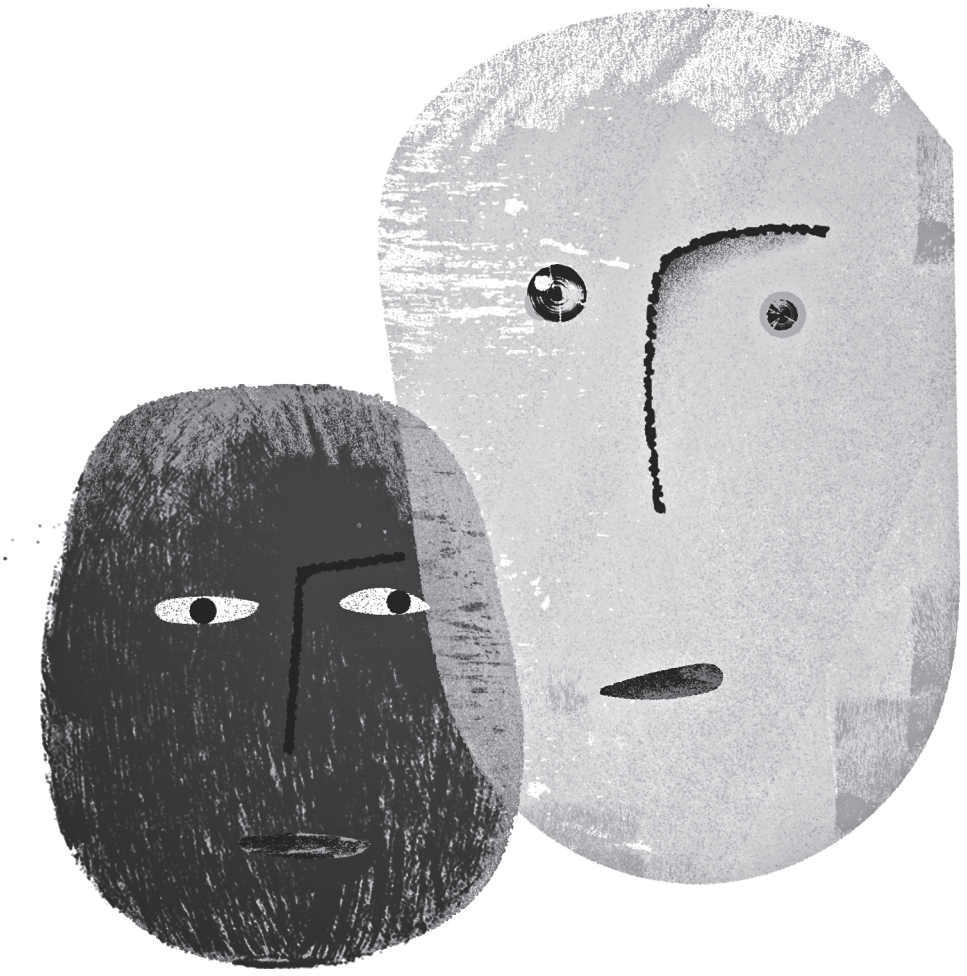

Chapter 4

Factors influencing the probability of a diagnosis of autism spectrum disorder in girls versus boys

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Abstract

In order to shed more light on why referred girls are less likely to be diagnosed with ASD than boys, the present study examined whether behavioral characteristics influence the probability of an ASD diagnosis differently in girls versus boys derived from a multicenter sample of consecutively referred children aged 2.5 to 10 years old. Based on information from the short version of the Developmental, Dimensional and Diagnostic Interview (3Di) and the Autism Diagnostic Observation Schedule (ADOS), 130 children (106 boys and 24 girls) received a diagnosis of ASD according to DSM-IV-TR criteria and 101 children (61 boys and 40 girls) did not. Higher overall levels of parent-reported RRB symptoms were less predictive of an ASD diagnosis in girls than in boys (*OR* interaction = .41, 95% CI = .18-.92, p = .03). In contrast, higher overall levels of parent-reported emotional and behavioral problems increased the probability of an ASD diagnosis more in girls than in boys (*OR* interaction = 2.44, 95% CI = 1.13-5.29, p = .02). No differences were found between girls and boys in the prediction of an ASD diagnosis by overall autistic impairment, sensory symptoms and cognitive functioning. These findings provide insight into possible explanations for the assumed underidentification of ASD in girls in the clinic.

Introduction

Boys are more likely to be diagnosed with ASD than girls, but reasons for this discrepancy remain unclear. It has been estimated that boys are four times more likely to be diagnosed with ASD than girls, with estimates rising to 6-8:1 in samples with an average IQ or higher (Fombonne, 2003; Fombonne, 2005). In contrast, recent population studies suggest a lower male-to-female ratio in the range of 2-3:1 (Lai et al., 2015). This has raised the question whether females with ASD are underidentified in clinical samples, contributing to exaggerated male-to-female ratios (Lai et al., 2015; Kreiser and White, 2014), in addition to a real discrepancy in the occurrence of ASD between boys and girls possibly due to a female protective effect (e.g., Robinson et al., 2013; Jacquemont et al., 2014). Similar findings have also been reported for attention-deficit/hyperactivity disorder (ADHD; Taylor et al., 2016; Willcutt, 2012). The underidentification hypothesis for ASD is supported by findings that girls are less likely to be diagnosed with ASD than boys despite demonstrating similar levels of autistic symptoms (Russell et al., 2011; Dworzynski et al., 2012). Furthermore, there is evidence that girls with ASD are diagnosed later than boys (Begeer et al., 2013; Giarelli et al., 2010), suggesting that some girls with ASD are missed at an early age using current diagnostic practices. Therefore, a better understanding of how gender influences the expression and diagnosis of ASD is needed to improve the identification and treatment of girls with ASD.

Because ASD samples have been predominantly male, our current understanding of ASD and the behavioral criteria used to diagnose ASD may be biased towards males. Therefore, a different behavioral expression of the underlying biological liability for ASD in females compared to males, possibly due to different sociocultural influences, may contribute to the difficulty of identifying ASD in girls (Kreiser and White, 2014). Although results have been mixed, findings suggest that girls with ASD show similar or heightened levels of social communication difficulties compared to boys, but less repetitive and restricted behavior (RRB; Van Wijngaarden-Cremers et al., 2014; Hartley and Sikora, 2009; Frazier et al., 2014). In addition, it is possible that girls show other types of RRB symptoms than boys that are less well identified using current assessment tools (Mandy et al., 2012; Hiller et al., 2016). To date, little is known about whether sensory symptoms, that are newly added in the DSM-5 as part of the RRB domain, also differ between boys and girls with ASD.

The clinical presentation and identification of girls with ASD may also be affected by symptoms outside the ASD core domains. The few studies that have explored this indicate that girls are less likely to show externalizing problems (Mandy et al., 2012; Hiller et al., 2014; May et al., 2012) and more likely to show internalizing problems than boys (Hartley and Sikora, 2009; Mandy et al., 2012; Solomon et al., 2012), but results have been inconsistent and seem to vary according to the informant used. Moreover, few studies used comparison groups, so little is known about whether these differences are specific for individuals with ASD.

Research regarding gender differences in behavioral characteristics in ASD samples is complicated by a possible bias in the ascertainment of girls with ASD, risking a circularity of reasoning (Lai et al., 2015). A population study found that girls were more likely to be diagnosed with ASD than boys when they had higher levels of additional behavioral and cognitive difficulties despite showing similarly elevated levels of autistic symptoms (Dworzynski et al., 2012). This could reflect a diagnostic bias, resulting in girls with ASD being more likely to be overlooked in the absence of additional problems (Dworzynski et al., 2012). Therefore, the field could benefit from a different approach to examining the identification of ASD in females, not only focusing on phenotypic differences between boys and girls within ASD samples, but also on how autistic symptoms and associated problems influence the probability of receiving an ASD diagnosis in girls versus boys.

The present study aimed to contribute to a better understanding of gender differences in the expression of behavioral characteristics associated with a diagnosis of ASD in a sample of predominantly cognitively able children who had been consecutively referred to one of six participating mental health centers. Firstly, we investigated differences in the proportions of boys and girls who received a positive screen for ASD or a best-estimate consensus diagnosis of ASD based on gold-standard diagnostic assessment. Secondly, we investigated whether overall autistic impairment, RRB symptoms, sensory symptoms, emotional and behavioral problems, and cognitive functioning differentially influenced the probability of the best-estimate ASD diagnosis in girls versus boys. Because previous studies found different results regarding the phenotypic characteristics of boys and girls with ASD according to the informant used (e.g., Mandy et al., 2012), we included both parent and teacher ratings of autistic symptoms and emotional/behavioral problems. Based on

the study of Dworzynski et al. (2012), we hypothesized that higher levels of emotional and behavioral problems and lower levels of cognitive functioning would increase the probability that girls receive an ASD diagnosis, whereas this would be less so in boys. In addition, because many studies have found lower levels of RRB symptoms in girls with ASD than in boys with ASD (e.g., Van Wijngaarden-Cremers et al., 2014), we hypothesized that RRB symptoms would be less predictive of an ASD diagnosis in girls than in boys.

Methods

Participants

Participants were derived from the Social Spectrum Study, a prospective multicenter cohort of clinically referred children with a focus on ASD. This study will be described in more detail elsewhere (Duvekot et al., 2016). Figure 1 presents the flow of the participants through the various stages of the study and the proportions of boys and girls at each stage. First, all children aged 2.5 to 10 years who had been referred to one of six child and adolescent mental health services (CAMHS) in the South-West of the Netherlands were routinely screened for ASD using the parent-reported Social Responsiveness Scale (SRS; Constantino and Gruber, 2012). Participating CAMHS included both secondary and tertiary (specialized) mental health services. Screening took place during a six-month window varying between April 2011 and July 2012. Children were referred by the general practitioner or other medical doctor for a variety of problems, including concentration/hyperactivity problems (24%), behavior problems (24%), social/contact problems (23%), anxiety/mood problems (12%), learning/cognitive problems (7%) or other developmental concerns (10%). The reason for referral did not differ significantly by gender, $\chi^2(5,3311) = 13.1$, $p = .13$.

Second, 428 of the 1,281 screened children (118 girls and 310 boys) were identified as at risk for ASD (total raw score ≥ 75 on the parent-reported SRS) and approached to participate in a comprehensive diagnostic assessment for ASD, including the short version of the Developmental, Dimensional and Diagnostic Interview (3Di; Santosh et al., 2009), the second edition of the Autism Diagnostic Observation Schedule (ADOS-2; Lord et al., 2012; De Bildt et al., 2013) and several questionnaires (including the Repetitive Behavior Scale-Revised

and the Short Sensory Profile, see Measures section for further information). In addition, we asked a random selection of children who screened negative (n = 240; 76 girls and 164 boys) to participate in the same assessments in order to enable generalization of the results to the total sample of screened children.

To be included in the current analyses, both a 3Di and ADOS assessment had to be available for the child in order to establish a best-estimate consensus diagnosis of ASD. Of the children who were selected and did not meet this inclusion criterion (n = 437), 348 did not participate in any diagnostic assessment and 89 were excluded because there was only one diagnostic assessment available. The final sample of children who completed full diagnostic assessment (n = 231) consisted of 64 girls and 167 boys aged 2 to 12 years at the time of diagnostic assessments. Screen-positive children were more likely to participate than screen-negative children ($\chi^2(1) = 13.91$, $p < .001$). There was no statistically significant difference in the participation rates of screen-negative boys and girls, $\chi^2(1) = 1.89$, $p = .17$, or screen-positive boys and girls, $\chi^2(1) = .22$, $p = .64$ (see Figure 1). IQ scores of the final sample ranged from 50 to 145, but the majority of the sample had IQ scores in the normal range: 11% of the children showed an indication of an intellectual disability (Full Scale IQ, Verbal IQ or Performance IQ < 70), with no gender difference in this proportion, $\chi^2(1,230) = .59$, $p = .53$.

Diagnostic procedure

The comprehensive diagnostic assessment included the short version of the Developmental, Dimensional and Diagnostic Interview (3Di; Santosh et al., 2009) and the second edition of the Autism Diagnostic Observation Schedule (ADOS-2; Lord et al., 2012; De Bildt et al., 2013), and an IQ assessment was performed if IQ was unknown or based on an assessment that had been conducted more than two years ago. In addition, parents completed questionnaires regarding characteristics of the child (see Measures below), parent and family. At the time of these assessments, written informed consent was obtained from the participating families. The study was approved by the Ethics Committee of the Erasmus Medical Center (MEC-2011-078).

Information from the 3Di and ADOS assessments was used to determine the presence or absence of an ASD diagnosis (i.e., Autistic Disorder, Asperger's Syndrome or PDD-NOS) according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revision (DSM-IV-TR). All administrators of the

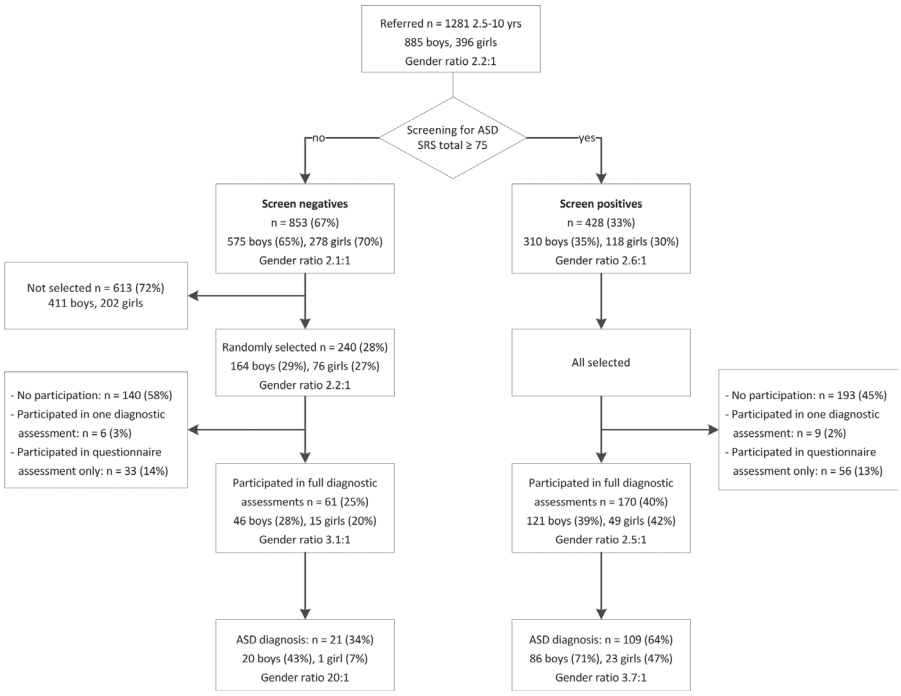

Figure 1. Flow chart of the participants

3Di and ADOS had achieved the standard of research reliability. If both the 3Di and ADOS were performed as part of the research protocol (*n* = 176, 76%), the diagnosis was based on consensus by two of the psychologists of the research team who administered these instruments. First, they each independently rated a DSM-IV-TR symptom checklist based on the information from the specific instrument they administered. Then, they discussed their checklists and exchanged information until they reached consensus about the presence of each symptom and formed a best-estimate consensus ASD diagnosis based on information from both instruments. Interrater reliability between the indication of an ASD diagnosis based on the DSM-IV-TR symptom checklist that was based on information from each instrument and the consensus diagnosis was good: kappa = .78 for the checklist based on the 3Di and kappa = .70 for the checklist based on the ADOS (similar findings for boys and girls). In 55 of the 231 cases (24%), the 3Di and/or ADOS had been conducted during the clinical evaluation, mostly at a tertiary CAMHS specialized in ASD. In these cases, the diagnosis that was formed by a team of experienced clinicians at the

CAMHS was used. There was no difference in the proportion of boys and girls who received a diagnosis determined by the research or clinical team, $\chi^2(1) = .07$, $p = .79$.

Measures

Autistic symptoms. The *Social Responsiveness Scale, 2nd edition* (SRS-2; Constantino and Gruber, 2012) is a 65-item questionnaire designed to assess the severity of autistic symptoms. In the present study, we used the version for school-age children as well as the version for preschool children, which are largely similar with a few differences in the content of items to make them more age-appropriate. Parents and teachers/day care providers completed the questionnaire as part of the routine referral procedure. Items are scored on a four-point Likert scale ranging from 0 ('not true') to 3 ('almost always true'). A total score is created by summing all 65 items, with higher scores indicating more overall autistic impairment. In a general population sample (n = 1,104), boys obtained higher scores on the SRS than girls with an effect size (Cohen's d) of .19 for parent ratings and of .37 for teacher ratings (Constantino and Gruber, 2012). Internal consistency of the total score was high in the present study (Cronbach's $\alpha = .95$ for the parent-report and teacher-report). The SRS has been found to discriminate well between children with ASD and children with other psychiatric problems (e.g., Bölte et al., 2011; Charman et al., 2007; Constantino and Gruber, 2012), supporting its validity as an indicator of ASD symptom severity. Because the SRS predominantly contains items related to social-communication impairment, we also used the Repetitive Behavior Scale-Revised (RBS-R) and the Short Sensory Profile (SSP) to assess symptoms that fall under the domain of repetitive and restricted behavior.

The *Repetitive Behavior Scale-Revised* (RBS-R; Bodfish et al., 2000) is a parent-reported questionnaire designed to assess a variety of restricted and repetitive behaviors (i.e., self-injurious behavior, stereotypic behavior, compulsive behavior, ritualistic behavior, insistence on sameness, and restricted interests) that are characteristic of individuals with ASD with both lower and higher levels of intellectual functioning (Lam and Aman, 2007; Bishop et al., 2013). It consists of 43 items that are rated on a four-point Likert scale ranging from 0 ('behavior does not occur') to 3 ('behavior occurs and is a serious problem'). We used the total score including 38 of the original 43 items that was based on a factor analysis (Lam and Aman, 2007) as an overall indicator of severity

of RRB. Consistent with previous research (Lam and Aman, 2007; Esbensen et al., 2009), internal consistency of the total scale in our sample was good, with a Cronbach's α of .93. Solomon et al. (2012) reported no gender differences between typically developing girls and boys (both *n* = 19) on this measure.

The *Short Sensory Profile* (SSP; McIntosh et al., 1999) is a parent-reported questionnaire consisting of 38 items assessing the frequency of the child's reactions to different sensory experiences. It is a shortened version of the Sensory Profile (Dunn, 1999). The items are scored on a five-point Likert scale (1 = 'always', 2 = 'frequently', 3 = 'occasionally', 4 = 'seldom', 5 = 'never'). We used the total score as an indicator of overall sensory processing ability. Note that lower scores reflect more sensory processing difficulties. In the present study, the internal consistency of the total scale was .92. Criterion-validity of the SSP has been supported by findings that scores on the SSP discriminated between children with ASD and typically developing children or children with developmental delays (Tomchek and Dunn, 2007). In a general population sample (n = 1,115), gender differences on the Sensory Profile were found to be negligible (effect sizes <.10; Dunn and Westman, 1997).

Emotional and behavioral problems. The *Child Behavior Checklist* (CBCL), a parent-reported questionnaire, and a parallel form for teachers, the *Teacher Report Form* (TRF), were collected as part of the routine referral procedure to assess a broad variety of emotional and behavioral problems. Items are scored on a 3-point scale ranging from 0 ('not true') to 3 ('very true'). The CBCL and TRF have one version for children aged 1,5 to 5 years old (Achenbach and Rescorla, 2000) and one for children aged 6 to 18 years (Achenbach and Rescorla, 2001; Verhulst and Van der Ende, 2013). Both versions were used in the present study. In addition to the Total Problems score, we used the two empirically-derived broadband scales: Internalizing and Externalizing problems. In the general population, boys score higher than girls on the Total and Externalizing problems scale and lower on the Internalizing problems scale (Crijnen et al., 1997). Because of the two age versions, we used *T* scores that are based on normative data to make the scores more comparable. The CBCL and TRF have good psychometric properties (Achenbach and Rescorla, 2000; Achenbach and Rescorla, 2001; Verhulst and Van der Ende, 2013) which has also been confirmed in ASD samples (Pandolfi et al., 2009; Pandolfi et al., 2012).

Cognitive functioning. Because we obtained the majority of intelligence quotient (IQ) scores from the patient file (74%), a variety of tests were used to

estimate the level of cognitive functioning: the Wechsler Intelligence Scale for Children, third Dutch edition (WISC-III-NL; Kort, 2005), the Wechsler Preschool and Primary Scale of Intelligence, third Dutch edition (WPPSI-III-NL; Hendriksen and Hurks, 2009), the Snijders-Oomen Nonverbal intelligence test (SON-R; Tellegen, 1998), the Bayley Scales of Infant Development, Dutch edition (BSID-II-NL; Meulen et al., 2004) or, as part of the research protocol (26%), the Wechsler Abbreviated Scale of Intelligence (WASI; Axelrod, 2002). All of these tests are standardized with a mean score of 100 and a standard deviation of 15. The WASI full scale IQ has shown good concurrent validity with the WISC-III full scale IQ (r = .87; Wechsler, 1999), the SON-R with the WISC-R full scale (r = .74; Tellegen, 1998) and the mental development index of the BSID-II with the WPSSI-R full scale IQ (r = .73; Bayley, 1993).

Statistical analyses

Chi-square analyses were used to investigate differences in the probability of attaining a positive screen for ASD on the parent-reported SRS and a best-estimate consensus diagnosis of ASD (Aim 1). Differences in mean levels of characteristics between boys and girls in the total sample were tested using the complex samples general linear modeling procedure in SPSS 20 (SPSS Inc., Chicago, IL).

To investigate gender differences in the factors influencing the diagnosis of ASD (Aim 2), a series of logistic regression analyses were performed using the presence of an ASD diagnosis as the outcome variable, and gender and age as covariates. In separate analyses, predictors included were: (*a*) autistic symptoms: parent-reported SRS total score, teacher-reported SRS total score, RBS-R total score, SSP total score; (*b*) emotional/behavioral problems: internalizing, externalizing, and total problems *T* scores of the CBCL and TRF; (*c*) cognitive functioning: verbal, performance and full-scale IQ scores. First, the main effects of these predictors were investigated. Then, to test whether the associations between these predictors and the probability of an ASD diagnosis differ for boys and girls, we included interaction terms between the predictors and gender. An interaction effect would indicate that there is a difference between boys and girls in how this characteristic is associated with an ASD diagnosis. To facilitate interpretation, the continuous predictors were standardized (transformed to *z*-scores).

The logistic regression analyses were performed using Mplus 7.3 (Muthén

& Muthén, 1998-2012) using maximum likelihood estimation with robust standard errors (MLR) as estimator. Mplus uses the full information maximum likelihood estimation (FIML) to produce robust parameter estimates for the missing data based on available information in the data. To maximize this information, we added auxiliary variables that were related to the predictors in the model as additional dependent variables (Graham, 2003). The parent-reported SRS (0% missing), the teacher-reported SRS (12% missing), CBCL (7 % missing) and TRF (20% missing) were used as auxiliary variables in each other's models. The same was done for the verbal IQ (16% missing), performance IQ (10% missing), and full-scale IQ (6% missing). For the RBS-R (20% missing) and SSP (20% missing), we used the RRB scales of the parent-reported SRS, 3Di and ADOS (calibrated score), and the total score of the CBCL as auxiliary variables. Because we oversampled children with a positive screen for ASD compared to children with a negative screen, we used sampling weights in our analyses to increase the generalizability of the results to the referred population from which we sampled. Statistical significance was determined at $p < 0.05$.

Results

Gender differences in ASD ascertainment

A similar proportion of clinically referred boys (310 of 885, 35%) and girls (118 of 396, 30%) screened positive on the parent-reported SRS, $\chi^2 = 3.36$, $p = .07$). Of the 231 children who underwent full diagnostic assessments (consisting of the ADOS and 3Di), 106 boys and 24 girls (unweighted counts) received a best-estimate diagnosis of ASD. Correcting for sampling weights, 55% of the boys (weighted $n = 154$) and 25% of the girls (weighted $n = 27$) were estimated to have a best-estimate consensus diagnosis of ASD, indicating that boys were 2.18 times more likely to receive an ASD diagnosis than girls, $\chi^2 = 15.978$, $p < .001$. Children who did not receive an ASD diagnosis (weighted $n = 209$) had a range of psychiatric diagnoses reported in the patient file, with ADHD as the most common diagnosis (39%), followed by anxiety/mood disorders (11%). The rates of these non-ASD diagnoses did not differ by gender, $\chi^2(3,297) = 4.4$, $p = .39$.

Gender differences in the total sample

Table 1 shows the descriptive characteristics of the total included sample

Table 1. Descriptive statistics of boys and girls in the total sample and grouped by ASD diagnosis

	Total sample						Non-ASD						ASD					
	Boys			Girls			Boys			Girls			Boys			Girls		
Characteristics	*N*	*M*	*SD*	*N*	*M*	*SD*	*N*	*M*	*SD*	*N*	*M*	*SD*	*N*	*M*	*SD*	*N*	*M*	*SD*
Age screening (yrs)	167	6.7	2.3	64	7.9	2.0	61	6.8	2.3	40	8.2	2.1	106	6.6	2.3	24	7.3	1.8
Age diagnostic assessment (yrs)	167	7.5	2.4	64	8.9	2.1	61	7.7	2.4	40	9.2	2.2	106	7.4	2.4	24	8.2	1.9
SRS parent total	167	70.5	27.7	64	66.4	30.7	61	60.5	25.8	40	57.6	32.1	106	78.9	26.6	24	92.8	22.6
SRS teacher total	146	69.5	30.0	58	54.2	25.1	54	61.8	27.8	36	52.0	23.1	92	76.2	30.3	22	60.4	28.6
CBCL internalizing	156	63.0	9.9	60	65.7	8.6	59	62.7	9.9	40	64.5	8.6	97	63.3	9.9	20	70.0	8.1
CBCL externalizing	156	64.7	10.8	60	65.2	9.4	59	65.2	10.9	40	64.3	9.4	97	64.2	10.7	20	68.5	9.6
CBCL total	156	67.1	8.5	60	66.8	7.2	59	67.4	8.4	40	65.6	7.6	97	66.8	8.7	20	71.1	6.0
TRF internalizing	133	60.8	8.8	53	60.7	9.2	50	61.0	10.0	34	60.8	9.8	83	60.6	8.1	19	60.3	8.1
TRF externalizing	133	60.0	10.3	53	62.2	9.4	50	60.5	10.1	34	62.9	8.3	83	59.5	10.3	19	60.2	11.1
TRF total	133	61.9	9.1	53	62.2	6.8	50	62.6	9.8	34	62.7	5.6	83	61.3	8.6	19	60.7	8.7
RBS-R total	133	12.7	14.0	53	11.0	14.6	50	8.9	12.0	32	9.8	16.4	83	16.6	14.4	21	14.3	11.2
SSP total[a]	133	149.0	20.5	53	156.7	25.8	50	152.6	20.7	32	163.3	22.5	83	145.6	19.8	21	137.6	26.3
VIQ	136	96.0	15.1	57	103.8	17.6	53	94.2	15.4	36	105.3	17.0	83	97.8	14.9	21	98.9	19.1
PIQ	151	96.6	16.9	58	101.5	17.5	56	95.3	14.9	37	101.1	19.2	95	97.7	17.9	21	102.9	13.8
FSIQ	158	94.3	16.8	59	102.9	18.6	57	93.0	15.9	37	103.9	18.8	101	95.3	17.4	22	99.9	18.9

Note. Means (*M*) are weighted, counts (*N*) are unweighted. SRS = Social Responsiveness Scale, RBS-R = Repetitive Behavior Scale-Revised, SSP = Short Sensory Profile, CBCL = Child Behavior Checklist, TRF = Teacher Report Form, VIQ = Verbal IQ, PIQ = Performance IQ, FSIQ = Full Scale IQ.

[a]Higher scores indicate less sensory processing difficulties.

and non-ASD and ASD groups by gender. There were several general gender differences in the total sample, irrespective of ASD diagnosis. Compared to boys, girls were on average older, Wald $F = 10.40$ (230), $p = .001$, had higher levels of average IQ scores, Wald $F \geq 3.96$ (192), $p < .05$, more internalizing problems as reported by parents on the CBCL, Wald $F = 5.54$ (215), $p = .02$, and lower levels of autistic symptoms as reported by teachers on the SRS, Wald $F = 7.63$ (203), $p = .006$. These findings resembled gender differences in the initial screened sample, but for IQ this could not be examined because this data was not present for all screened children.

Gender differences in factors related to an ASD diagnosis

Table 2 shows the results of the prediction of an ASD diagnosis by standardized measures of various behavioral characteristics and their interactions with gender (see Supplement 1 for the results using unstandardized predictors, available online). Parent-reported and teacher-reported autistic symptoms on the SRS and sensory symptoms on the SSP significantly predicted an ASD diagnosis irrespective of gender. A significant interaction effect with gender was found for the RBS-R total scale, indicating that higher scores of restricted and repetitive behavior tended to be less predictive of an ASD diagnosis in girls than in boys. The odds ratio of .41 indicates that an increase of one standard deviation on the RBS-R total scale increased the odds of an ASD diagnosis in girls (*OR* = 1.10, 95% CI .48-2.45) less than half of what it increased the odds in boys (*OR* = 2.67, 95% CI 1.50-4.75). In addition, there was a significant interaction between gender and the total score on the CBCL, indicating that girls were more likely to be diagnosed with ASD when they had higher total levels of behavioral problems (*OR* = 2.40, 95% CI 1.13-5.29), whereas this effect was not present in boys (*OR* = .98, 95% CI .70-1.38). To illustrate these interactions, Figure 2 and 3 show the mean levels on these scales in boys and girls with and without ASD. No main effect nor interaction effect with gender was found for IQ and TRF scores.

Table 2. Logistic regression analyses predicting the probability of an ASD diagnosis

	Main effects			Interaction with gender		
Characteristics	*OR*	*95% CI*	*p*	*OR*	*95% CI*	*p*
SRS parent total	**2.13**	**1.54-2.95**	**<.001**	1.38	.34-2.05	.40
SRS teacher total	**1.72**	**1.19-2.50**	**.004**	.88	.97-1.02	.77
RBS-R total	1.76	.94-3.30	.08	**.41**	**.18-.92**	**.03**
SSP total[a]	**.58**	**.40-.85**	**.005**	.63	.30-1.31	.21
CBCL internalizing	1.20	.86-1.65	.28	2.00	.88-4.56	.10
CBCL externalizing	1.02	.75-1.39	.88	1.73	.90-3.32	.10
CBCL total	1.13	.84-1.53	.43	**2.44**	**1.13-5.29**	**.02**
TRF internalizing	1.01	.69-1.48	.96	.81	.37-1.76	.59
TRF externalizing	.91	.61-1.34	.62	.71	.26-1.94	.50
TRF total	.89	.61-1.31	.56	.67	.22-2.03	.48
Verbal IQ	1.02	.75-1.39	.90	.56	.28-1.11	.09
Performance IQ	1.07	.78-1.47	.67	.93	.48-1.81	.83
Full scale IQ	1.08	.78-1.50	.65	.73	.37-1.44	.37

Note. Boldface type indicates that interactions with gender reached significance ($p < .05$). Predictor variables are standardized (*z*-scores).

[a]Higher scores indicate less sensory processing difficulties.

SRS = Social Responsiveness Scale, RBS-R = Repetitive Behavior Scale-Revised, SSP = Short Sensory Profile, CBCL = Child Behavior Checklist, TRF = Teacher Report Form, VIQ = Verbal IQ, PIQ = Performance IQ, FSIQ = Full Scale IQ.

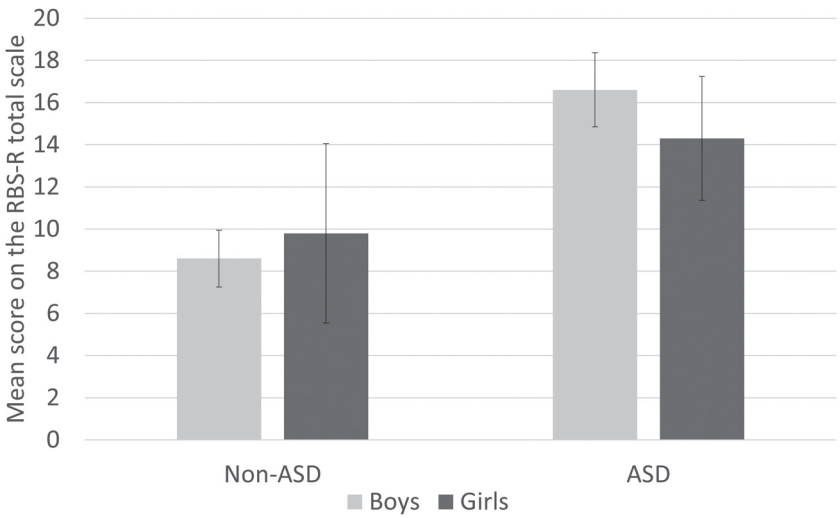

Figure 2. Mean levels of total RRB symptoms on the Repetitive Behavior Checklist Revised (RBS-R) in boys and girls with and without ASD

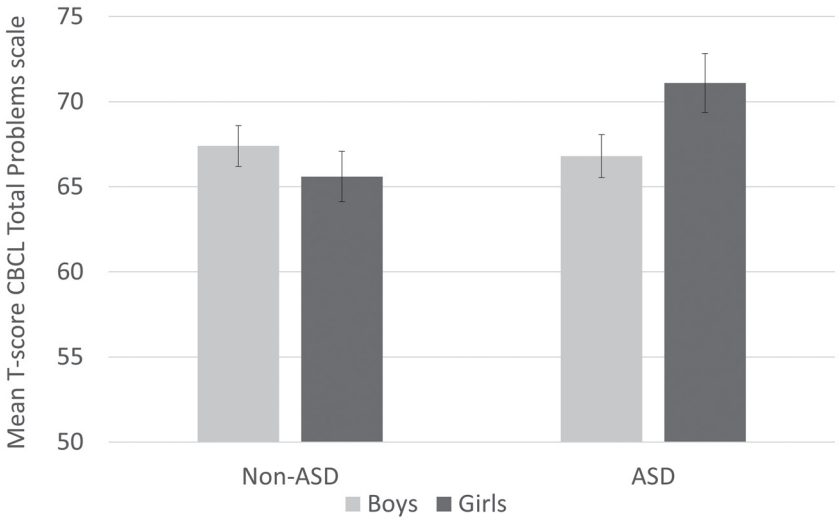

Figure 3. Mean levels of total emotional and behavioral problems on the Child Behavior Checklist (CBCL) in boys and girls with and without ASD

Discussion

The present study examined whether there are differences in how individual characteristics influence an ASD diagnosis in clinically referred girls versus boys. We found that higher overall levels of parent-reported RRB symptoms were less predictive of an ASD diagnosis in girls than in boys. In contrast, higher overall levels of parent-reported emotional and behavioral problems increased the probability of an ASD diagnosis in girls, but not in boys. No gender differences were found in the prediction of an ASD diagnosis by overall levels of autistic symptoms, sensory symptoms, and cognitive functioning. These findings may contribute to our understanding of why girls are less likely to be diagnosed with ASD than boys.

In our sample of clinically referred children, similar proportions of boys and girls were identified as having elevated ASD symptoms as indicated on the SRS. Since we do not know of any other study that screened for ASD in a clinically referred sample irrespective or referral reason, we cannot say whether our screening rates are consistent with other studies. However, despite similar screening rates in boys and girls, girls were less likely to receive an ASD diagnosis based on the standardized diagnostic instruments. This could mean that girls with ASD are at risk of being underidentified using current diagnostic

instruments. Consistently, using an adult sample, Lai et al. (2011) reported that only 21% of women with ASD met criteria for an ASD classification on the ADOS, compared to 58% of the men with ASD. A possible reason is that females with ASD may be better at masking their problems during a short observation (e.g., Hiller et al., 2016; Kreiser and White, 2014; Rynkiewicz et al., 2016). So, diagnostic instruments and/or their manuals may need to be adapted to improve the identification of ASD in girls. For instance, some scoring items may need to be adapted to provide examples that are more characteristic of girls. In addition, administrators may need to gain more training/experience in scoring these instrument in girls. A more profound adaptation would be the development of gender-specific cut-offs. This could lead to more girls with ASD being identified, but possibly also to an overinclusion of girls who deviate too much from the conceptualization of ASD. Clearly, before more specific recommendations can be made about possible adaptations, more information is needed about why females are less likely to reach the diagnostic threshold and whether adaptations truly result in an improved discriminative ability of these instruments in girls.

As hypothesized, we found that overall RRB symptoms were less strongly associated with ASD in girls than in boys. Thus, whereas there was a notable contrast in the level of RRB symptoms between boys with ASD and non-ASD, with boys with ASD showing higher levels of RRB symptoms, this was not the case for girls. One possible explanation is that girls with ASD are characterized by lower levels of RRB symptoms than boys, suggesting a quantitative difference, in line with findings of previous studies that investigated mean differences in RRB symptoms between boys and girls with ASD (Frazier et al., 2014; Mandy et al., 2012; Szatmari et al., 2012). However, we did not find an overall quantitative difference in the level of RRB symptoms between referred boys and girls, which may imply that it is not just a matter that girls have a lower likelihood of ASD because of lower levels of RRB symptoms in general. It also possible that RRB symptoms in girls with ASD are qualitatively different from those in boys and are therefore not adequately captured by current instruments or less likely to recognized by clinicians as being characteristic of ASD (Hiller et al., 2016; Mandy et al., 2012; Hiller et al., 2014). For example, girls with ASD may be less likely to show stereotyped use of objects (e.g., lining up toys) and their restricted interests may concern topics that are socially accepted for girls (e.g., horses or Barbie dolls; Attwood, 2007) or that seem random (e.g., rocks, stickers,

pens; Hiller et al., 2014). It should be noted that the measure for RRB symptoms used in the present study, the RBS-R, only contains few items on restricted interests and may therefore lack sensitivity to a differential expression of this domain in cognitively able girls with ASD. A failure of instruments to capture the expression of these symptoms in girls, could also contribute to apparent quantitative differences between boys and girls with ASD (Van Wijngaarden-Cremers et al., 2014). Therefore, further research at a more detailed level is needed to advance our understanding of the expression of RRB symptoms in girls with ASD.

In contrast, sensory symptoms, which are added to the RRB domain in the DSM-5, were positively associated with an ASD diagnosis in both boys and girls. In the light of the finding that overall RRB symptoms did not contribute to an ASD diagnosis in girls, this might suggest that the evaluation of sensory symptoms is particularly important for the evaluation of ASD in girls. Few studies have yet compared the expression of sensory symptoms associated with ASD between girls and boys. In a study among adults, there was preliminary evidence that women with ASD showed more sensory symptoms on the ADI-R than men with ASD (Lai et al., 2011). This needs to be examined further, with attention to different types of sensory symptoms.

The finding that higher overall levels of emotional and behavioral problems increased the probability that girls, but not boys, received an ASD diagnosis, is in line with a previous general population study (Dworzynski et al., 2012). There are several possible explanations for this finding. First, this could indicate that girls with ASD are vulnerable for experiencing high levels of co-occurring emotional and behavioral problems. Case reports described that cognitively able girls with ASD can be sensitive to social expectations and sometimes copy social behaviors from peers or characters in books or television shows (Bargiela et al., 2016). In that way, they camouflage their limitations, but this takes a lot of their energy, which may lead to drained or edgy feelings and behaviors that are noticeable in the home setting. Second, this finding may reflect a diagnostic bias, indicating that girls with ASD without these problems are overlooked. Qualitative studies have also reported how some girls have struggled a long time before they received an ASD diagnosis (Cridland et al., 2014; Bargiela et al., 2016). The timely identification of girls with ASD may not only be important to provide them with services to improve their outcomes, which is an important subject for further investigation (Wong et al., 2015), but

also to provide these girls with a sense of belonging and understanding of their difficulties (Bargiela et al., 2016). Third, and not necessarily in contradiction with the former explanation, girls without high levels of emotional and behavioral problems may be better able to compensate for possibly elevated ASD problems (Dworzynski et al., 2012; Mandy et al., 2012). However, it is debatable whether this latter group—if they would not meet diagnostic criteria for ASD when subtle variations in the expression of symptoms are taken into account—should be regarded in the light of the autism phenotype. In addition, further research is needed to investigate whether these girls are at risk of developing more problems or significant distress over time or whether they really function better (Kreiser and White, 2014).

We found some important informant differences. Only emotional and behavioral problems reported by parents, but not by teachers, increased the probability that girls received an ASD diagnosis. Although Dworzynski et al. (2012) did find that girls for whom the teacher reported high levels of total behavioral and hyperactivity problems were more likely to be diagnosed with ASD, these findings are difficult to compare to our own because they used a general population sample and did not include parent ratings. For ADHD, some differences were found between boys and girls with ADHD in the general population that could not be detected in clinical samples, possibly because referred girls are more severely affected (Gaub and Carlson, 1997). The informant discrepancy in our study could indicate that teachers are less likely to recognize difficulties in girls with ASD. Teachers reported lower levels of autistic symptoms in referred girls than in referred boys, which is consistent with previous studies using ASD samples (Mandy et al., 2012; Hiller et al., 2014) and general population samples (Posserud et al., 2006; Constantino and Gruber, 2012). Previous studies also found that teachers reported lower levels of externalizing behavior in girls than in boys with ASD (Mandy et al., 2012; Hiller et al., 2014). The 'camouflaging' abilities of some cognitively able girls with ASD may also contribute to the discrepancy between teacher and parent ratings. So, caution is needed in relying on teacher ratings to screen for ASD in girls, though they still can provide valuable information in addition to parent ratings (Duvekot et al., 2015). More research is needed to better understand these informant effects in relation to gender differences and how these can be dealt with in order to improve the identification of ASD in girls.

In contrast to the study by Dworzynski et al. (2012), we did not find that lower levels of IQ were more strongly associated with an ASD diagnosis in girls than in boys. This is surprising, given that is often assumed that girls with ASD have a greater risk of cognitive impairments than boys with ASD (Frazier et al., 2014; Volkmar et al., 1993; Fombonne, 2003; Fombonne, 2005). However, several recent studies also failed to find gender differences for IQ (Mandy et al., 2012; Hartley and Sikora, 2009). Similar to these studies, our sample showed a wide range of IQ, but with the majority of children showing a normal/high IQ level, because that was the target population of the majority of the participating CAMHS. It is possible that there is only an increase in the probability of an ASD diagnosis in girls with an intellectual impairment (IQ < 70). This should be examined further in samples with more individuals in the lower IQ range.

Several studies reported that girls with ASD have higher levels of internalizing problems than boys with ASD (Mandy et al., 2012; Oswald et al., 2016; Hartley and Sikora, 2009; Solomon et al., 2012). Although we found that girls had higher levels of internalizing problems than boys in the total sample, the absence of a significant interaction effect with gender in the prediction of an ASD diagnosis suggests that this may reflect a general gender difference in internalizing problems, consistent with findings of gender differences in internalizing symptoms in other referred populations (Compas et al., 1997) and the general population (Crijnen et al., 1997), rather than a specific vulnerability of girls with ASD to develop internalizing problems. Future research should also examine this in older samples, as it could be that ASD-specific gender differences in internalizing symptoms emerge later during adolescence (Oswald et al., 2016). However, even if internalizing problems are not specific for girls with ASD, the heightened vulnerability of girls to develop internalizing problems has implications for the treatment needs of girls with ASD.

Strengths and Limitations

A strength of the present study is that we screened a large sample of children who had been referred to multiple mental health services and used well-established standardized instruments for the diagnosis of ASD in a selection of this sample. Importantly, we did not only perform diagnostic assessment for ASD in children with a positive screen for ASD, but also in a random selection of children with a negative screen. This design may have reduced the diagnostic bias that may be pronounced in clinical samples that recruited children with a

previously established diagnosis of ASD. Moreover, because we did not use the presence of an ASD diagnosis as an inclusion criterion, our design was suitable to investigate factors that determine the probability of receiving an ASD diagnosis. Other strengths are that we assessed a wide variety of characteristics and used multiple informants for some assessments.

Our study also has several limitations. Since we used a clinically referred sample, our findings cannot be generalized to the general population. Certain gender biases may already have been present at referral. Consistent with the literature, the initial referred sample already consisted of fewer girls than boys, and referred girls were also significantly older than referred boys. This could reflect that girls are more likely to be referred for internalizing problems, which tend to increase with age, whereas boys are more likely to be referred for externalizing problems (Zwaanswijk et al., 2003). Furthermore, girls with ASD might only be referred if they have severe symptoms or symptoms that more closely resemble those in males. Therefore, it also important to investigate factors related to identification of ASD in general population samples.

In addition, we used two different versions of the CBCL. Because girls were older than boys, a greater proportion of girls (82%) than boys (64%) received the CBCL/6-18 instead of the CBCL/1.5-5. Although we have taken measures to account for the age difference between boys and girls and the use of different age versions of the CBCL by correcting for age in our analyses and using standardizing scores, we cannot rule out the possibility that this may have influenced our findings. Another limitation is that the number of girls with ASD included in the sample was small, which limited the power to detect small interaction effects. To limit the number of tests conducted in our small sample, we examined total scores rather than subscale scores for most measures. Moreover, we used conventional, standardized measures that may be biased towards symptoms that are characteristic of males with ASD and may therefore be less sensitive to detect subtle differences between boys and girls with ASD (Lai et al., 2015). So, further research using other methods is needed to investigate fine-grained differences between boys and girls at a more detailed level in larger samples.

Conclusion

Our results suggest that some individual behavioral characteristics (i.e., RRB symptoms and emotional and behavioral problems) affect the diagnosis of ASD

differently in girls than in boys, possibly contributing to an underidentification of ASD in girls. One of the factors that may contribute to a lower probability of girls to be diagnosed with ASD, is that RRB symptoms are not as predictive of an ASD diagnosis in girls than in boys. The finding that sensory symptoms were equally predictive of an ASD diagnosis in girls as in boys needs to be investigated further and suggest the importance of assessing sensory symptoms in the diagnostic evaluation of ASD in girls. We also found support that girls, but not boys, were more likely to be diagnosed with ASD if they had higher levels of emotional and behavioral problems. This highlights that it is important to be aware of high levels of co-occurring emotional and behavioral problems in girls with ASD and the possibility that girls with ASD who do not display high levels of co-occurring emotional and behavioral problems may be at risk of being overlooked. Further research is needed to also investigate the possibility that girls who display subclinical levels of autistic symptoms in the absence of these problems have compensatory abilities that prevent them from reaching the clinical threshold and whether these girls are at risk of developing more autistic or other difficulties over time.

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Part 2

The co-occurrence of autism and anxiety

Chapter 5

Symptoms of autism spectrum disorder and anxiety: shared familial transmission and cross-assortative mating

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Abstract

Background: In order to shed more light on the frequent co-occurrence of Autism Spectrum Disorder (ASD) and anxiety in children, the aims of the study were (1) to examine whether ASD and anxiety share familial transmission indicated by cross-symptom associations between parental and children's symptoms (e.g., parental anxiety predicting children's ASD) in addition to associations for similar symptoms; (2) to investigate the possibility that cross-assortative mating (i.e., whether ASD symptoms in one parent are positively associated with anxiety symptoms in the other parent) increases the risk for both ASD and anxiety in children.

Method: In 231 families of clinically referred children, parents rated both their own and the other parent's ASD and anxiety symptoms and one parent those of the index child and siblings ($n = 447$, aged 2.5-18 years). ASD symptoms were assessed using the Social Responsiveness Scale (SRS-2) and anxiety symptoms using the Achenbach System of Empirically Based Assessment (ASEBA) instruments.

Results: Parental ASD and anxiety symptoms predicted similar symptoms in children, dependent on the informant type. Additionally, parental anxiety symptoms across both self-report and informant-report predicted children's ASD symptoms and maternal self-reported ASD symptoms predicted children's anxiety symptoms. ASD and anxiety symptoms were correlated within parents, but we found no cross-symptom associations between parents.

Conclusions: Cross-symptom associations between parental and children's ASD and anxiety symptoms suggest shared familial transmission of ASD and anxiety, but further research is needed to clarify the underlying mechanisms. Cross-assortative mating does not seem a likely explanation for the co-occurrence of ASD and anxiety in children.

Introduction

The frequent co-occurrence of ASD and anxiety in children has been well established. Nearly 40% of children with ASD have anxiety symptoms in the clinical range or meet criteria for at least one anxiety disorder (van Steensel, Bogels, & Perrin, 2011). Inversely, children with anxiety disorders are at risk for elevated levels of ASD symptoms (Pine, Guyer, Goldwin, Towbin, & Leibenluft, 2008). A twin study suggested some etiological overlap between ASD and anxiety (Hallett, et al., 2013). In addition, an increased prevalence of anxiety disorders has been found in the relatives of individuals with ASD (Bolton, Pickles, Murphy, & Rutter, 1998; Mazefsky, Folstein, & Lainhart, 2008; Micali, Chakrabarti, & Fombonne, 2004; Piven & Palmer, 1999). Despite evidence of familial aggregation of ASD and anxiety, it remains unclear whether ASD and anxiety are transmitted independently within families or whether they have a shared familial transmission. In order to shed more light on whether shared familial transmission could contribute to the frequent co-occurrence of ASD and anxiety, the present study examined associations across ASD and anxiety symptoms among parents and children.

Research has demonstrated that symptoms of ASD (Constantino & Todd, 2005; De la Marche, et al., 2014; Klusek, Losh, & Martin, 2014; Lyall, et al., 2014; Maxwell, Parish-Morris, Hsin, Bush, & Schultz, 2013) and anxiety (Beidel & Turner, 1997; Last, Hersen, Kazdin, Orvaschel, & Perrin, 1991) are transmitted within families without consideration of co-occurring symptoms. In addition, parental anxiety symptoms have been related to co-occurring anxiety symptoms in children with ASD (Conner, Maddox, & White, 2013; Park, Park, Kim, & Yoo, 2013). However, it remains to be elucidated whether ASD and anxiety have a shared familial transmission. Evidence exists that attention-deficit/hyperactivity disorder (ADHD) in mothers is not only related to ADHD but also to ASD in children, supporting shared familial transmission of ASD and ADHD (Musser, et al., 2014; van Steijn, et al., 2012). Yet, for the co-occurrence of ASD and anxiety this still needs to be examined.

An alternative explanation for the co-occurrence of ASD and anxiety is cross-assortative mating, meaning that a parent with high levels of ASD symptoms may be more likely to select a partner with high levels of anxiety symptoms or vice versa (Piven & Palmer, 1999). This could put the child at a double risk for ASD as well as anxiety symptoms. Several studies found evidence for

assortative mating for ASD, that is the tendency for parents to have similar ASD characteristics (Constantino & Todd, 2005; Lyall, et al., 2014; Seidman, Yirmiya, Milshtein, Ebstein, & Levi, 2012), but other studies did not (Hoekstra, Bartels, Verweij, & Boomsma, 2007; van Steijn, et al., 2012). Assortative mating has also been reported for anxiety symptoms (Maes, et al., 1998). The only study to date that has examined the possibility of cross-assortative mating for ASD and anxiety demonstrated that elevated levels of anxiety symptoms in parents of children with ASD were associated with their own ASD symptoms, but not with the ASD symptoms of their spouses (Lau, Gau, Chiu, & Wu, 2014). However, a limitation of this study is that they only used self-report data. Research has shown that estimates of within-parent and between-parent associations could be biased if only one informant method (self-report or informant-report) is used (Orth, 2013). Because the study of Lau, et al. (2014) only relied on self-report data, the associations between ASD and anxiety symptoms within parents were estimated using data from the same informant, and thus may be inflated by shared method variance, whereas the associations between parents were based on information from different informants.

Using a multi-informant assessment of parental symptoms, the current study aimed to contribute to our understanding of the co-occurrence of ASD and anxiety by investigating: (1) whether associations between these two types of symptoms in parents and children support possible shared familial transmission of ASD and anxiety (e.g., whether parental anxiety symptoms are related to children's ASD symptoms as well as anxiety symptoms); (2) whether associations between ASD and anxiety symptoms among parents indicate the possibility of cross-assortative mating (e.g., whether a parent with higher levels of ASD symptoms is more likely to have a partner with higher levels of anxiety symptoms). Consistent with an increasing recognition that characteristics of many childhood disorders vary along a continuum (Coghill & Sonuga-Barke, 2012; Constantino, 2011), we used a dimensional approach to the assessments of ASD and anxiety symptoms within families. This dimensional approach is considered important to increase our understanding of the etiological underpinnings of child psychopathology (e.g., Hudziak, Achenbach, Althoff, & Pine, 2007) and is supported by evidence that subclinical autistic traits are transmitted in families of children who are not diagnosed with ASD (Lyall, et al., 2014).

Method

Participants and procedure

Families were recruited as part of a larger study, the Social Spectrum Study, which used a two-phase screening procedure to oversample children at risk for ASD among 2.5- to 10-year-old children who had been consecutively referred for various mental health problems to one of six mental health care centers in the Netherlands. All 428 children who were considered at risk for ASD because of a total raw score ≥ 75 on the parent-reported Social Responsiveness Scale (Constantino & Gruber, 2012) and a random selection of children who scored below this cut-off (n = 240 out of 853) were invited to participate in further assessments. As part of these assessments, both parents were asked to report on their own symptoms and those of the other parent living in the same household.

In the current analyses, we included 231 families for which we had at least one measure of parental ASD or anxiety symptoms (self-report or informant-report). This sample consisted of 159 families of children at risk for ASD (parent-report SRS total score ≥ 75) and 72 families of children who were not considered at risk for ASD (parent-report SRS total score < 75). Attrition analyses showed that children of included families (n = 231) scored higher than children of families that were not included (n = 433) on parent-reported ASD symptoms, $t(662) = -2.84$, $p = .005$; and anxiety symptoms, $t(593) = -2.26$, $p = .02$. No significant differences with respect to the child's sex, $\chi^2(1) = .47$, $p = .50$; or the child's age, $t(662) = .23$, $p = .82$, were found.

In order to represent the full range of the continuum of ASD symptoms and increase statistical power to detect associations, we also included data regarding symptoms of siblings of the index child (i.e., referred child). For two families with more than three siblings, questionnaires were completed for the three siblings closest in age and biologically related to the index child. We had data for 216 out of the 227 siblings aged 2.5 to 18 years in these families (for four families this information was missing), thus for 447 children in total. Of the 216 siblings, 28 siblings had elevated ASD symptoms (parent-report SRS total score ≥ 75) according the parent-reported SRS. Questionnaires for all children were in 92% of the cases completed by the biological mother, in 6% by the biological father, and in 2% by another parent (adoptive parent, stepparent, or foster parent). In total, 96% of the mothers, 87% of the fathers, and 88%

of the siblings were biologically related to the index child. Because familial transmission can occur through genetic as well as environmental mechanisms we used all data for our analyses. Table 1 presents the descriptive characteristics of the index children, siblings, and parents.

The study was approved by the local medical ethics committee and participating mental health care centers (MEC-2011-078) and informed consent was obtained from all included families.

Measures

ASD symptoms of the children and their parents were assessed using parallel versions of the Social Responsiveness Scale 2nd edition (SRS-2; Constantino & Gruber, 2012). All versions of the SRS contain 65 items that are scored on a 4-point scale from 0 (*not true*) to 3 (*almost always true*) and summed up to a total raw score representing ASD symptom severity. We used the preschool version for children aged 2.5 to 4 years (n = 42, 9%) and the school-age version for children aged 4 to 18 years (n = 405, 91%). The preschool version is largely similar to the school-age version; 10 items were adapted to make the wording more appropriate for preschoolers while preserving the content (e.g., "Is able to communicate his or her feelings to others in words or gestures" replaces "Is able to communicate his or her feelings to others"). The SRS for school-age children has been found to have good internal consistency, inter-rater reliability, and ability to discriminate between children with ASD and children with other psychiatric disorders (Constantino & Gruber, 2012), which has been confirmed for the Dutch school-age version (Duvekot, van der Ende, Verhulst, & Greaves-Lord, 2015; Roeyers, Thys, Druart, De Schryver, & Schittekate, 2011). Parental ASD symptoms were assessed using the self-report and informant-report adult versions of the SRS, which were also derived versions of the school-age version of the SRS. The adult versions of the SRS have also been reported to have good reliability and validity (Bölte, 2012; Constantino & Gruber, 2012).

Anxiety symptoms of the children and parents were assessed using the DSM-oriented Anxiety Problems scale from parallel forms of the Achenbach System of Empirically Based Assessment (ASEBA) instruments. Items of the ASEBA instruments are scored on a 3-point scale (0 = *not true*, 1 = *somewhat or sometimes true*, 2 = *very true or often true*). We used the Child Behavior Checklist (CBCL) for children aged 1.5 to 5 years (n = 127, 30%) and for children aged 6 to 18 years (n = 300, 70%). The DSM-oriented Anxiety Problems scale contains

Table 1 *Descriptive characteristics of the participants*

	Index children (*N* = 231)			Siblings (*N* = 216)			Mothers (*N* = 224)			Fathers (*N* = 182)		
	M	*SD*	Range	*M*	*SD*	Range	*M*	*SD*	Range	*M*	*SD*	Range
Age, years	6.77	2.26	2-10	8.35	4.12	2-18	37.74	5.4	26-53	40.55	5.67	27-58
Sex, male, %	73%			53%								
Ethnicity[a], %												
Dutch	81%											
Other Western	7%											
Non-Western	13%											
Education[b], *n* (%)												
High							23%			28%		
Medium							49%			43%		
Low							29%			28%		
Birth order	1.78	1.03	1-6	2.06	1.11	1-7						
Total IQ	97.83	17.28	50-145									
ASD symptoms[c]												
Parent-report	83.00	27.92	18-142	41.89	29.41	5-159						
≥ *T* score 60, %	78%			23%								
Adult self-report							33.70	19.55	4-97	34.71	21.77	3-136
≥ *T* score 60, %							7%			7%		
Adult informant-report							29.04	18.79	2-81	38.38	25.88	1-129
≥ *T* score 60, %							6%			14%		
Anxiety symptoms[d]												
Parent-report	63.67	9.48	50-95	54.60	7.83	50-84						
≥ *T* score 65, %	53%			15%								
Adult self-report							54.43	6.41	50-80	52.91	4.96	50-73
≥ *T* score 65, %							10%			5%		
Adult informant-report							53.76	5.62	50-75	53.42	5.45	50-77
≥ *T* score 65, %							7%			7%		

Note. *N* displays the number of children and parents for whom at least one symptom measure was available. Missing data for the 231 families: birth order children 5.6%, anxiety symptoms children 4.5%, maternal education 6.5%, paternal education 25.1%, maternal self-report data 6.5%, paternal self-report data 48.1%, paternal informant-report data 29.4%, maternal informant-report data 51.9%.

[a]Ethnicity was determined by the country of birth of the parents and classified as other Western or non-Western if at least one parent was born abroad.

[b]Education was categorized as low (primary school or lower vocational education), medium (intermediate vocational education), and high (higher vocational education or university).

[c]Autism spectrum disorder (ASD) symptoms were assessed using the Social Responsiveness Scale 2nd edition (SRS-2): total raw scores are reported.

[d]Anxiety symptoms were assessed using the DSM-oriented Anxiety Problems scale of the Achenbach System of Empirically Based Assessment (ASEBA) instruments: *T* scores are reported.

10 items in the CBCL/1,5-5 and six items in the CBCL/6-18. Internal consistency and test-retest reliability for the DSM-oriented Anxiety Problems scale of both versions are adequate to good (Achenbach & Rescorla, 2000; Verhulst & Van der Ende, 2013). In addition, this scale has been found to discriminate well between children with and without anxiety disorders (Ebesutani, et al., 2010). Because the DSM-oriented Anxiety Problems scale is not equivalent for the CBCL/1,5-5 and CBCL/6-18, we used *T* scores to make the scores across both versions comparable. Parental anxiety symptoms were assessed using the Adult Self-report (ASR), completed by parents about themselves, and the Adult Behavior Checklist (ABCL), completed by parents about the other parent. The DSM-oriented Anxiety Problems scale contains seven items in the ASR and six items in the ABCL. The reliability and validity of this scale has been supported for these questionnaires as well (Achenbach & Rescorla, 2003).

Statistical analyses

Because we included multiple children per family, associations between parental and children's ASD and anxiety symptoms (Aim 1) were examined using multilevel analysis. Multilevel analysis takes the clustering of data within families into account and enables the evaluation of predictors both at the individual and family level. In the present study, we used two-level path models to examine the effect of parental symptoms on children's ASD and anxiety symptoms simultaneously, while controlling for children's sex and age, and maternal and paternal age. First, we analyzed associations of similar symptoms between parents and children, thus parental ASD predicting children's ASD symptoms and parental anxiety predicting children's anxiety symptoms. Second, we investigated cross-symptom associations by including both parental ASD and anxiety symptoms, adjusting for each other, to predict children's ASD and anxiety symptoms. The hypothesized associations are depicted in Figure 1. Models were run separately for maternal and paternal symptoms by informant type (self-report and informant-report) to investigate potential specific effects for parent-of-origin and informant type. To examine whether the magnitude of relationships differ between the index children and siblings, we tested for possible interactions between parental symptoms and a dummy variable indicating whether the child was an index child or sibling. Consistent with previous studies (e.g., Lyall, et al., 2014), we used raw scores to examine familial associations, except for the CBCL, for which we used *T* scores

(see Measures section). In addition, scores on all continuous variables (parental symptoms, child symptoms, age) were transformed into *z* scores to facilitate comparisons across variables.

To examine the possibility of cross-assortative mating for ASD and anxiety symptoms between parents (Aim 2), we used structural equation modeling to estimate an actor-partner interdependence model (APIM; Kenny, Kashy, & Cook, 2006). This model accounts for the dependence between individuals in a dyadic relationship by testing simultaneously how individuals are affected by their own characteristics (actor effects) as well as by the characteristics of their partner (partner effects). In the current study, we investigated whether anxiety symptoms in parents affected their own ASD symptoms (actor effect) and the ASD symptoms of the other parent (partner effect), with the latter possibly indicating cross-assortative mating. In line with the study by van Dulmen and Goncy (2010), we extended the APIM by including cross-informant associations of parental ASD and anxiety symptoms. To allow for model identification, we constrained several correlations among the predictor variables and the outcome variables to be equal (see Figure 2): (1) intrapersonal correlations between self-report and informant-report; (2) interpersonal correlations using the same informant; (3) interpersonal correlations using different informants. The fit of the model to the data was evaluated using the comparative fit index (CFI), the root mean squared error of approximation (RMSEA) and the standardized root-mean-square residuals (SRMSR). Model fit was considered good if CFI ≥ .95, RMSEA ≤ .06 and SRMR ≤ .08 (Hu & Bentler, 1999). In addition, we tested for differences in the magnitude of actor and partner effects and for differences between mothers and fathers by constraining effects to be equal. A significant chi-square change of the constrained model compared to the baseline model would indicate a worse fit of the constrained model and thus that effects significantly differ.

All analyses were conducted using Mplus 7.2 using full information maximum likelihood estimation to accommodate missing data. The Mplus estimator MLR provides standard errors that are robust for skewed data (Muthén & Muthén, 1998-2012). An alpha level of .05 (two-tailed) was used to indicate significant results.

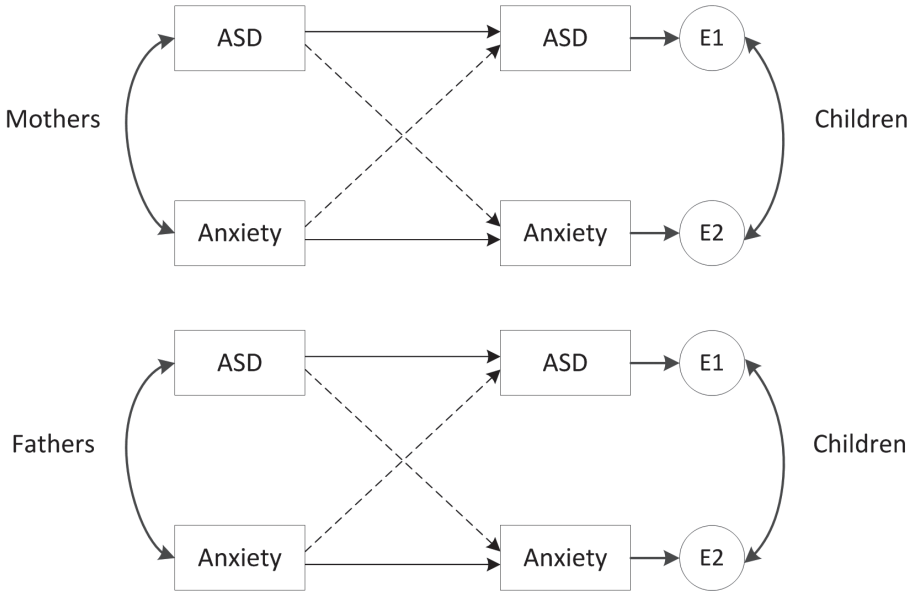

Figure 1. Conceptual model of hypothesized associations between parents' and children's symptoms of ASD and anxiety (Aim 1). Solid lines represent associations for similar symptoms and broken lines represent cross-symptom associations

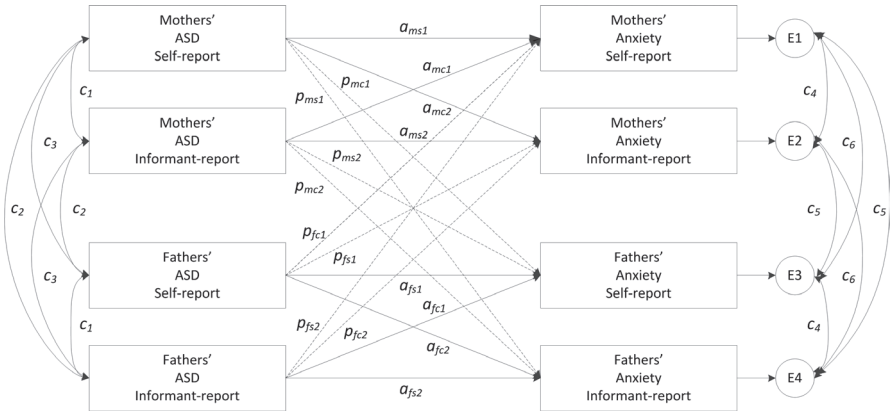

Figure 2. The actor-partner interdependence model (APIM) to investigate cross-assortative mating (Aim 2). *a*'s represent actor effects and *p*'s represent partner effects, with subscript *m* representing mother's effects, subscript *f* representing father's effects, subscript *s* representing effects for data from the same informant and subscript *c* representing effects for cross-informant data; E_1 and E_2 respectively represent the residual variance in mothers' and fathers' anxiety symptoms, after controlling for *a* and *p* effects; $c_{1\text{-}3}$ represent the correlations between the parents' ASD symptoms and $c_{4\text{-}6}$ represent the residual correlations between the parents' anxiety symptoms, after controlling for *a* and *p* effects; *c*'s with the same number were constrained to be equal to allow for model identification.

Sensitivity analyses

We conducted several sensitivity analyses to test whether the parent-child associations were consistent when using only (1) biologically related parents and children; (2) cases with complete data on parental variables; and (3) children aged 6 years or older, for whom the same version of the CBCL and SRS was completed. In order to check whether results may be confounded by overlap in the measurement instruments, we calculated a modified SRS score for children without items that can be considered as tapping into anxiety problems as well (items 9, 30, 43, and 64) and repeated analyses with this modified SRS score. Since the adult versions of the SRS and the ASR/ABCL showed less overlap and we already adjusted for parental ASD or anxiety symptoms in the cross-symptom analyses, we did not use modified SRS scores for parents.

Results

Parent-child associations

Figure 3 illustrates the significant associations between parental and child ASD and anxiety symptoms for self-reported and informant-reported symptoms in mothers and fathers. The estimates of these associations are shown in Table 2. In all models, we controlled for the children's sex and age, and maternal and paternal age. The estimates of these covariates are shown in the supplementary Table S1 (available online).

With respect to the associations of similar symptoms, we found that maternal and paternal ASD symptoms reported by the mother significantly predicted children's ASD symptoms (i.e., maternal self-reported and paternal informant-reported symptoms). Parental ASD symptoms reported by the father were only significantly associated with children's ASD symptoms when parental anxiety symptoms were not included in the model (Model 1). Parental anxiety symptoms were also significantly related to children's anxiety symptoms, except for self-reported anxiety symptoms in fathers.

With respect to the cross-symptom associations, parental anxiety symptoms significantly predicted children's ASD symptoms, even after correcting for parental ASD symptoms. This was consistent for both self-reported and informant-reported symptoms in mothers as well as fathers. Parental anxiety symptoms reported by fathers were even a stronger predictor of children's ASD symptoms than parental

ASD symptoms, partly accounting for the association between parental ASD and children's ASD symptoms. In addition, maternal self-reported ASD symptoms were independently associated with children's anxiety symptoms, but this was not found for maternal informant-reported ASD symptoms. We did not find cross-symptom associations between paternal ASD symptoms and children's anxiety symptoms when correcting for paternal anxiety symptoms.

We found one significant interaction effect indicating a significant difference between index children and siblings in the magnitude of the effect of informant-reported anxiety symptoms in fathers on children's anxiety symptoms (b = 1.01, SE = .34, p < .001); the interaction effect on children's ASD symptoms was borderline significant (b = .57, SE = .30, p =.05). Running separate analyses for index children and siblings showed that the effect of informant-reported anxiety symptoms in fathers on children's anxiety symptoms was stronger in siblings (siblings: b = .30, SE = .06, p < .001) than in index children (b = .14, SE = .08, p = .10). A similar result was found for the effect on children's ASD symptoms (siblings: b = .23, SE = .05, p < .001 vs. index children: b = .02, SE = 0.07, p = .75).

Sensitivity analyses

We found largely similar results in subsamples of (1) biologically related parents and children, (2) cases with complete data on parental variables, and (3) children aged 6 years or older (see supplementary Tables S2-4, at the end of this chapter). After removal of items in the SRS that showed overlap with anxiety problems, the correlation between ASD and anxiety symptoms in children decreased from .65 to .62. The parent-child associations using this modified SRS score were also largely similar (see supplementary Table S5, at the end of this chapter).

Associations among parents

The baseline APIM model, illustrated in Figure 4, had a good fit to the data, χ^2 (6) = 9.38, p =.15, CFI = .98, RMSEA = .05 and SRMR = .03. Higher levels of parents' ASD symptoms significantly predicted higher levels of their own anxiety symptoms (actor effects), particularly when symptoms were reported by the same informant, indicating that these relationships may be inflated due to shared method variance. However, in fathers we also found a significant cross-informant actor effect for informant-reported ASD symptoms on self-reported

Table 2 *Associations between parental and children's ASD and anxiety symptoms*

	Model 1				Model 2			
	Child ASD symptoms		Child anxiety symptoms		Child ASD symptoms		Child anxiety symptoms	
	b (SE)	*p*	*b (SE)*	*p*	*b (SE)*	*p*	*b (SE)*	*p*
Self-reported symptoms								
Mother								
ASD	**.16 (.04)**	**<.001**			**.17 (.04)**	**<.001**	**.14 (.06)**	**.01**
Anxiety			**.18 (.05)**	**<.001**	**.13 (.04)**	**.003**	**.20 (.05)**	**<.001**
Father								
ASD	**.10 (.04)**	**.03**			.06 (.05)	.27	.01 (.09)	.94
Anxiety			.06 (.06)	.32	**.11 (.05)**	**.04**	.11 (.08)	.19
Informant-reported symptoms								
Mother								
ASD	**.13 (.03)**	**<.001**			.08 (.04)	.06	-.04 (.06)	.48
Anxiety			**.24 (.05)**	**<.001**	**.13 (.04)**	**.003**	**.33 (.06)**	**<.001**
Father								
ASD	**.18 (.04)**	**<.001**			**.19 (.04)**	**<.001**	.09 (.06)	.14
Anxiety			**.17 (.04)**	**<.001**	**.12 (.04)**	**.002**	**.22 (.06)**	**<.001**

Note. Model 1 includes parent-child associations for the same type of symptoms. Model 2 additionally includes cross-symptom associations, thus children's symptoms of Autism Spectrum Disorder (ASD) and anxiety are predicted by both parental ASD and anxiety symptoms (adjusted for each other). Statistical significant coefficients are presented in bold. All models are also adjusted for the child's sex and age and the parents' age. Continuous variables are transformed to *z* scores. Families (level 2) $n = 231$, children (level 1) $n = 447$.

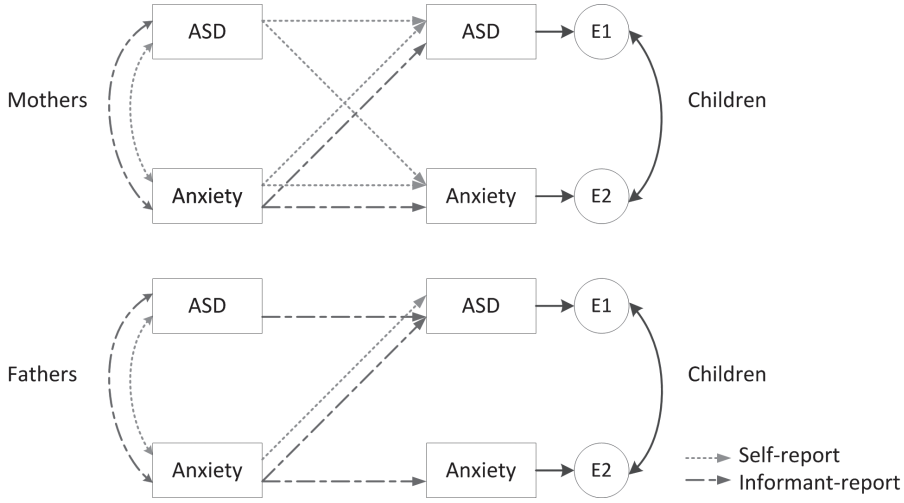

Figure 3. Significant associations of ASD and anxiety symptoms between parents and children (Aim 1). Estimates for the associations are presented in Table 2 Model 2.

anxiety symptoms, which cannot be explained by shared method variance. In addition, one significant partner effect was found: Higher levels of fathers' ASD symptoms reported by mothers predicted higher levels of mothers' self-reported anxiety symptoms. Again, this finding may have been affected by shared method variance.

Constraining actor and partner effects to be equal indicated a significant difference in the magnitude of actor and partner effects (χ^2 (8) = 23.87, p = .002). Because the actor and partner effects on each dependent variable were constrained using data from the same informant (e.g., the effect of mothers' self-reported ASD symptoms on mothers' self-reported anxiety symptoms is equal to the effect of fathers' informant-reported ASD symptoms on mothers' self-reported anxiety symptoms), the difference between actor and partner effects cannot be explained by a differential influence of shared method variance on these effects. Constraining effects for mothers and fathers to be equal indicated that there was no significant difference between mothers and fathers in the magnitude of actor (χ^2 (6) = 5.25, p = .51) nor partner effects (χ^2 (6) = 2.65, p = .85). Together, these findings suggest that the associations between ASD and anxiety symptoms among parents were primarily actor-oriented.

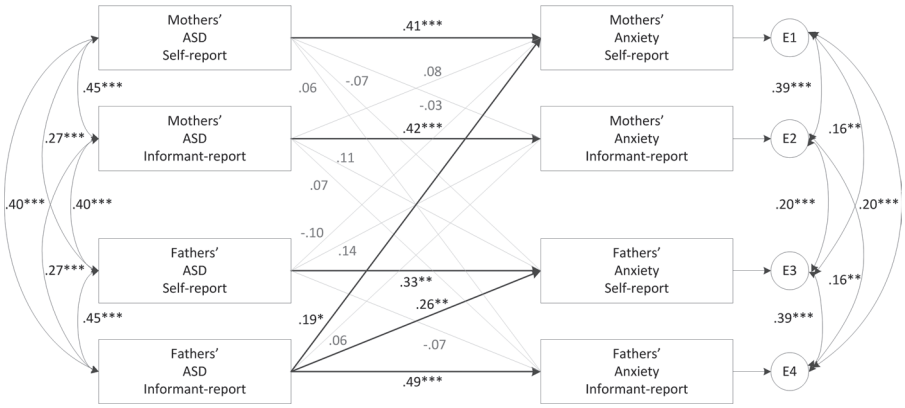

Figure 4. Results of the actor–partner interdependence model for associations among parental ASD and anxiety symptoms (Aim 2). Black lines represent significant effects and grey lines represent non-significant effects. *p < .05, **p < .01, ***p < .001.

Discussion

The current study examined shared familial transmission and cross-assortative mating of ASD and anxiety symptoms as possible explanations for the frequent co-occurrence of ASD and anxiety. In line with the literature regarding familial transmission of ASD symptoms (Constantino & Todd, 2005; De la Marche, et al., 2014; Klusek, et al., 2014; Lyall, et al., 2014; Maxwell, et al., 2013) and anxiety symptoms (Beidel & Turner, 1997; Last, et al., 1991), we found that parental ASD and anxiety symptoms predicted similar symptoms in children, although results differed depending on the informant type. No clear parent-of-origin effects were found in the transmission of symptoms from parents to children. A new finding of the current study was that parental anxiety symptoms were also related to ASD symptoms in children, even after correcting for parental ASD symptoms. This was consistent for self-reported as well as informant-reported anxiety symptoms in both parents. We also found a significant cross-symptom association between maternal ASD symptoms and children's anxiety symptoms, but only for maternal self-reported symptoms, which may have been influenced by shared method variance. These findings suggest that the co-occurrence of ASD and anxiety may be partly explained by a shared familial transmission of ASD and anxiety, as has been found for ASD and ADHD (Musser, et al., 2014; van Steijn, et al., 2012). Associations among parental symptoms provided little evidence for cross-assortative mating, but indicated that parental ASD and anxiety symptoms were mainly related within parents.

Shared familial transmission for ASD and anxiety symptoms could entail genetic as well as environmental factors. Although from our study no inferences can be made about possible underlying mechanisms, we found that the results of our analyses that included parents and siblings who were biologically unrelated to the index child were largely similar to the results of the analyses that were restricted to biologically related individuals. In our study, we were not able to separate genetic and environmental influences, but these explorations might indicate that environmental factors have an important influence. This is in line with findings from a twin study in the general population that suggested a larger contribution of shared environmental factors than of shared genetic factors to the co-occurrence of autistic-like and internalizing symptoms (Hallett, Ronald, Rijsdijk, & Happe, 2010). In addition, an adoption-based study found that children's ADHD symptoms were not only related to ADHD symptoms in their biological mothers but also to ADHD symptoms in their biologically unrelated rearing mothers (Harold, et al., 2013). Further research is needed to investigate and disentangle genetic and environmental influences for the possible shared familial transmission of ASD and anxiety. An environmental factor that may be worth further exploration is the extent to which parents make adjustments to prevent their child from experiencing distress/anxiety, also called family accommodation (Storch, et al., 2015).

Most of the familial associations did not significantly differ between the index (i.e., clinically referred) children and their siblings, but the effect of informant-reported anxiety symptoms in fathers on children's ASD and anxiety symptoms was stronger for siblings than for index children. This could indicate that mothers who report higher levels of problem behavior in fathers have a tendency to report more problem behavior in the siblings of referred children. This is supported by our results regarding the associations among parents, which showed that mothers who reported higher levels of ASD symptoms in fathers also reported that they experienced more anxiety symptoms themselves. Alternatively, results may have been influenced by a different symptom distribution in the index children versus the siblings. Although both groups consisted of children with higher and lower levels of ASD symptoms according to the SRS, the majority of the index children were high-scorers whereas the majority of the siblings were low-scorers.

Anxiety symptoms in parents were more strongly associated with their own ASD symptoms (i.e., actor effects) than with the ASD symptoms of their partner (i.e., partner effects), which does not support cross-assortative mating. The only partner effect we found was that mothers who reported higher levels of ASD symptoms in their partner also reported higher levels of anxiety symptoms in themselves, which could have been influenced by shared method variance. Our study supports previous results of Lau, et al. (2014) using the actor-partner interdependence model (APIM; Kenny, et al., 2006), which has the advantage of simultaneously testing both intrapersonal and interpersonal relationships, taking their mutual influence into account. Moreover, because we included multiple informants in our APIM, we found support for larger actor effects than partner effects while controlling for shared method variance. Although associations between symptoms of ASD and anxiety within parents were stronger for symptoms reported by the same informant than for symptoms reported by different informants—suggesting an influence of shared method variance—we found additional support that symptoms of ASD and anxiety were associated within fathers using cross-informant data. The co-occurrence of (subclinical) ASD and anxiety symptoms within parents has been hypothesized to indicate a shared underlying vulnerability for ASD and anxiety or that parents with higher levels of ASD symptoms may be more vulnerable to develop co-occurring anxiety symptoms (Piven, et al., 1991). Previous studies also reported that subclinical ASD symptoms in mothers increased their risk for depressive symptoms (Ingersoll, Meyer, & Becker, 2011). In contrast, earlier studies found no association between elevated rates of anxiety or depression and ASD characteristics in the parents of individuals with ASD (Bolton, et al., 1998; Piven & Palmer, 1999). This discrepancy in results could be explained by a shift from the reliance on categorical measures in earlier studies to the increased use of dimensional measures in recent studies.

A strength of the present study is that we used a multi-informant assessment of mothers' as well as fathers' symptoms. An interesting finding was that results differed according to which informant was used. In the model with both parental ASD and anxiety symptoms, we only found effects for parental ASD symptoms on children's ASD symptoms when the mother was the informant. When the father was the informant, parental anxiety symptoms accounted for most of the variance in children's ASD symptoms explained by the parental ASD symptoms. Although the associations for mother-reported ASD

symptoms could be influenced by shared method variance, it could also mean that mothers provide more informative ratings of parental ASD symptoms than fathers. These informant differences highlight the importance of using multiple informants in the assessment of parental symptoms (De la Marche, et al., 2014; Seidman, et al., 2012).

Several limitations should be considered. First, we had a considerable amount of missing data on the parental variables. This was mainly due to the difficulty acquiring ratings from fathers and because not every parent had a partner who could complete the informant-report. To examine possible biases due to missing data, we repeated analyses with complete data. Results of these analyses were comparable to our main analyses, which allowed for missing values on parental variables by including them in the model. Second, as the study was cross-sectional in nature, no inferences can be made about the direction of associations. Although we framed from a theoretical point of view that parental symptoms influence the child's symptoms, the influence can also be the other way around. Higher levels of ASD and behavior symptoms in children have also been associated with higher levels of parental stress (Davis & Carter, 2008), which may result in higher levels of anxiety symptoms in parents of children with ASD. However, as several studies found that parents already had elevated levels of anxiety before the birth of the child with ASD, this probably cannot fully explain the familial association of ASD and anxiety (Bolton, et al., 1998; Micali, et al., 2004; Piven & Palmer, 1999). Future studies using a longitudinal design are needed to examine bidirectional effects of parents' and children's symptoms over time. Third, mothers were an important source of information for their children's symptoms as well as their own and fathers' symptoms. Associations of symptoms reported by the same informant are likely to be inflated due to shared method variance. For example, mothers with higher levels of anxiety may have a tendency to overestimate symptoms in their children (Conner, et al., 2013). However, we also found associations between parental and children's symptoms using father reports of parental symptoms, which reduces the likelihood that our results were solely due to rater bias. Future research should also consider including multiple informants for the assessment of children's symptoms. Finally, it should be noted that this study focused on current *symptoms,* not *diagnoses*. Although this dimensional approach can provide important insights into possible prevention targets and etiology of these symptom dimensions, the meaning of these results for

individuals who meet diagnostic criteria for ASD or an anxiety disorder are less clear. Therefore, future studies should use both dimensional and categorical conceptualizations to further increase our understanding of the co-occurrence of ASD and anxiety.

In addition, a common concern in research on ASD and anxiety is the possible overlap in the measurement of ASD and anxiety symptoms, which could inflate estimates of co-occurrence and shared risk (van Steensel, et al., 2011). An advantage of the DSM-oriented Anxiety Problems scale used in this study is that it does not contain items measuring aspects of social phobia or obsessive-compulsive disorder, which are two anxiety disorders that most clearly have symptom overlap with ASD (Williams, Leader, Mannion, & Chen, 2015). Furthermore, our results did not change after eliminating items that may be anxiety-related from the SRS, which suggests that our results are probably not just due to measurement overlap.

Conclusion

Associations between parental and children's ASD and anxiety symptoms demonstrated both associations for similar symptoms and cross-symptom associations, which may suggest that ASD and anxiety have some overlap in familial risk. This shared familial risk seems to be particularly implicated in the risk for ASD, which further highlights the complexity and heterogeneity of this disorder, on a behavioral level as well as in the risk factors involved. Cross-assortative mating does not seem a likely explanation for the co-occurrence for ASD and anxiety in children, but ASD and anxiety symptoms seem to co-occur within parents. Results of our study also indicate that it is important to be aware that mothers with higher levels of anxiety may overestimate problem behavior in their children as well as their partner. The finding that fathers' reports of their own symptoms and mothers' symptoms also predicted children's symptoms underlines the importance of also including fathers as informants. Further research is needed to replicate our findings and deepen our understanding of the possible etiological mechanisms underlying the patterns of associations between parental and child symptoms. Given that parental symptoms have been found to influence treatment response in children with anxiety disorders (Hudson, et al., 2015), it may be important to take parental symptoms into account to provide more individualized treatments that address the needs of children as well as their families.

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Table S1 Associations between parental and children's ASD and anxiety symptoms including all covariates

	Self-reported parental symptoms				Informant-reported parental symptoms			
	Child ASD symptoms		Child anxiety symptoms		Child ASD symptoms		Child anxiety symptoms	
	b (SE)	*p*	*b (SE)*	*p*	*b (SE)*	*p*	*b (SE)*	*p*
Mothers								
Level 1								
Child sex	**-.37 (.10)**	**<.001**	-.15 (.09)	.10	**-.39 (.10)**	**<.001**	**-.18 (.09)**	**.04**
Child age	-.12 (.04)	**.01**	.02 (.05)	.68	**-.12 (.05)**	**.01**	.03 (.05)	.62
Level 2								
Maternal age	-.01 (.06)	.87	.07 (.07)	.31	-.06 (.07)	.35	.01 (.07)	.84
Paternal age	.04 (.06)	.45	-.01 (.07)	.92	.05 (.07)	.49	-.01 (.07)	.92
Maternal ASD	**.17 (.04)**	**<.001**	**.14 (.06)**	**.01**	.08 (.04)	.06	-.04 (.06)	.48
Maternal anxiety	**.13 (.04)**	**.003**	**.20 (.05)**	**<.001**	**.13 (.04)**	**.003**	**.33 (.06)**	**<.001**
Fathers								
Level 1								
Child sex	**-.39 (.10)**	**<.001**	-.17 (.09)	.06	**-.37 (.04)**	**<.001**	-.16 (.09)	.07
Child age	**-.11 (.05)**	**.01**	.02 (.05)	.70	**-.10 (.05)**	**.02**	.03 (.05)	.58
Level 2								
Maternal age	-.06 (.05)	.27	.02 (.09)	.94	-.06 (.06)	.30	-.00 (.07)	.99
Paternal age	.04 (.07)	.54	-.00 (.07)	.97	.05 (.06)	.40	.01 (.06)	.86
Paternal ASD	.06 (.05)	.27	.01 (.09)	.94	**.19 (.04)**	**<.001**	.09 (.06)	.14
Paternal anxiety	**.11 (.05)**	**.04**	.11 (.08)	.19	**.12 (.04)**	**.002**	**.22 (.06)**	**<.001**

Note. Models display coefficients of parental ASD and anxiety symptoms as well as those of the other covariates (child's sex and age and the parents' age). Continuous variables are transformed to *z* scores. Families (level 2) $n = 231$, children (level 1) $n = 447$.

Table S2 *Associations between parental and children's ASD and anxiety symptoms using only biologically related relatives*

	Model 1				Model 2			
	Child ASD symptoms		Child anxiety symptoms		Child ASD symptoms		Child anxiety symptoms	
	B (SE)	*p*	*B (SE)*	*p*	*B (SE)*	*p*	*B (SE)*	*p*
Self-reported symptoms								
Mother								
ASD	**.17 (.04)**	**<.001**	-	-	**.18 (.04)**	**<.001**	**.15 (.05)**	**.004**
Anxiety	-	-	**.17 (.05)**	**<.001**	**.15 (.04)**	**.002**	**.20 (.05)**	**<.001**
Father								
ASD	**.10 (.04)**	**.02**	-	-	**.10 (.05)**	**.04**	.07 (.08)	.39
Anxiety	-	-	.05 (.06)	.42	.08 (.05)	.10	.06 (.08)	.46
Informant-reported symptoms								
Mother								
ASD	**.12 (.03)**	**<.001**	-	-	*.08 (.04)*	*.05*	-.04 (.06)	.49
Anxiety	-	-	**.25 (.05)**	**<.001**	**.11 (.04)**	**.01**	**.32 (.06)**	**<.001**
Father								
ASD	**.21 (.04)**	**<.001**	-	-	**.22 (.05)**	**<.001**	.09 (.06)	.14
Anxiety	-	-	**.16 (.05)**	**<.001**	**.10 (.05)**	**.03**	**.20 (.06)**	**.002**

Note. **Model** 1 includes parent-child associations for the same type of symptoms. Model 2 additionally includes cross-symptom associations, i.e. children's Autism Spectrum Disorder (ASD) and anxiety symptoms are predicted by both parental ASD and anxiety symptoms (adjusted for each other). Statistical significant coefficients are presented in bold. All models are also adjusted for the child's sex and age and the parents' age. Continuous variables are transformed to z-scores. *n* = 403 for the analyses of mothers and *n* = 325 for the analyses of fathers.

Table S3 *Associations between parental and children's ASD and anxiety symptoms using complete data on the parental variables*

	Model 1						Model 2					
	Child ASD symptoms			Child anxiety symptoms			Child ASD symptoms			Child anxiety symptoms		
	N	*B (SD)*	*p*	*N*	*B (SD)*	*p*	*N*	*B (SD)*	*p*	*N*	*B (SD)*	*p*
Self-reported symptoms												
Mother												
ASD	415	**.16 (.04)**	**<.001**		-	-	415	**.18 (.04)**	**<.001**	415	**.15 (.05)**	**.005**
Anxiety		-	-	415	**.19 (.04)**	**<.001**	415	**.12 (.05)**	**.01**	415	**.20 (.05)**	**<.001**
Father												
ASD	240	.08 (.05)	.10		-	-	240	.04 (.07)	.60	240	.01 (.08)	.92
Anxiety		-	-	240	.03 (.05)	.52	240	**.15 (.07)**	**.03**	240	.12 (.08)	.13
Informant-reported symptoms												
Mother												
ASD	226	**.13 (.04)**	**.002**		-	-	226	.06 (.05)	.26	226	-.03 (.07)	.68
Anxiety		-	-	226	**.22 (.06)**	**<.001**	226	**.19 (.06)**	**.001**	226	**.34 (.07)**	**<.001**
Father												
ASD	341	**.18 (.04)**	**<.001**		-	-	341	**.18 (.05)**	**<.001**	341	.09 (.06)	.13
Anxiety		-	-	341	**.16 (.04)**	**<.001**	341	**.14 (.05)**	**.002**	341	**.21 (.06)**	**<.001**

Note. Model 1 includes parent-child associations for the same type of symptoms. Model 2 additionally includes cross-symptom associations, thus children's symptoms of Autism Spectrum Disorder (ASD) and anxiety are predicted by both parental ASD and anxiety symptoms (adjusted for each other). Statistical significant coefficients are presented in bold. All models are also adjusted for the child's sex and age and the parents' age. Continuous variables are transformed to z-scores.

Table S4 *Associations between parental and children's ASD and anxiety symptoms using data children aged 6 years or older*

	Model 1				Model 2			
	Child ASD symptoms		Child anxiety symptoms		Child ASD symptoms		Child anxiety symptoms	
	b (SE)	*p*	*b (SE)*	*p*	*b (SE)*	*p*	*b (SE)*	*p*
Self-reported symptoms								
Mother								
ASD	**.20 (.05)**	**<.001**	-	-	**.21 (.06)**	**<.001**	**.16 (.07)**	**.01**
Anxiety	-	-	**.22 (.06)**	**<.001**	**.19 (.06)**	**.001**	**.25 (.06)**	**<.001**
Father								
ASD	.03 (.06)	.60	-	-	-.02 (.07)	.76	.04 (.10)	.70
Anxiety	-	-	.07 (.07)	.27	**.16 (.06)**	**.02**	.13 (.10)	.21
Informant-reported symptoms								
Mother								
ASD	**.15 (.05)**	**.001**	-	-	**.13 (.06)**	**.03**	.00 (.08)	.97
Anxiety	-	-	**.26 (.05)**	**<.001**	**.15 (.06)**	**.007**	**.35 (.06)**	**<.001**
Father								
ASD	**.18 (.05)**	**<.001**	-	-	**.18 (.06)**	**.001**	.09 (.07)	.24
Anxiety	-	-	**.18 (.05)**	**<.001**	**.21 (.05)**	**<.001**	**.28 (.07)**	**<.001**

Note. Model 1 includes parent-child associations for the same type of symptoms. Model 2 additionally includes cross-symptom associations, thus children's symptoms of Autism Spectrum Disorder (ASD) and anxiety are predicted by both parental ASD and anxiety symptoms (adjusted for each other). Statistical significant coefficients are presented in bold. All models are also adjusted for the child's sex and age and the parents' age. Continuous variables are transformed to z-scores. *n* = 311

Table S5 *Associations between parental and children's ASD and anxiety symptoms using modified SRS score for children*

	Model 1				Model 2			
	Child ASD symptoms		Child anxiety symptoms		Child ASD symptoms		Child anxiety symptoms	
	b (SE)	*p*	*b (SE)*	*p*	*b (SE)*	*p*	*b (SE)*	*p*
Self-reported symptoms								
Mother								
ASD	**.16 (.04)**	**<.001**	-	-	**.17 (.04)**	**<.001**	**.14 (.06)**	**.01**
Anxiety	-	-	**.19 (.05)**	**<.001**	**.12 (.05)**	**.007**	**.20 (.05)**	**<.001**
Father								
ASD	**.10 (.04)**	**.03**	-	-	.07 (.05)	.20	.01 (.09)	.93
Anxiety	-	-	.06 (.06)	.27	**.10 (.05)**	**.05**	.11 (.08)	.18
Informant-reported symptoms								
Mother								
ASD	**.13 (.03)**	**<.001**	-	-	.08 (.04)	.06	-.04 (.06)	.49
Anxiety	-	-	**.25 (.05)**	**<.001**	**.12 (.04)**	**.006**	**.33 (.06)**	**<.001**
Father								
ASD	**.18 (.04)**	**<.001**	-	-	**.18 (.04)**	**<.001**	.09 (.06)	.13
Anxiety	-	-	**.18 (.04)**	**<.001**	**.12 (.04)**	**.004**	**.22 (.06)**	**<.001**

Note. Model 1 includes parent-child associations for the same type of symptoms. Model 2 additionally includes cross-symptom associations, thus children's symptoms of Autism Spectrum Disorder (ASD) and anxiety are predicted by both parental ASD and anxiety symptoms (adjusted for each other). Statistical significant coefficients are presented in bold. All models are also adjusted for the child's sex and age and the parents' age. A modified SRS score that did not include items that show overlap with anxiety symptoms (items 9, 30, 43, and 64) was used to assess ASD symptoms in children. Continuous variables are transformed to *z* scores. *n* = 447

Chapter 6

Examining bidirectional effects between the Autism Spectrum Disorder (ASD) core symptom domains and anxiety in children with ASD

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Abstract

Background: Although a bidirectional relationship between Autism Spectrum Disorder (ASD) and anxiety symptoms is assumed, few studies have investigated this. Moreover, little is known about potential differential relationships of the two core symptom domains of ASD—social communication impairment and restricted, repetitive behavior—with anxiety over time.

Method: Participants were 130 children with an autism spectrum disorder (ASD; *M* age 6.7 years, 81.5% boys) of whom 79 participated in a follow-up assessment two years later. We used cross-lagged models to test whether social communication impairment and restricted, repetitive behavior at T0 predicted anxiety at T2 and vice versa.

Results: Cross-lagged models showed that anxiety symptoms predicted social communication impairment over time (β=.22, *p*=.008), but not vice versa (β=-.07, *p*=.49). There were no significant paths from anxiety symptoms to later restricted, repetitive behavior (β=.11, *p*=.34) or vice versa (β=-.11, *p*=.27).
Conclusions: Our results do not support a bidirectional relationship between the ASD core symptom domains and anxiety, but suggest that higher levels of anxiety symptoms increase the risk of more social communication impairment over time in children with ASD. This underlines the importance of treating anxiety symptoms to improve their social as well as their emotional functioning.

Introduction

Autism spectrum disorder (ASD) is characterized by impairment in social communication and interaction, and restricted and repetitive behavior or interests. In additions to these core features, nearly 40% of the children with ASD are estimated to have clinically elevated levels of anxiety or at least one anxiety disorder (van Steensel, Bogels, & Perrin, 2011), which is over two times more prevalent than in typically developing children (Costello, Egger, & Angold, 2005). Co-occurring anxiety symptoms in children with ASD have been associated with impaired functioning in several domains (Factor, Ryan, Farley, Ollendick, & Scarpa, 2017; Kerns et al., 2015), and may lower the child's quality of life (van Steensel, Bögels, & Dirksen, 2012). Despite accumulating evidence that ASD and anxiety symptoms are associated, a developmental understanding of how they influence each other over time is still limited.

Wood and Gadow (2010) have proposed a theoretical model in which they hypothesize that the ASD core symptoms predispose individuals with ASD to experiencing various stressors (e.g. unpredictable and confusing social interactions, peer rejection, aversive sensory experiences, environmental demands to engage in other activities than their preferred routines and interests) that make them more vulnerable to developing anxiety symptoms. In turn, heightened levels of anxiety may also exacerbate their ASD symptom severity. For example, anxiety might lead to avoidance of social situations and therefore limit the child's opportunities to practice social skills (White et al., 2014), contributing to their social impairment. In addition, restricted/repetitive behavior may be a reaction to higher levels of anxiety or arousal as a coping mechanism (Rodgers, Glod, Connolly, & McConachie, 2012). Consistently, levels of anxiety have been associated with autistic social impairment (Sukhodolsky et al., 2008), social skill deficits (Bellini, 2006), repetitive and stereotyped behavior (Magiati et al., 2016; Rodgers et al., 2012), and sensory symptoms (Ben-Sasson, 2009) in mostly cross-sectional studies.

Although theoretical models assume a bidirectional relationship between ASD and anxiety symptoms, as the majority of studies has been cross-sectional, the direction of this relationship remains unclear. Only a few longitudinal studies have examined the hypothesized bidirectional effects. Using a population-based twin sample, Hallett, Ronald, Rijsdijk, and Happe (2010) demonstrated that autistic-like traits and internalizing problems influenced

each other bidirectionally across childhood, with a greater influence of autistic-like traits on internalizing problems than the other way around. In addition, a recent longitudinal study using a large population-based sample that focused more specifically on social and communication difficulties found that these contributed to a risk for social anxiety, but not vice versa (Pickard, Rijsdijk, Happe, & Mandy, 2017). In a sample of toddlers with ASD, Green, Ben-Sasson, Soto, and Carter (2012) found that sensory hypersensitivity predicted increasing levels of anxiety over time, but not vice versa.

In summary, the above-mentioned longitudinal studies cast doubt on the bidirectionality of the relationship between ASD and anxiety symptoms, but are difficult to compare because they each investigated a different aspect of the ASD phenotype, different measures of anxiety, and different age groups. Little is known about the potential differential relationships of the core symptom domains of the ASD phenotype—social communication impairments and restricted/repetitive behavior—with anxiety. In addition, two of the studies (Hallett et al., 2010; Pickard et al., 2017) were general population studies that did not rely on a clinical diagnosis of ASD, so it remains uncertain whether these results can be generalized to individuals with a clinical diagnosis of ASD.

The present study aimed to extend previous research by investigating longitudinally how the ASD core symptoms—social communication and restricted/repetitive behavior—and anxiety influence each other over time in a sample of children with ASD. This knowledge may help to identify targets that are important to address in subsequent interventions. If ASD symptom severity contributes to the risk of developing anxiety symptoms, cognitive behavioral interventions addressing anxiety in individuals with ASD may also need to target that component of the ASD phenotype (White et al., 2010). Additionally, if high levels of anxiety worsen ASD symptom severity over time, this would highlight the importance of treating anxiety problems timely to improve overall functioning of individuals with ASD. Consistent with the prevailing view in the literature (White et al., 2014; Wood & Gadow, 2010), we expect a bidirectional relationship between ASD and anxiety symptoms, though based on previous studies, a larger of effect may be expected of the ASD core symptoms on anxiety than the other way around.

Methods

Participants

Participants were 130 children who received a best-estimate diagnosis of Autism Spectrum Disorder based on a diagnostic evaluation for ASD using the 2nd edition of the Autism Diagnostic Observation Schedule (ADOS-2; De Bildt, Greaves-Lord, & De Jonge, 2013; Lord et al., 2012) and the short version of the Developmental, Dimensional and Diagnostic interview (3Di-sv; Skuse et al., 2004; Slappendel et al., 2016). They had an average age of 6.7 years (SD =2.2) and 106 (81.5 %) were male.

Participants were derived from a larger multicenter-study of clinically referred children, named the Social Spectrum Study. In this study, a two-phase sampling strategy was used to oversample children at risk for having ASD. Initially, 1,281 children aged 2.5 to 10 years old who had been referred for various mental health difficulties to one of six mental health care centers in the Netherlands were screened for ASD using the Social Responsiveness Scale (SRS-2; Constantino & Gruber, 2012; Roeyers, 2015). Based on a total raw score of 75 on the parent-reported SRS as screening cut-off for ASD, we invited all children with a positive screen for ASD (n = 428) and a random selection of children with a negative screen (n = 240) to participate in a comprehensive assessment, including the ADOS and the 3di. Of the 668 selected children, 231 (170 screen-positive, 74%) participated in full diagnostic assessment (ADOS and 3Di) of which 130 received a best-estimate diagnosis of ASD according to the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV-TR; American Psychiatric Association, 2000). The research team consisted of six psychologists who had been trained and were experienced in the diagnostic evaluation of ASD. In addition, the team included several master-level psychology students or medical students who also had received training in the diagnostic evaluation of ASD and were always supervised by one of the experienced psychologists. In 55 cases (24%), the 3Di and/or ADOS had been performed by clinicians as part of the clinical evaluation at the mental health care center. In these cases, we used the clinical DSM-IV-TR diagnosis from the patient file established by the clinical staff, including experienced psychologists or psychiatrists, based on the standardized diagnostic assessments in combination with other information assessed during the clinical evaluation. Further details of the total cohort and the procedure of establishing a best-estimate diagnosis of ASD have been

described elsewhere (Duvekot et al., 2017). The study was approved by the local medical ethics committee and participating mental health care centers (MEC-2011-078) and informed consent was obtained from all included families.

Parents completed questionnaires regarding the characteristics of the child at referral, at the time of the diagnostic assessments and at a follow-up approximately one year later. Since our main measures were collected at the baseline assessment at referral (Time 1 in the current study) and the follow-up (Time 2 in the current study), we only used these two time points in our analyses. The average time between the Time 1 and Time 2 assessment was 24 months (SD = 4). Of the 130 children with ASD, 79 participated in the follow-up assessment. Logistic regression in the current sample showed that an older age of the child (OR = 1.6, $p < .001$), non-Western ethnicity of the child (OR = 13.9, $p = .01$), and a single-parent family (OR = 4.68, $p = .02$) were related to attrition at T2. The child's gender, reason for referral, educational level of the mother, urbanicity, parental age, ASD symptom severity, anxiety symptom severity, and Full-Scale IQ were all not related to attrition at T2. These findings are similar to attrition in the broader sample (Duvekot et al., 2017).

Measures

ASD symptoms

ASD symptoms of the children were assessed using the Social Responsiveness Scale 2nd edition (SRS-2; Constantino & Gruber, 2012; Roeyers, 2015) that was completed by the parent/caregiver. The SRS consists of 65 items that are scored on a 4-point scale from 0 (*not true*) to 3 (*almost always true*). In addition to a total score, scores for five treatment subscales can be calculated. Four of these subscales (Social Awareness, Social Cognition, Social Communication, Social Motivation) are combined into the DSM-5 compatible scale assessing the ASD symptom domain of Social Communication and Interaction (SCI). The fifth scale (Autistic Mannerisms) assesses the DSM-5 symptom domain of Restricted Interests and Repetitive Behavior (RRB). Children aged 2.5 to 4 years received the preschool version and children aged 4 to 18 years the school-age version of the SRS. These versions are largely similar: 10 items were adapted in the preschool version to make the wording more appropriate for preschoolers, without changing the content of the items. The reliability and validity of the SRS has been well-established (Constantino & Gruber, 2012), and has also been confirmed for the Dutch version (Duvekot, van der Ende, Verhulst, & Greaves-

Lord, 2015; Roeyers, 2015). The internal consistency (Cronbach's alpha) of the SRS-2 subscales in our sample was good: α = .89 at T1 and α = .95 at T2 for the SRS-2 SCI subscale and α = .75 at T1 and α = .83 at T2 for the SRS-2 RRB subscale.

Anxiety symptoms

We used the DSM-oriented Anxiety Problems scale of the Child Behavior Checklist (CBCL) to assess anxiety symptoms. The CBCL is a parent-reported questionnaire that assesses a variety of emotional and behavioral problems. It is possible to calculate scores of two broadband scales, Internalizing Problems and Externalizing Problems, as well as several empirically constructed Syndrome scales and top-down constructed DSM-oriented subscales. The DSM-oriented Anxiety Problems scale contains items related to generalized anxiety disorder [GAD], separation anxiety disorder [SAD], and specific phobia. Internal consistency and test-retest reliability for the DSM-oriented Anxiety Problems scale have been found to be adequate to good (Achenbach & Rescorla, 2000, 2001; Verhulst & Van der Ende, 2013). In addition, this scale has been found to discriminate well between children with and without anxiety disorders (Ebesutani et al., 2010). We used both the version of the CBCL for children aged 1,5-5 years and the version for children 6-18 years old in our sample. Because the DSM-oriented Anxiety Problems scale is not equivalent for the CBCL/1,5-5 and CBCL/6-18, we used T scores to make the scores across both versions comparable. The internal consistency (Cronbach's alpha) of the DSM-oriented anxiety problems scale in our sample was reasonable to good: α = .67 at T1 and α = .79 at T2 for the CBCL/6-18 and α = .82 at both T1 and T2 for the CBCL/1,5-5.

Intellectual functioning

IQ was obtained from the patient file or performed by the research team and therefore assessed using a variety of tests: the Wechsler Intelligence Scale for Children, third Dutch edition (WISC-III-NL; Kort et al., 2005), the Wechsler Preschool and Primary Scale of Intelligence, third Dutch edition (WPPSI-III-NL; Hendriksen & Hurks, 2009), the Snijders-Oomen Nonverbal intelligence test (SON-R; Tellegen, 1998), the Bayley Scales of Infant Development, Dutch edition (BSID-II-NL; Meulen, van der, Lutje Spelberg, & Smrkovský, 2004) or, as part of the research protocol (26%), the Wechsler Abbreviated Scale of Intelligence (WASI; Axelrod, 2002). All of these tests are standardized with a mean score of 100 and a standard deviation of 15.

Statistical analysis

Raw mean scores of age, IQ, SRS, CBCL and their standard deviations at both time points were calculated. To explore associations between all study variables prior to the main analyses, Spearman's correlations were used. We used SPSS version 21.0 (IBM, Armonk, NY) for these analyses.

To address our main objective, the examination of longitudinal bidirectional relationships between the ASD core symptoms and anxiety symptoms, we applied cross-lagged analyses using Mplus version 7.3 (Muthén & Muthén, 1998–2012). Mplus uses full information maximum likelihood to account for missing data. We used the maximum likelihood estimation with robust estimation of standard errors (MLR) to account for possible non-normal distribution of the variables.

We tested two series, one for the SRS-2 subscale social communication impairment and one for SRS-2 subscale restricted, repetitive behavior, of two models each. First, we tested a baseline model which contained only auto-regressive paths, reflecting the stability of a variable over time (e.g., from T1 social communication impairment to T2 social communication impairment and from T1 anxiety to T2 anxiety). In addition, the model also includes covariances between concurrent variables (e.g., concurrent associations between social communication impairment and anxiety at both time points). In a next step, cross-lagged paths were added, representing the prediction of one variable on another variable at a later time point (e.g., from T1 social communication impairment to T2 anxiety and from T1 anxiety to T2 social communication impairment). This indicates the direction of the effects between these variables, independent of the autoregressive paths and concurrent associations between the variables. The same steps were repeated for the SRS-2 subscale of restricted, repetitive behavior.

We tested for differences between the model with the autoregressive paths only and the cross-lagged model using the chi-square difference, applying the Satorra Bentler scaling correction because we used the MLR estimator. The fit of the models was evaluated using the comparative fit index (CFI), the root mean squared error of approximation (RMSEA) and the standardized root-mean-square residuals (SRMR). Model fit was considered good if CFI $\geq$ .95, RMSEA $\leq$ .06 and SRMR $\leq$ .08 (Hu & Bentler, 1999).

Covariates

In order to rule out the effects of potential confounding factors, gender, age, IQ and the CBCL Externalizing scale were included as covariates in all models. These covariates were regressed on the ASD and anxiety symptoms at T2. Gender was included because gender effects on ASD symptom severity (Constantino & Gruber, 2012) and anxiety symptoms (Gotham, Brunwasser, & Lord, 2015) are commonly reported. In addition, age was included because higher rates of anxiety symptoms are often reported in older ASD samples (van Steensel et al., 2011). Full Scale IQ was included because several studies have found that higher levels of IQ are related to higher rates of anxiety (Gotham et al., 2015; Hallett et al., 2013), although findings have been mixed (van Steensel et al., 2011). Finally, the CBCL Externalizing scale was included to check whether the associations between ASD core symptoms and anxiety were not explained by associations with another type of psychopathology (i.e., externalizing symptoms).

Results

Preliminary analyses

Table 1 presents the frequencies or mean scores and standard deviations of the demographic and clinical characteristics of the sample. The level of ASD and anxiety symptoms at T2 were not significantly different for children who received treatment by a mental health care specialist in the past year before T2 (n = 31) and those who did not (n = 47), though it must be noted that sample sizes were small. In addition, Table 2 presents the correlations of all variables included in the cross-lagged models. The correlations between the variables representing the same construct over time were high. In addition, social communication impairment and anxiety symptoms as well as restricted/repetitive behavior and anxiety symptoms were significantly positively related at each time point.

Cross-lagged models

The model with the cross-lagged paths from T1 social communication impairment to T2 anxiety and T1 anxiety to T2 social communication impairment had a significantly better fit than the model with the autoregressive/parallel paths only (Santorra Bentler scaled χ^2 = 6.27 (2), p = .01). The fit indices of

Table 1. Demographics of the sample and descriptive statistics of study variables

	N	*M (SD) / n(%)*	Range
Gender (% boys)	130	106 (81.5%)	-
Ethnicity (% Dutch)	128	104 (81.3%)	-
Maternal education (% high)	122	29 (23.8%)	-
Two-parent family (%)	128	108 (84.4%)	-
T1 Age (years)	130	6.7 (2.2)	2-10
T1 Full Scale IQ	123	96.4 (17.6)	50-141
T1 SRS parent total	130	93.3 (26.0)	26-152
T1 SRS parent SCI	130	77.1 (21.1)	24-121
T1 SRS parent RRB	130	16.2 (6.5)	2-34
T1 CBCL Anxiety problems	117	64.7 (9.7)	50-95
T1 CBCL Externalizing problems	117	67.1 (10.6)	40-97
T2 Age (years)	79	8.4 (2.3)	4-13
T2 Received mental health treatment in the past year (%)	78	31 (39.7%)	-
T2 SRS parent total	79	89.2 (26.4)	10-139
T2 SRS parent SCI	79	73.6 (21.7)	6-116
T2 SRS parent RRB	79	15.6 (6.2)	1-30
T2 CBCL Anxiety problems	79	62.5 (9.8)	50-89
T2 CBCL Externalizing problems	79	60.3 (10.2)	33-81

Note. CBCL = Child Behavioral Checklist; SRS = Social Responsiveness Scale; SCI = Social Communication Impairment scale; RRB = Restricted and Repetitive Behavior scale.

Table 2. Correlations between the study variables

	T1 Age	T1 FSIQ	T1 SRS SCI	T1 SRS RRB	T1 CBCL ANX	T1 CBCL EXT	T2 SRS SCI	T2 SRS RRB	T2 CBCL ANX	T2 CBCL EXT
T1 Age	1.00	-	-	-	-	-	-	-	-	-
T1 FSIQ	.18*	1.00	-	-	-	-	-	-	-	-
T1 SRS SCI	.20*	-.05	1.00	-	-	-	-	-	-	-
T1 SRS RRB	-.01	.01	.63**	1.00	-	-	-	-	-	-
T1 CBCL ANX	.14	.09	.30**	.31**	1.00	-	-	-	-	-
T1 CBCL EXT	.07	-.03	.33**	.39**	.32**	1.00	-	-	-	-
T2 SRS SCI	.11	.04	.60**	.41**	.42**	.32**	1.00	-	-	-
T2 SRS RRB	.05	.08	.40**	.58**	.31**	.25*	.69**	1.00	-	-
T2 CBCL ANX	.19	.01	.22	.25*	.64**	.26*	.49**	.37**	1.00	-
T2 CBCL EXT	-.01	-.05	.22*	.31**	.39**	.68**	.48**	.35**	.46**	1.00

Note. CBCL = Child Behavioral Checklist; FSIQ = Full Scale IQ; SCI = Social Communication Impairment scale; SRS = Social Responsiveness Scale; RRB = Restricted and Repetitive Behavior scale.
$^{*}p < .05$, $^{**}p < .01$

the cross-lagged model indicated a good fit to the data (CFI = .95, RMSEA = .07 and SRMR = .06). The standardized path estimates of the cross-lagged model are shown in Figure 1. The auto-regressive paths indicate that social communication impairment and anxiety symptoms were significantly stable over time. There were also significant concurrent associations between social communication impairment and anxiety symptoms at both time points. We found one significant cross-lagged path: the effect of T1 anxiety on T2 social communication impairment. T1 Social communication impairment did not significantly predict T2 anxiety. Of the covariates, only gender significantly predicted anxiety symptoms at T2 (β = -.22, p = .03), indicating that in girls the level of anxiety problems decreased more over time than in boys. Age, IQ, CBCL externalizing symptoms were not significantly related to social communication impairment and anxiety symptoms at T2.

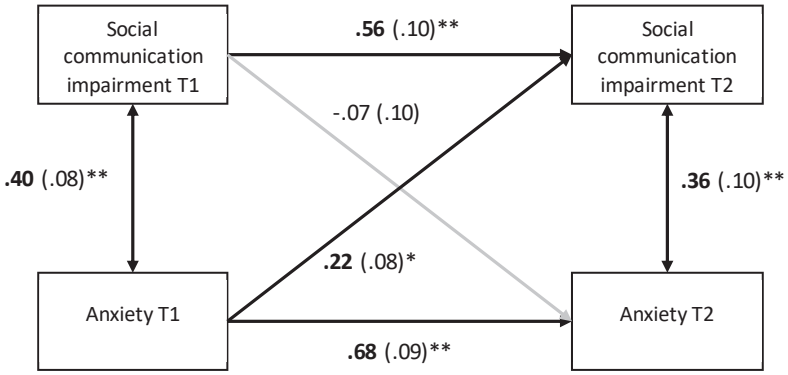

Figure 1. Cross-lagged model of the longitudinal relationship between autistic social impairment and anxiety problems. Note: All analyses are controlled for gender, age, Full Scale IQ, and CBCL Externalizing problems. Standardized coefficients are displayed. Significant paths are shown in bold.

* p < .01, ** p < .001

The model with the cross-lagged paths from T1 restricted, repetitive behavior to T2 anxiety and T1 anxiety to T2 restricted, repetitive behavior was not significantly better than the model with the autoregressive/parallel paths only (Santorra Bentler scaled χ^2 = 2.16 (2), p = .34). The fit indices of the cross-lagged model indicated a good fit to the data (CFI = .99, RMSEA = .03 and SRMR = .04). However, no cross-lagged paths were significant (see Figure 2), indicating that there were no unidirectional or bidirectional effects between restricted/repetitive behavior and anxiety over time. The autoregressive paths indicated stability of restricted, repetitive behavior and anxiety over time. In

addition, there were significant concurrent associations between restricted, repetitive behavior and anxiety symptoms at both time points. With respect to the covariates, similar results were found as for the model with the social communication impairment subscale.

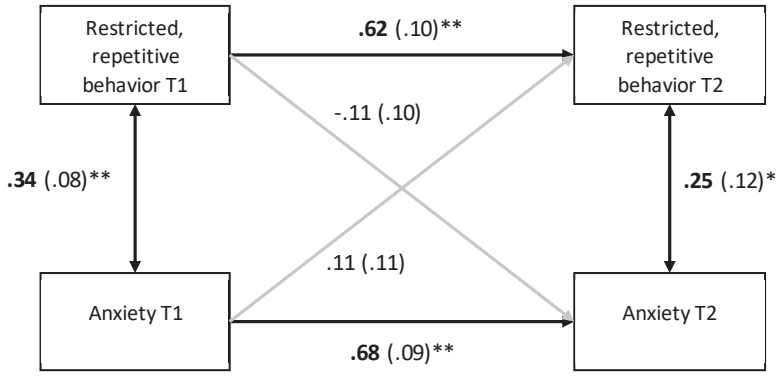

Figure 2. Cross-lagged model of the longitudinal relationship between RRB problems and anxiety problems. Note: All analyses are controlled for gender, age, Full Scale IQ, and CBCL Externalizing problems. Standardized coefficients are displayed. Significant paths are shown in bold. * $p < .05$, ** $p < .001$

Discussion

This longitudinal study aimed to investigate bidirectional effects of the two core symptom domains of ASD—social communication impairment and restricted/repetitive behavior—with anxiety symptoms over time in a sample of children with ASD. Both ASD symptom domains and anxiety symptoms were strongly correlated at both time points and stable over time. Anxiety symptoms contributed to higher levels of social communication impairment over time, but social communication impairment did not contribute to the development of anxiety symptoms in our sample. This suggests a unidirectional effect of anxiety on social communication impairment, but no bidirectional relationship. There were no unidirectional or bidirectional influences between restricted/repetitive behavior and anxiety symptoms over time.

The finding that anxiety symptoms predicted higher levels of social communication impairment over time is in line with current theories that anxiety symptoms may lead to avoidance of social situations and thereby reducing the opportunities to practice social skills, interfere with processing

social information, and prevent the execution of learned skills (White et al., 2014). In addition, anxiety symptoms may predispose the individual to negative reactions from peers and contribute to peer rejection and bullying, which may exacerbate their social difficulties and feelings of social incompetence. For example, observational studies have shown that typically developing adolescents with high levels of social anxiety receive more negative responses from their peers than adolescents with low levels of social anxiety (Blöte, Kint, & Westenberg, 2007; Spence, Donovan, & Brechman-Toussaint, 1999). In adolescents with ASD, higher levels of anxiety symptoms have been related to experiencing more difficulties with peer relations, such as being bullied or having few social contacts (Eussen et al., 2013). Another possibility is through a role of family factors (Kelly, Garnett, Attwood, & Peterson, 2008). For example, anxiety symptoms may increase parental stress (Kerns et al., 2015) or evoke overprotective reactions from parents (McLeod, Wood, & Weisz, 2007), strengthening avoidance behavior, which may have a negative effect on the social communication impairment of the child. These are several possible mechanisms that require further investigation.

The effect of anxiety symptoms on social communication impairment in children with ASD also highlights the importance of early assessment and treatment of anxiety problems in addition to interventions targeting social skills in order to improve the social communication impairment of children with ASD. Fortunately, the results of modified cognitive behavioral interventions for individuals with ASD are promising (Sukhodolsky, Bloch, Panza, & Reichow, 2013; Wood et al., 2015). In line with our findings, a recent study demonstrated that cognitive-behavioral therapy for anxiety in adolescents with ASD also lead to long-term improvements in social impairment (Maddox, Miyazaki, & White, 2016).

However, there is also research reporting contrasting results (Hallett et al., 2010; Pickard et al., 2017). Pickard et al. (2017) found that social and communication difficulties in early childhood increased the risk for social anxiety symptoms later in childhood, but not vice versa. A notable difference is that they specifically focused on social anxiety, whereas we used a more generic anxiety measure. It could be that social communication impairment specifically increases the risk for social anxiety, possibly through a lack of confidence in social situations and the experience of negative peer relations due to their social and communication difficulties (Bellini, 2006; White et al., 2010),

whereas non-social anxiety symptoms may be better predicted by a diverse and complex constellation of risk factors other than social communication impairment (Simonoff et al., 2013).

Also in contrast to our expectations, we did not find that (non-social) anxiety symptoms were predicted by higher levels of restricted and repetitive behavior, or vice versa. This suggests that concurrent relationships exist but that restricted/repetitive behavior and anxiety do not influence each other's developmental course. However, this needs to be investigated further using a measure that can differentiate between the different characteristics within this symptom domain. For example, anxiety symptoms might be particularly related to insistence on sameness (Gotham et al., 2013) or sensory problems (Green et al., 2012). These contrasting results indicate that more research is needed to further our understanding of how different types of ASD characteristics and anxiety symptoms influence each other over childhood.

ASD and anxiety symptoms were significantly stable over the two-year period. This is in agreement with stability coefficients from previous studies (Hallett et al., 2010; Pickard et al., 2017). Despite this large group-level stability in symptom severity, there may be significant changes in symptom severity in some individuals over time (Louwerse et al., 2015). In addition, the types of anxiety symptoms that are most common may differ across different developmental periods. For example, higher levels of generalized anxiety and social anxiety symptoms have been associated with an older age and higher levels of separation anxiety symptoms with a younger age in ASD samples (Magiati et al., 2016; van Steensel et al., 2011), consistent with developmental changes in the prevalence of anxiety subtypes in the general population (Copeland, Angold, Shanahan, & Costello, 2014; Van Oort, Greaves-Lord, Verhulst, Ormel, & Huizink, 2009). This indicates the need to replicate findings across different age groups.

Strengths of the present study are that we used a well-defined sample of children with ASD who were assessed using standardized diagnostic instruments and the use of longitudinal data. However, limitations include our moderate sample size, the presence of some selective attrition based on demographic factors, and the use of only parent-reported data. It would be recommended to use a multi-informant approach for the assessment of childhood psychopathology, even though that is a challenge in longitudinal studies. We also a used a very generic scale containing few items to assess

anxiety symptoms. Considering the inconsistent findings in the literature regarding the direction of the relationship between autistic social impairment and anxiety, future research could benefit from including a measure of anxiety that allows for differentiation between different types of anxiety. In addition, the subscale of the SRS-2 may not be the most optimal measure of restricted and repetitive behavior. The SRS-2 contains many items on social communication impairment (53 items), but relatively few on restricted and repetitive behavior (12 items). Future studies should include a more extensive measure of restricted, repetitive behavior as well as sensory symptoms, to better disentangle relationships between these ASD symptoms and anxiety.

Conclusion

Overall, our results do not support a bidirectional relationship between the ASD core symptoms and anxiety in children with ASD, but suggest a unidirectional relationship of anxiety symptoms contributing to higher levels of social communication impairment over time. This indicates the importance of assessing and treating anxiety problems timely to improve both the social and emotional functioning of children with ASD and supports recent efforts to combine cognitive behavioral approaches with social skills interventions (White, 2010). Further research is needed to increase our understanding of the mechanisms involved and to investigate whether this relationship may differ according to the type of anxiety symptoms.

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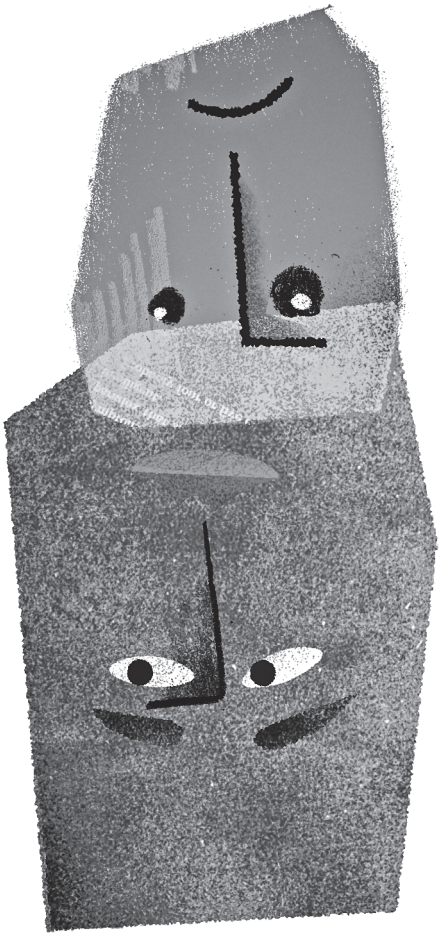
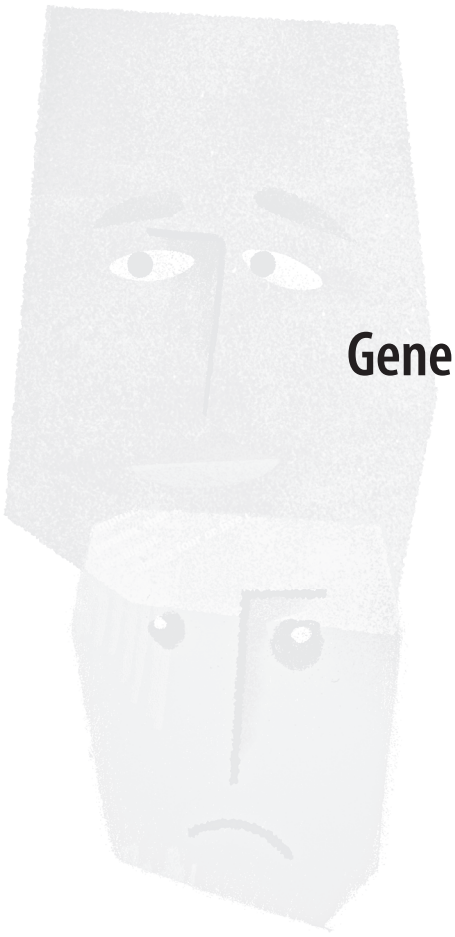


Chapter 7



General Discussion

Rationale

Autism Spectrum Disorder (ASD) is a complex and heterogeneous disorder, making it difficult to accurately identify ASD, especially in certain groups such as girls (Dworzynski, Ronald, Bolton, & Happe, 2012). The first aim of this thesis was to contribute to the identification of ASD by examining the role of screening instruments, informants, and changes in diagnostic criteria, and differences between boys and girls in the identification and diagnosis of an Autism Spectrum Disorder. The heterogeneity of ASD does not only consist of variations in the levels of core symptoms but also includes variations in associated psychopathology. One of the most frequently reported co-occurring psychiatric problems in children with ASD are anxiety problems (de Bruin, Ferdinand, Meester, de Nijs, & Verheij, 2007; Leyfer et al., 2006; Simonoff et al., 2008). Therefore, the second aim of this thesis was to increase our understanding of the frequent co-occurrence of ASD and anxiety by investigating interrelationships between ASD and anxiety, both in families and in children with ASD over time. These research questions were investigated in the Social Spectrum Study, a multicenter cohort of clinically referred children, who were all screened for the presence of ASD characteristics, of which a subsample received in-depth diagnostic assessment to establish to presence of ASD.

In this chapter, I will describe the main findings of this thesis and discuss them in a broader context. Then, I will discuss some important overarching methodological considerations regarding the studies included in this thesis. Last, I will address the recommendations for future research and implications for clinical practice.

Part I: Screening and diagnostic assessment of autism spectrum disorder

In Part I of this thesis, I included three studies that focused on screening and diagnostic assessment of ASD. In the first study (Chapter 2), I describe how we used a two-phase sampling design, including a screening and a diagnostic phase, to identify children with ASD in a multicenter study of clinically referred children, named the Social Spectrum Study. The study provides an overview of the design and measures of the Social Spectrum Study, the characteristics of the cohort and predictors of attrition, and discusses the implications of the changing diagnostic system. In the second study (Chapter 3), we investigated

the screening accuracy of a screening questionnaire for ASD, the Social Responsiveness (SRS), and the added value of teacher report to the use of parent report. In the third study (Chapter 4) on this topic, we investigated differences between boys and girls in the characteristics contributing to a diagnosis of ASD.

Main findings

At the time of our study, the field was anticipating the release of the new diagnostic criteria of ASD of the DSM-5. We took these new developments into account by establishing in a subsample a diagnosis according to the DSM-5 criteria in addition to the DSM-IV-TR criteria. An important finding in Chapter 2 was that although most of the children with a diagnosis of Autistic Disorder or Asperger's Syndrome according to the DSM-IV-TR received a diagnosis according to the DSM-5, only a small portion (16%) of the children with a diagnosis of PDD-NOS according to the DSM-IV-TR, met DSM-5 criteria for ASD. This is consistent with other studies indicating that the DSM-5 criteria may be more restrictive than the DSM-IV-TR criteria and may primarily include the more severe affected ASD cases on the ASD continuum (Maenner et al., 2014; Mazefsky, McPartland, Gastgeb, & Minshew, 2012). The children with PDD-NOS who did not meet the DSM-5 criteria had elevated levels of social communication impairments, but not elevated levels of RRB symptoms, in comparison to the non-ASD children. These children might be eligible for a diagnosis of social communication disorder, a newly introduced diagnostic category in the DSM-5 for individuals who primarily have problems with pragmatic aspects of social communication. However, the question remains whether these children might not be better considered as belonging to the ASD continuum, representing a group with milder, possibly subclinical (in the light of the DSM-5), levels of ASD symptomatology that might still impact on the individual's functioning.

In order to obtain a sample of children diagnosed with ASD, we first used the Social Responsiveness Scale (SRS) to screen for ASD among a large sample of clinically referred children. One of the aims of the study, described in Chapter 3, was to evaluate the screening accuracy of this instrument against 'gold' standard standardized diagnostic instruments: a parent interview, the Developmental, Dimensional and Diagnostic Interview (3Di), and a semi-structured observation, the Autism Diagnostic Observation Schedule (ADOS).

Using a cut-off of 75, we found that *the parent report of the SRS alone* showed good sensitivity (85% and 100%) and specificity (83% and 75%) in comparison the 3Di and the stringent criteria of receiving an ASD classification on both the 3Di and ADOS. These results support the utility of the SRS as a screening instrument for ASD in a sample of clinically referred children who had been referred for a variety of mental health problems.

Although the use of multiple informants is generally recommended (Achenbach, 2006; De Los Reyes & Kazdin, 2005), the use of multiple informants when screening for ASD has rarely been investigated. In Chapter 3, we therefore also investigated *the added value of the teacher-reported SRS* when screening for ASD. We found that the teacher-reported SRS in addition to the parent-reported SRS significantly improved the ability to discriminate between children who met cut-off scores for ASD on the ADOS and those who did not. Thus, although parents are valuable informants, it is helpful to add the perspective of the teacher to identify children for whom a clinician indicates the presence of possible ASD on the ADOS. Overall, these results indicate that the SRS is a useful screening questionnaire for ASD in a diverse sample of clinically referred children and that is important to use different sources of information (parent and teacher) as these information sources add unique information needed to acquire a complete picture of the child. Consistently with our results, a recent study found that agreement or discrepancies between parent and teacher reports of ASD was informative for characterizing children with ASD (Lerner, Reyes, Drabick, Gerber, & Gadow, 2017). Children for whom both the parent and teacher indicated high levels of ASD symptoms showed more functional impairments and were more likely to receive an ASD classification on the ADOS, supporting our results of the added value of the teacher.

Additionally, the identification of ASD may be especially complicated in certain groups, such as in girls. In Chapter 4, we examined whether different behavioral characteristics predicted a diagnosis of ASD in girls than in boys. Interestingly, similar proportions of boys and girls (ca. 30%) received a positive screen on the parent-reported SRS. However, boys were more than two times more likely to be diagnosed with ASD than girls. Possibly partly explaining a lower likelihood of girls to be diagnosed with ASD, is our finding that higher overall levels of parent-reported RRB symptoms were less predictive of an ASD diagnosis in girls than in boys. It remains unresolved whether this reflects lower rates of RRB symptoms in girls with ASD or that RRB symptoms in girls

are qualitatively different and therefore not well captured using current instruments or recognized by clinicians as being characteristic of ASD. In contrast, higher overall levels of parent-reported emotional and behavioral problems increased the probability of an ASD diagnosis in girls, but not in boys. It could be that girls with ASD who do not display high levels of co-occurring emotional and behavioral problems may be at risk of being missed as having ASD. Several studies have reported possible camouflaging of girls with ASD (Dean, Harwood, & Kasari, 2016; Lai et al., 2016), making it harder for the outer world to notice their difficulties. These camouflaging/compensating abilities may come with the cost of mental tiredness resulting in high levels of emotional and behavioral problems (Bargiela, Steward, & Mandy, 2016; Cridland, Jones, Caputi, & Magee, 2014). Whether teachers are also valuable in the identification of ASD in girls remains to be further investigated in a larger sample of girls. However, teachers have the tendency to score lower levels of ASD symptoms and emotional/behavioral problems in girls with ASD than in boys with ASD than parents do, both in our sample and in other studies (Mandy et al., 2012; Posserud, Lundervold, & Gillberg, 2006). This suggests that teachers do not easily recognize the difficulties faced by girls with ASD, possibly because girls with ASD are also able to camouflage their difficulties at school (Dean et al., 2016).

Methodological considerations

Two-phase sampling design

The current study used a two-phase sampling design in which we first applied a screening instrument for ASD, the Social Responsiveness Scale (SRS), to a large and diverse sample of children referred various mental health services for a variety of developmental/psychiatric problems, and subsequently provided further diagnostic assessments to a subgroup of children, consisting of children at risk for ASD (screen positives) and a random selection of children who were not at risk for ASD (screen negatives). Using this prospective design, we aimed to obtain a more representative sample of children with ASD and a comparison group of children without ASD compared to prior research in which often convenience samples are used of children who already had been diagnosed with ASD or referred to a specialized service for children with ASD. Instead, we used standardized and well-validated measures for the identification of children

at risk for ASD and for the diagnostic evaluation of ASD to prevent biases that may arise when relying on the referral reason and clinical community diagnosis. To optimize representativeness of our sample, we included the referrals to six mental health care centers, providing both secondary and tertiary care, covering a large part of the mental health care provided in the South-West of the Netherlands. However, it should be noted that it is not a sample drawn from the general population and that certain biases may still be present due to factors that influence the probability whether a child is referred or not and attrition. In addition, a disadvantage is that this design required a large time investment and increases the complexity of the analysis of results (Dunn, Pickles, Tansella, & Vazquez-Barquero, 1999).

Diagnostic accuracy

There are several issues that require some attention when interpreting the results of a diagnostic accuracy study. First, in psychiatric research there is no perfect "gold standard" to which the test can be compared (Faraone & Tsuang, 1994). Therefore, we used a combination of different reference standards that have been found to be reliable and valid in Chapter 3. However, this complicates the interpretation of results as these reference standards do not completely agree with each other. Second, important for the accurate estimation of diagnostic accuracy is using a prospective design in which (a subgroup of) children with a negative screen are assessed using the reference standard (Whiting, Rutjes, Westwood, & Mallett, 2013), as we did in our study. Third, the diagnostic accuracy of a test varies according the prevalence in the population, characteristics of the ASD sample and comparison group, and reference standard used, complicating the generalization of results of a particular study to clinical practice (Charman & Gotham, 2013). Thus, our results in Chapter 3 only apply to screening in a clinically referred sample and cannot be translated to screening in the general population. In addition, our study indicates that diagnostic accuracy indices differ depending on whether the screener and reference standards rely on the same informant or on different informants. Fourth, the optimal cut-off of a test also depends on the purpose of the test in particular setting (Charman & Gotham, 2013). There is always a trade-off between maximizing sensitivity (i.e., identifying as much children with ASD as possible) and minimizing the false positives (i.e., excluding the children who do not have ASD).

Part II: The co-occurrence of autism and anxiety

In Part II of this thesis, we included two studies that focused on the relationship between ASD and anxiety. We aimed to gain more insight into why ASD and anxiety problems frequently co-occur, by examining relationships between ASD and anxiety among families (Chapter 5) and in children with ASD over time (Chapter 6).

Main findings

In Chapter 5, we investigated whether the co-occurrence of ASD and anxiety in children could be explained by *familial transmission* of these symptoms from parents to children. Previous studies have reported parent-child associations for the same type of symptoms, thus for ASD symptoms (e.g., De la Marche, Noens, Kuppens, et al., 2015; Lyall et al., 2014) and for anxiety symptoms (Beidel & Turner, 1997; Last, Hersen, Kazdin, Orvaschel, & Perrin, 1991). Our study extends previous research by also examining familial transmission across symptom types. In addition, to associations between parental and children's symptoms for the same type of symptoms, we found that parental anxiety symptoms were associated with children's ASD symptoms and some indication that maternal ASD symptoms were associated with children's anxiety symptoms. This could indicate some *shared vulnerability* for ASD and anxiety.

We also hypothesized that the familial transmission of psychopathology may be influenced by the tendency of parents to resemble each other more in certain characteristics than would be expected by chance, also called assortative mating. There is some evidence for assortative mating for some psychiatric disorders (Maes et al., 1998), but little attention to assortative mating across different types of psychiatric symptoms, which we called *cross-assortative mating* in Chapter 5. Cross-assortative mating has important complications because it increases the child's risk for psychopathology, possibly by an increase in the genetic additive variance for genes associated with both phenotypes or by impacting environmental factors, such as family conflict, stress or parenting practices (Nordsletten et al., 2016). Consistent with a previous study (Lau, Gau, Chiu, & Wu, 2014), we did not find support for the presence of cross-assortative mating. In contrast, a recent study examining registered clinical diagnoses did find evidence for cross-assortative mating for ASD and other psychiatric disorders, including anxiety disorders (Nordsletten et al., 2016). A possible reason for this discrepancy in findings is that cross-assortative mating may not be present at the level of subclinical traits.

To further increase our understanding of the co-occurrence of ASD and anxiety, we also investigated how ASD and anxiety symptoms influence each other over time (Chapter 6). In contrast to theoretical assumptions (White et al., 2014; Wood & Gadow, 2010), we did not find a longitudinal *bidirectional relationship* between the core ASD symptoms and anxiety. However, anxiety symptoms increased the risk of having more social communication impairments over time. These findings could be consistent with a moderator function of anxiety in children with ASD, meaning that children with ASD and high levels of anxiety show more autistic social impairment than children with ASD without high levels of anxiety (Wood & Gadow, 2010). It has also been suggested that anxiety can be a mediator, such that ASD symptoms leads to social anxiety, resulting in avoidance of social situations, exacerbating the social and communication difficulties due to reduced learning opportunities (Bushwick, 2001; White et al., 2010). We did not find evidence for such a relationship, because then we would expect to have found bidirectional influences. To further advance our understanding of how ASD and anxiety symptoms influence each other over time, research is needed that uses multiple time points and a measure of anxiety that can differentiate between different types of anxiety (social versus non-social anxiety).

Methodological considerations

Familial transmission

The study of familial transmission of symptoms is complicated by several methodological issues. First, most studies used the same informant (mostly the mother) for the assessment of symptoms in the parent and the child. This could introduce inflated associations due to shared method variance. Characteristics of the parent might influence the way he/she reports about him/herself and the child. For example, it has been shown that depressive symptoms or parental stress colors the way the parent perceives him/herself and the child and tend to rate their child as having more ASD symptoms (Bennett et al., 2012). It has also been questioned whether parents with high levels of ASD symptoms are able to adequately report those for themselves and their children. The present study aimed to overcome this by using multiple informants (self-report and spouse-report) in both mothers and fathers. This allowed us to say which associations were only present when the same informant was used and

which were confirmed using different informants. The associations between ASD and anxiety symptoms within parents were only present when the same informant was used, which indicates caution in interpreting these findings and those of previous studies as they may have been influenced by shared method variance. The same was true for parent-child associations of ASD symptoms. Our most important finding, however, was that anxiety symptoms in parents were also associated with ASD symptoms in children. This was reported for both informants, suggesting that this cannot be solely explained by shared method variance. Future research would ideally also use a multi-informant assessment of the child's symptoms. Because we did not have the information of multiple informants for all children included, this was not feasible in the current study. A recent study that did use both mothers' and fathers' reports of the child's symptoms concluded that there was no evidence for report bias in these associations (Moricke, Buitelaar, & Rommelse, 2016). However, they only found a positive mother-child association for ASD symptoms when the mother reported on both her own and the child's symptoms or when father was the informant for both. Thus, the association was replicated by a different informant, but it was only found when both measures were completed by the *same* informant.

Second, our study and most previous studies on the familial transmission of ASD assessed concurrent symptoms in parents and children at one time point. Therefore, we cannot be certain of the direction of the effect. For a better understanding of the direction of the effects, it is necessary to assess symptoms of parents and children at multiple time points.

Lastly, on the basis of our results, we cannot say anything about the possible mechanisms underlying this shared vulnerability. It is possible that genetic factors are involved, given the high heritability of both disorders and the finding of a modest genetic overlap between ASD and emotional symptoms in a recent twin study (Tick et al., 2016). Yet, little is known about which genes may be responsible for both types of conditions, also called the "missing heritability" problem (Eichler et al., 2010). Environmental factors, such as parenting or modeling, are also hypothesized to influence the familial transmission of anxiety (Affrunti & Woodruff-Borden, 2015; Aktar, Majdandžić, de Vente, & Bögels, 2013) and might also partly mediate the association between parental anxiety and children's ASD symptoms.

To conclude, our results could point to a shared vulnerability between ASD and anxiety, but more research is needed before any specific conclusions can be drawn. These findings do indicate that is important to investigate common risk factors across disorders, consistent with the current move of the field towards studying Research Domain Criteria (RDOC; Insel, 2014) to advance our understanding of the etiology of psychiatric disorders.

Differentiation between autism and anxiety

In Chapters 5 and 6, we investigated interrelationships between ASD and anxiety symptoms. This research is based on the assumption that ASD and anxiety are separate constructs. It should be noted, though, that there is also probably some overlap between these two constructs and how they were measured. For example, avoidance of social situations may be part of the autistic difficulties in social communication or part of a social anxiety disorder. In addition, non-ASD specific factors, such as emotional and behavioral problems and IQ, have been found to influence the scores and the discriminative ability of the SRS and other standardized measures of ASD (e.g., the ADOS; Havdahl et al., 2016; Hus, Bishop, Gotham, Huerta, & Lord, 2012). Wood and Gadow (2010) described four potential explanations for the co-occurrence of ASD and anxiety. First, this relationship may reflect true comorbidity, thus the presence of two separate, coexisting disorders in an individual. The risk factors for anxiety may then be similar to those in typically developing individuals. Second, the expression of anxiety may be moderated by the presence of ASD, reflecting a different manifestation of anxiety than in the general population. There is support that many children with ASD show anxiety symptoms similar to those of typically developing children, thus indicating true comorbidity, as well as atypical anxiety symptoms that are influenced by the ASD symptoms (e.g., fear of change and unusual specific fears such as fears of baby crying; Kerns et al., 2014). Third, anxiety may be caused by similar etiological factors that are involved in the risk for ASD, possibly representing a specific subgroup. Fourth, the relationship may be artificial due to difficulty in differentiating between symptoms of ASD and anxiety. However, it is not likely that the co-occurrence is only explained by an overlap in symptoms. Using a structural equation model with different measures of ASD and anxiety symptoms (Renno & Wood, 2013) showed that the constructs (or latent variables) of ASD and anxiety were largely independent of each other, supporting the validity of ASD and anxiety as separate constructs.

Of course, we cannot be entirely sure whether this would generalize also to our sample and measures. We did not use a measurement model to estimate latent factors in our structural equation model in Chapter 5 and 6, because we lacked an adequate sample size to reliably estimate factors using a confirmatory factor analysis and we would preferably need more indicators to estimate the latent factors.

General methodological considerations

Some of the specific methodological considerations in relation to each study have already been discussed in the previous chapters and in the previous sections of this general discussion. In this section, I will discuss some overarching methodological considerations.

Categorical versus dimensional approach

Traditionally, the field of psychiatry focuses on disorders: discrete disease entities with a certain symptom profile that is thought to have a specific biological origin. Nowadays, it is widely acknowledged that the symptoms of many psychiatric disorders fall on a continuum, which means that the symptoms that are characteristic of the disorder are more or less present in the entire general population. Research in the general population using questionnaires, such as the Social Responsiveness Scale, that have been designed to assess the full spectrum of mild to severe levels of autistic traits have confirmed that autistic traits are continuously distributed in the general population (Constantino, 2011). The use of these quantitative instruments is considered important to increase our understanding of the etiology of the autism phenotype and the complex interrelations between different characteristics that constitute the autism phenotype or are associated with the autism phenotype. However, there is still a discussion about whether these traits or characteristics in the general population are similar to the symptoms of the individuals that have a diagnosis (de la Marche, Noens, & Steyaert, 2015). Furthermore, we are not yet so far that we have formed a taxonomy based on dimensional characteristics and their neurobiological/genetic correlates to guide clinical decision-making (Volkmar & McPartland, 2016). In clinical practice, it is still necessary to, albeit somewhat arbitrarily, draw a line to what we consider ASD in order to provide individuals with ASD access to care and treatments that have been found to be effective for this group and to avoid medicalization of individuals who are functioning

well and do not need this care. Therefore, we combined the two approaches in our study, we used the continuous measure of autistic symptoms, the Social Responsiveness Scale, in the broader sample of clinically referred children, but also used gold standard diagnostic instruments to delineate a well-defined sample of children with ASD.

Multi-informant assessment

It is commonly accepted that child assessments should be based on information from various informants to gain a complete picture of the child's behavior (Achenbach, 2006; De Los Reyes & Kazdin, 2005). This is important to account for differences in the perspectives of informants and variation in the child's behavior across contexts. Consequently, the information from different informants often do not agree. In child and adult assessment studies of different characteristics, the correspondence between different informants is often low to moderate (Achenbach, Krukowski, Dumenci, & Ivanova, 2005; Achenbach, McConaughy, & Howell, 1987; van der Ende, Verhulst, & Tiemeier, 2012). This was also reflected in the studies reported in the current thesis. We used both parents and teachers as informants of the child's symptomatology. These two informants provide valuable information regarding the child's current everyday functioning in various settings (home, school) and across time. Also indispensable in the diagnostic assessment of ASD, is direct observation by a clinician, for which we used the Autism Diagnostic Observation Schedule (ADOS). Consistent with prior research, we also found low to moderate correspondence between parent and teacher ratings on the SRS as well as the result of the ADOS scored by the clinician in Chapter 3.

The sole informant we did not use in our study was the child. The reason we did not have self-report of the child is that the majority of the children were too young to report about their problems reliably using questionnaires (Luby, Belden, Sullivan, & Spitznagel, 2007). The use of self-report measures in individuals with ASD is also controversial, as it is thought that individuals with ASD often do not have full awareness of their difficulties and have difficulties with identifying and reporting emotions, such as anxiety or depression, consistent with findings of alexithymia in this population (Milosavljevic et al., 2016; Rieffe, Meerum Terwogt, & Kotronopoulou, 2007). Research regarding the validity of self-report measures in children and adolescents with ASD is still in its infancy and have often focused on measures of anxiety and depression

(Kaat & Lecavalier, 2015; Mazefsky, Kao, & Oswald, 2011; Ozsivadjian, Hibberd, & Hollocks, 2014). The internal consistencies of the self-reported questionnaires were good, indicating that children with ASD did understand the questions well enough to provide consistent answers. Additionally, the correspondence between the self-reported and parent-reported questionnaires was found to be better in older children with lower levels of ASD symptoms and higher IQ levels (Kaat & Lecavalier, 2015). Therefore, I believe that using self-report in older high-functioning children or adolescents can be an important addition as it gives insight into how they perceive their difficulties. Even if this would not be a good predictor of whether the child has ASD or a psychiatric comorbid disorder, this information could be important for treatment planning and evaluation.

Multi-informant assessment is less frequently applied when assessing the behavior of adults/parents, but our results in Chapter 5 indicate this is important as well. Our results revealed important informant differences whether the mother or the father was the informant. For example, the parent-child association for ASD symptoms was only found when mother ratings were used. This could be explained by shared method variance, since mothers mostly rated also rated the symptoms of the child, but it could also indicate that fathers were less likely to report the presence of ASD symptoms in themselves or the mother. This underlines the importance of collecting information from both parents.

The difficulty with multi-informant assessment is how to deal with informant discrepancies, which, as we discussed before, are more often the rule than the exception. There are different ways to analyze multi-informant data in research, as extensively discussed by De Los Reyes, Thomas, Goodman, and Kundey (2013). One approach is to treat the data from each informant separately. This is the approach we adopted in most of studies (see Chapter 3, 4 and 5). The reason we chose this approach is because we wanted to take into account the uniqueness of the information of each informant and to test whether associations could be replicated across different informants. However, the disadvantage of this approach is that multiple tests increase the chance of type I errors. A second approach is to combine the information from different informants using the "and" rule (i.e., the scores of both informants indicate the presence of a certain behavior above a cut-off) or the "or" rule (i.e., one informant scores above the cut-off). This approach can only be used with dichotomous data. For continuous data, data from different informants is often combined by pooling the standardized means of each informant's scores. These approaches are relatively straightforward, but cannot disentangle the

contribution of each informant when informant discrepancies are to be expected. This means that reported associations can still be driven by only one of the informants. A third approach is to use a structural equation model to combine different reports of the same behavior into a latent factor. We did not choose this approach, as it focuses on the shared variance of the reports of multiple informants of the same behavior and treats differences between informants as measurement error rather than meaningful information representing the unique perspective of each informant (De Los Reyes et al., 2013), whereas we were more interested in the unique contribution of each informant. An alternative statistical technique that overcomes the limitations of the previous approaches is latent profile analysis. This technique can be used to identify subgroups of children from whom informant reports agree or disagree (Lerner et al., 2017), taking both informant discrepancies and the independence of observations into account. However, this technique requires a very large sample size and was therefore not feasible in our study.

Recommendations for future research

Based on the findings and methodological considerations I discussed before, I would like to make several recommendations for future research.

First, larger samples are needed in order to assess the influence of various characteristics (e.g., gender, IQ, co-occurring emotional/behavioral problems, characteristics of the informant) on the performance of screening and diagnostic instruments. This would help to better understand the performance of these instruments in various populations and translate findings to clinical practice. Because of the added value of the teacher report of the SRS in addition to the parent report of the SRS, a more thorough investigation of how both assessments can be combined to improve the identification of ASD in children is needed. Therefore, we would recommend the acquisition of Dutch norm data and cut-offs for the teacher report of the SRS in order to optimize the identification of children with ASD. Furthermore, we need to validate diagnostic instruments for ASD in samples of females with ASD, evaluate the addition of examples that are more characteristic of girls with ASD and investigate whether gender-specific cut-offs need to be developed to improve the identification of ASD in girls. Larger samples of girls that are followed over time could elucidate whether girls who do not fulfill criteria for ASD but show elevated symptoms of ASD may be identified later or are at increased risk of developing other psychiatric difficulties.

Second, it is important to assess characteristics of the parent as well as those of the child using multiple informants, to understand the unique contribution of each informant and avoid the problem of shared method variance. This approach should in particular be used more often in studies on the associations between parental and children's symptoms. Preferably, a third party, clinician or teacher, is also included as an informant for the child's symptoms as well as the child him/herself.

Third, I would recommend to conduct more longitudinal studies regarding the relationship between symptoms of ASD and anxiety within children and families, using multiple time points, to better unravel the direction of effects between symptoms of ASD and anxiety as well as how parents' and children's symptoms influence each other over time. The inclusion of additional child and family factors would help to understand possible mechanisms underlying or influencing these relationships.

Fourth, based on evidence of cross-symptom associations in our sample, indicating a possible shared vulnerability for ASD and anxiety, I support the current trend to look beyond the boundaries of diagnostic categories and attempts to find risk and protective factors that may be shared among different disorders. I hope this will also stimulate sharing of knowledge across different research fields that may now be only disseminated among researchers interested in the same disorder.

Fifth, there is a need of reliable and valid anxiety measures that can be used in children with ASD. It is a concern that the majority of existing anxiety measures are neither designed nor validated for ASD samples. Findings that the expression of anxiety in ASD may in some cases differ from traditional conceptualizations of anxiety (Kerns et al., 2014) suggest that anxiety measures developed for typically developing children cannot be merely applied in ASD samples. A promising anxiety measure that has recently been adapted and evaluated for ASD, is the Anxiety Scale for Children – ASD (ASC-ASD; Rodgers et al., 2016). This measure is based on the RCADS, has a child and parent report version, and measures various aspects of anxiety (anxiety related to performance, uncertainty, sensory issues and phobias). Preliminary psychometric properties in an ASD sample were good. Our understanding of the relationship between ASD and anxiety could be improved by using such a measure. In addition, more research is needed to continue the validation of anxiety measures in children with ASD.

Clinical implications

Several clinical implications follow from the results of Part I of this thesis concerning screening and assessment of ASD. First, our results suggest that a large group of children diagnosed with PDD-NOS would not qualify for an ASD diagnosis according to the DSM-5 criteria. Although we did not specifically assess this in our study, these children might be eligible for the diagnosis of a Social Communication Disorder (SCD), which is a new classification in the DSM-5. However, it remains unclear whether this represents a qualitatively different category or a quantitatively milder variant of ASD. Until this issue is clarified, it is important for clinical practice to regard the ASD core characteristics as dimensions and realize that there are children with social communication difficulties that resemble those in children with ASD, which may affect their prognosis and treatment. Second, our results indicate that is useful to screen for ASD in a diverse population of children referred for various mental health issues and support the importance of obtaining information from multiple informants (parent and teacher) when screening for ASD. Teachers provide unique and meaningful information that showed more agreement with clinical observation than parents. Third, it is important to be aware that girls with ASD may be at risk for being unrecognized, even when standardized diagnostic instruments are used for diagnosis, but are more likely to be identified as having ASD when they show high levels of emotional and behavioral problems in addition to ASD characteristics. Thus, it is important to provide attention to any co-occurring problems as well as to be alert not to miss girls when these problems are not (yet) present. Since RRB problems were less predictive of an ASD diagnosis in girls than in boys, it is important to be aware that the RRB characteristics may be expressed somewhat differently in girls than in boys (Sutherland, Hodge, Bruck, Costley, & Klieve, 2017) and ask beyond the common examples that are specific for boys about interests that may be more typical for girls (e.g., animals, books, art and music). Since the DSM-5 also includes sensory symptoms under the RRB domain and we found that those symptoms did predict an ASD diagnosis in girls as well as in boys, I recommend incorporating a measure of sensory symptoms in the diagnostic assessment for ASD to improve the identification of ASD in girls.

The results of Part II of this thesis suggest that it is important to assess and treat anxiety problems in individuals with ASD, as these negatively impacted the social functioning of individuals with ASD over time. This fits well with the

introduction of clinical specifiers, such as language and intellectual ability, onset age and pattern, concurrent genetic/medical or behavioral disorders, in the DSM-5 (Lai, Lombardo, Chakrabarti, & Baron-Cohen, 2013). Elevated anxiety levels, even if formal criteria for an Anxiety Disorder according to the DSM-5 are not met, are important to note as a clinical specifier as it has prognostic value and may be an important treatment target. Vice versa, it has been found that children with anxiety disorders who also showed elevated levels of ASD symptoms showed a better response to family CBT than individual CBT (Puleo & Kendall, 2011). Increasing evidence is also found for the efficacy of cognitive-behavioral therapies for anxiety in adolescents with ASD (Sukhodolsky, Bloch, Panza, & Reichow, 2013). Research evaluating the effects of CBT suggest that CBT may have influences beyond reducing anxiety symptoms only and could be combined with therapies targeting the core ASD symptoms to improve both the emotional and social functioning of children and adolescents with ASD. Since anxiety problems in parents were also related to ASD symptom severity, I would not only recommend to screen for anxiety problems in children and adolescents, but also to be aware of anxiety problems in their parents, thus adopting transdiagnostic thinking. Currently, clinicians may be more inclined to pay attention to whether family members show similar problems as the child, such as ASD symptoms if the child is suspected of having ASD, whereas our results indicate that it is important to obtain a broader perspective on the mental health difficulties of family members. Parental symptoms of anxiety have been shown to negatively affect treatment responses in children with anxiety (Bodden et al., 2008; Creswell, Jilletts, Murray, Singhal, & Cooper, 2008), although it remains unclear whether parental anxiety needs to targeted separately during treatment in order to improve child outcomes (Cobham, Dadds, Spence, & McDermott, 2010; Conner, Maddox, & White, 2013). In the treatment of children with ASD, parent involvement is generally considered an important element (Lang, Regester, Lauderdale, Ashbaugh, & Haring, 2010; Reaven, 2011; White et al., 2010). Therefore, it could be possible that parental anxiety symptoms interfere with a successful execution of their role in the treatment, though this is a hypothesis that needs to be investigated first. Overall, our results are in support of transdiagnostic thinking, both in research and in clinical practice.

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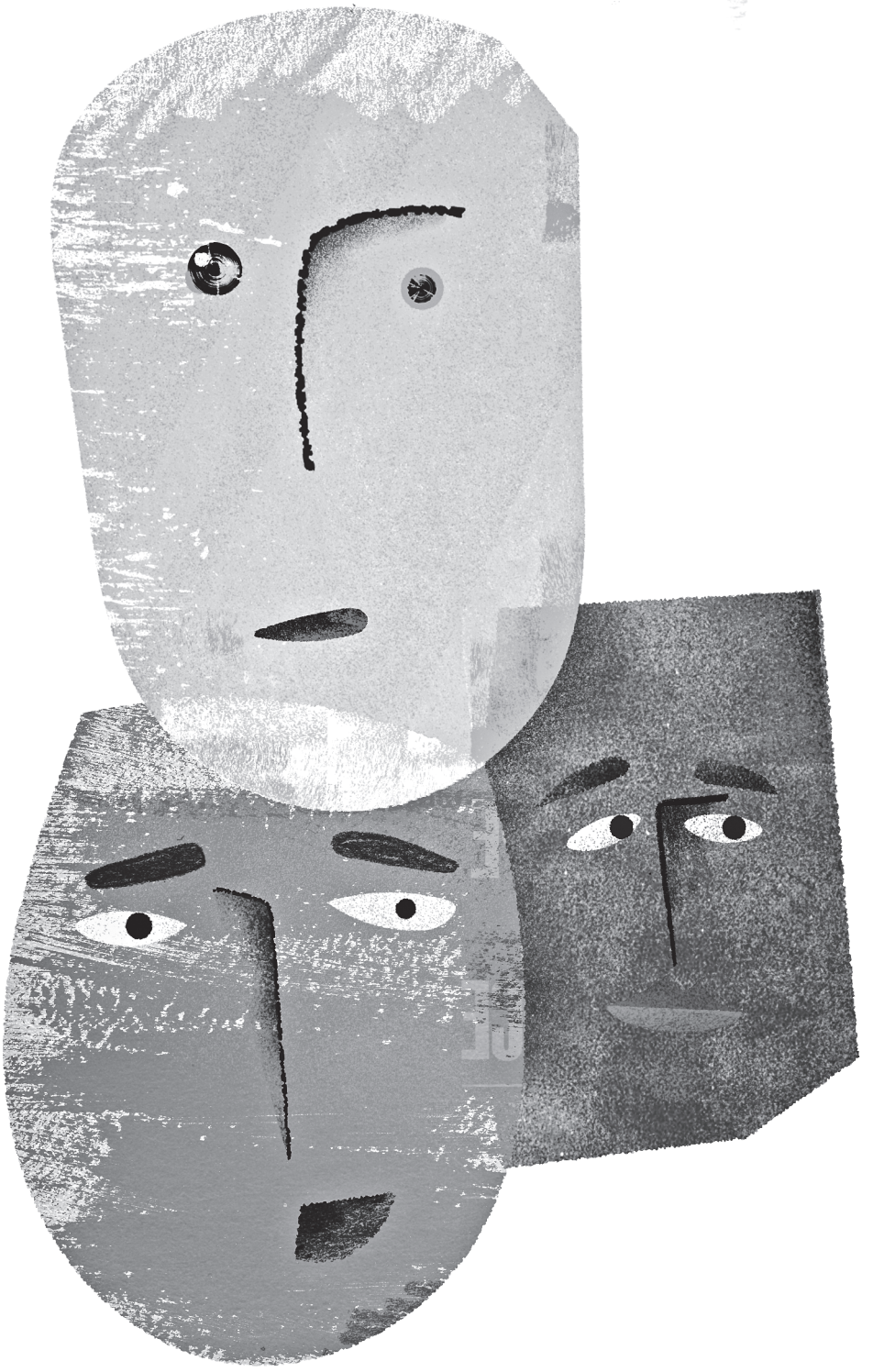

Chapter 8

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Dankwoord

Summary

Autism Spectrum Disorder (ASD) is a complex and heterogeneous neurodevelopmental disorder, with individuals showing high variability in the ASD core symptoms (e.g., social communication difficulties and repetitive/ restricted behavior and interests) as well as in comorbid psychiatric problems, such as anxiety. Moreover, recent research suggests that gender also affects the phenotypic presentation, possibly contributing to an under-identification of ASD in girls. This phenotypic heterogeneity poses important challenges to the diagnosis, prognosis and treatment of individuals with ASD as well as research into the etiological underpinnings of ASD. In order to contribute to an improved identification of ASD in children and a better understanding of the interrelationships between ASD and anxiety problems, the aims of the current thesis were twofold. The first aim of the study, addressed in part I of this thesis (chapters 2, 3 and 4), was to investigate the influence of diagnostic criteria, instruments, informants and gender of the child on the diagnosis of ASD. The second aim of the study, addressed in part II of this thesis (chapters 5 and 6), was to increase our understanding of the co-occurrence of ASD and anxiety symptoms by examining interrelationships between these two types of symptoms within families and the putative bidirectional influence of ASD and anxiety symptoms in children with ASD over time. More in-depth background information regarding the specific research aims of this thesis is provided in **chapter 1**.

All research aims described in the current thesis were investigated within the Social Spectrum Study. In **chapter 2**, we provided an overview of the design and characteristics of this multicenter cohort of clinically referred children, containing a subsample of children with ASD. In the Social Spectrum Study, all children aged 2.5 to 10 years who had been referred to one of the six participating mental health care centers, were screened for the presence of ASD characteristics, irrespective of the reason for referral. Subsequently, all children with a positive screen result and a random selection of children with a negative screen result were invited for an in-depth diagnostic assessment using the short version of the Developmental, Dimensional and Diagnostic Interview (3Di) and the Autism Diagnostic Observation Schedule (ADOS) to establish the presence of ASD. In addition, parents completed several questionnaires concerning characteristics of the child, parents themselves, the family and societal impact. After a year, a follow-up assessment using questionnaires was conducted. A

diagnosis of ASD was established following the DSM-IV-TR criteria, but for a subsample we also evaluated whether a child met DSM-5 criteria for ASD. A large portion of the children with a DSM-IV diagnosis of PDD-NOS did not meet DSM-5 criteria for ASD. These children were characterized by relatively low levels of repetitive/restricted behavior and interests, but showed significantly more social communication impairments than the non-ASD children.

In **chapter 3**, we investigated the screening accuracy of the screening questionnaire for ASD that was used in the study, the Social Responsiveness Scale (SRS), and the added value of teacher report to the use of parent report. Using a cut-off of 75, we found that the parent report of the SRS alone showed good sensitivity and specificity in comparison to the 3Di, a standardized parental interview, and the stringent criteria of receiving an ASD classification on the 3Di as well as the ADOS, a standardized clinical observation. However, the parent-reported SRS showed less agreement with the ADOS alone. We found that the teacher report significantly improved the correspondence to the ADOS classification over and above the parent report. Thus, we found that the SRS is a useful screening questionnaire in a diverse sample of clinically referred school-aged children, and that is useful to collect information from multiple informants (parents and teachers) when screening for ASD.

In **chapter 4**, we investigated differences between boys and girls in the behavioral characteristics related to the probability of receiving a diagnosis of ASD according to DSM-IV-TR criteria. Parent-reported restricted and repetitive behavior (RRB) symptoms were less strongly related to an ASD diagnosis in girls than in boys, which could contribute to an under-identification of ASD in girls. In contrast, sensory symptoms (e.g., sensory over- and undersensitivity) were as strongly related to an ASD diagnosis in girls as in boys, suggesting the importance of assessing this aspect of the RRB domain in the diagnostic assessment of ASD in girls. We also found that higher overall levels of parent-reported emotional and behavioral problems increased the probability of an ASD diagnosis more in girls than in boys. This could indicate a possible vulnerability of girls with ASD to develop co-occurring emotional and behavioral problems. On the other hand, this could mean that girls who do not display high levels of co-occurring emotional and behavioral problems may be at risk of being overlooked.

In **chapter 5**, we investigated shared familial transmission of ASD and anxiety symptoms from parents to children and cross-assortative mating (i.e.,

whether parents with higher levels of ASD symptoms are more likely to have a partner with higher levels of anxiety symptoms or vice versa) as possible explanations for the frequent co-occurrence of ASD and anxiety in children. Our results showed that parental symptoms were related to their children's symptoms. These associations were partly dependent on the informant used (the parent him/herself or the partner) and were not limited to the same type of symptoms. Parental anxiety symptoms, reported by the parent him/herself as well as by the other parent, also predicted children's ASD symptoms and maternal self-reported ASD symptoms predicted children's anxiety symptoms. These findings suggest that shared familial risk factors may affect the frequent co-occurrence of ASD and anxiety symptoms in children. We did not find evidence of cross-assortative mating, as no cross-symptom associations of ASD and anxiety symptoms were found between parents.

In **chapter 6**, we investigated whether ASD and anxiety symptoms influence each other bidirectionally over time in children with ASD. A cross-lagged model showed that anxiety symptoms predicted autistic social impairment, but autistic social impairment did not predict anxiety symptoms over time. This indicates the importance of treating anxiety problems timely to improve the emotional as well as the social functioning of children with ASD.

Finally, in **chapter 7**, I discuss the main findings of the above-mentioned studies in a broader context as well as some methodological considerations and implications of these studies for future research and clinical practice. Overall, our findings stress the importance of using multiple informants in the assessment of ASD and co-occurring problems in children and their family members. Further research is needed to investigate the utility and possible adaptation of standardized screening and diagnostic instruments in subgroups, such as girls, and delineate mechanisms that could underlie the shared familial transmission of ASD and anxiety as well as the contribution of anxiety symptoms to the autistic social impairments over time. A clinical implication is the importance of a dimensional and transdiagnostic approach (i.e., thinking outside the boundaries of diagnostic categories). I would recommend screening for ASD symptomatology in all children referred for developmental/psychiatric problems, as was done in the current study. In addition, clinicians should be alert for possible co-occurring anxiety problems in children with ASD as well as parents that could affect the level of ASD symptoms of the child.

Samenvatting

Autismespectrumstoornis (ASS) is een complexe en heterogene ontwikkelingsstoornis, waarbij individuen veel variatie laten zien in de kernsymptomen van ASS (problemen in de sociale communicatie en beperkte/repetitieve patronen van gedragingen en interesses) alsook in de mate van comorbide psychiatrische problemen, zoals angst. Bovendien zijn er aanwijzingen dat geslacht ook de klinische presentatie beïnvloedt, wat mogelijk bijdraagt aan een verminderde herkenning van ASS bij meisjes. Deze fenotypische heterogeniteit vormt een grote uitdaging voor de diagnose en behandeling van individuen met ASS alsook voor onderzoek naar de etiologie van ASS. Om een bijdrage te leveren aan de identificatie van kinderen met ASS en een beter begrip van de relaties tussen ASS en angstproblematiek, richt dit proefschrift zich op de volgende twee onderzoeksdoelen. Het eerste doel, behandeld in deel 1 van dit proefschrift (hoofdstukken 2, 3 en 4), was om de invloed van diagnostische criteria, instrumenten, informanten en geslacht van het kind op de diagnose ASS te onderzoeken. Het tweede doel, behandeld in deel 2 van dit proefschrift (hoofdstukken 5 en 6), was meer inzicht te krijgen waarom autisme- en angstproblematiek zo vaak samen voorkomen. Daarom hebben wij relaties onderzocht tussen deze twee typen symptomen binnen families en longitudinale, wederzijdse invloeden tussen angst en autistische sociale beperkingen bij kinderen met ASS. Meer achtergrondinformatie over deze twee doelen van het proefschrift wordt gegeven in **hoofdstuk 1**.

Alle onderzoeksdoelen beschreven in het proefschrift zijn onderzocht in de Social Spectrum Study. In **hoofdstuk 2** wordt het design en de kenmerken van dit multicenter cohort van klinisch verwezen kinderen met een subgroep van kinderen met ASS beschreven. Tijdens het onderzoek werden alle kinderen in de leeftijd van 2,5 t/m 10 jaar die werden aangemeld bij een van de zes deelnemende jeugd GGZ-instellingen gescreend op de aanwezigheid van ASS-kenmerken, ongeacht de reden voor verwijzing. Vervolgens werden alle kinderen met een positief screeningsresultaat en een willekeurige selectie van kinderen met een negatief screeningsresultaat uitgenodigd voor een uitgebreid diagnostisch onderzoek door middel van de verkorte versie van het Developmental, Dimensional, Diagnostic Interview (3Di) en het Autisme Diagnostische Observatie Schema (ADOS) voor het stellen van de diagnose ASS. Daarnaast vulden ouders vragenlijsten in over kenmerken van het kind,

de ouders zelf, de familie en de maatschappelijke impact. Na een jaar was er een follow-up door middel van vragenlijsten. Een diagnose ASS werd gesteld aan de hand van de DSM-IV-TR criteria en een deel van de steekproef werd ook geëvalueerd met de DSM-5 criteria. Een grote groep kinderen met een diagnose PDD-NOS (DSM-IV-TR) voldeed niet aan de DSM-5 criteria voor ASS. Deze kinderen werden gekenmerkt door lage niveaus van beperkte en repetitieve gedragingen en interesses, maar lieten significant meer sociaal-communicatieve problemen zien dan de kinderen die geen diagnose ASS volgens de DSM-IV-TR en DSM-5 criteria hadden.

In **hoofdstuk 3** onderzochten wij de screeningseigenschappen van de ASS-vragenlijst die wij in het onderzoek gebruikten, de Social Responsiveness Scale (SRS), en de toegevoegde waarde van de leerkrachtvragenlijst bovenop de oudervragenlijst. Wij vonden voor een afkapwaarde van 75 een goede sensitiviteit en specificiteit van de oudervragenlijst van de SRS ten opzichte van de 3Di, een ouderinterview en het strengere criterium van een ASS-classificatie op zowel de 3Di als de ADOS, een klinische observatie. De oudervragenlijst had echter een minder goede overeenkomst met de uitslag van de ADOS alleen. De toevoeging van de leerkrachtvragenlijst bovenop de oudervragenlijst verbeterde de overeenkomst met de uitslag van de ADOS significant. Concluderend vonden we dat de SRS een bruikbaar screeningsinstrument is in een steekproef van klinisch verwezen kinderen en dat het nuttig kan zijn om informatie van meerdere informanten (ouders en leerkrachten) te verzamelen in het screeningsproces.

In **hoofdstuk 4** onderzochten wij verschillen tussen jongens en meisjes in de gedragskenmerken die gerelateerd zijn aan het krijgen van een diagnose ASS. Beperkte en repetitieve gedragingen en interesses waren minder sterk gerelateerd aan een diagnose ASS bij meisjes dan bij jongens. Dit zou een verklaring kunnen zijn waarom meisjes minder vaak een diagnose ASS krijgen. Aan de andere kant, voorspelden sensorische symptomen even goed een diagnose ASS bij meisjes als bij jongens. Dit suggereert dat het in kaart brengen van sensorische symptomen een belangrijk onderdeel vormt van de ASS-diagnostiek bij meisjes. We vonden ook dat een hogere mate van emotionele en gedragsproblemen de kans op een diagnose ASS vergrootte bij meisjes, maar niet bij jongens. Dit zou enerzijds kunnen wijzen op een verhoogde kwetsbaarheid van meisjes met ASS op het ontwikkelen van comorbide emotionele en gedragsproblemen. Anderzijds zou het kunnen betekenen dat

ASS minder snel bij meisjes wordt herkend als zij geen comorbide emotionele en gedragsproblemen laten zien.

In **hoofdstuk 5** onderzochten wij de mogelijkheid van een gedeelde familiaire transmissie van autisme- en angstsymptomen van ouders op kinderen en een selectieve partnerkeuze (of een ouder met meer autismesymptomen vaker samen is met een partner met meer angstsymptomen of omgekeerd) als verklaringen voor het vaak samen voorkomen van autisme- en angstsymptomen. Uit de resultaten bleek dat autisme- en angstsymptomen van ouders voorspellend zijn voor deze symptomen in hun kinderen. Dit was deels afhankelijk van de informant (ouder zelf of de partner) en bleef niet alleen beperkt tot dezelfde type symptomen. Angstsymptomen bij ouders, zowel gerapporteerd door de ouder zelf als door de partner, voorspelden niet alleen angstsymptomen maar ook autismesymptomen bij hun kinderen. Deze bevindingen wijzen op mogelijke gedeelde familiaire risicofactoren voor autisme- en angstsymptomen. Wij vonden geen aanwijzingen voor een rol van selectieve partnerkeuze.

In **hoofdstuk 6** onderzochten wij of autisme- en angstsymptomen elkaar over de tijd wederzijds beïnvloeden bij kinderen met ASS door middel van een cross-lagged model. Uit de resultaten bleek dat angstsymptomen wel een hogere mate van autistische sociale beperkingen, maar autistische sociale beperkingen niet een hogere mate van angstsymptomen na verloop van tijd voorspelden. Dit wijst op het belang van het behandelen van angstproblematiek bij kinderen met ASS om zowel het emotionele als het sociale functioneren van kinderen te verbeteren.

In **hoofdstuk 7** bespreek ik de belangrijkste bevindingen van bovengenoemde onderzoeken in een bredere context naast een aantal methodologische overwegingen en implicaties van deze onderzoeken voor toekomstig onderzoek en de klinische praktijk. Een algemene bevinding is het belang van het gebruiken van meerdere informanten bij het in kaart brengen van ASS-symptomatologie en bijkomende problematiek in kinderen en hun ouders. Meer onderzoek is nodig om het nut en mogelijke aanpassingen van gestandaardiseerde screenings- en diagnostische instrumenten te onderzoeken in subgroepen, zoals meisjes, en om beter te begrijpen welke mechanismes ten grondslag liggen aan de familiaire relaties tussen autisme- en angstsymptomen en de invloed van angstsymptomen op autistische sociale beperkingen. Een klinische implicatie betreft het belang van een dimensionele

en transdiagnostische benadering. Ik wil aanbevelen om autismesymptomen in kaart te brengen bij alle kinderen die worden aangemeld voor psychiatrische of ontwikkelingsproblemen, zoals in het huidig onderzoek. Daarnaast denk ik dat clinici alert moeten zijn op mogelijke bijkomende angstproblemen bij kinderen met ASS en ouders omdat deze de ernst van de autismesymptomen van het kind zouden kunnen beïnvloeden.

Curriculum Vitae

Jorieke Duvekot was born on September 9th 1985, in Harderwijk, the Netherlands. In 2003, she finished secondary school (gymnasium) at the Christelijk College Nassau Veluwe in Harderwijk and went on to study Psychology at Leiden University. In 2007, she suspended her study and went to Peru to learn Spanish and work as a volunteer in a children's home. In 2008-2009, she completed the Master Child and Adolescent Psychology at Leiden University. She carried out the research for her Master's thesis at the department of Child and Adolescent Psychiatry/Psychology of the Erasmus MC Sophia Children's hospital and did a full year clinical internship at the Psychosocial care department of the Willem-Alexander Children's hospital of the Leiden University Medical Center. After graduating, she started her PhD in March 2010 at the department of Child and Adolescent Psychiatry/Psychology of the Erasmus MC Sophia Children's hospital, under the supervision of prof. dr. F. C. Verhulst and dr. K. Greaves-Lord, which resulted in the work described in this thesis. This thesis is a part of the Social Spectrum Study, a multicenter study on behavioral, familial and societal factors related to autism spectrum disorder (ASD), which was funded by an endowed chair of the Sophia Foundation. Participating mental health care centers were Emergis, GGZ Westelijk Noord-Brabant, Lucertis, Riagg Rijnmond, Yulius, and Erasmus MC Sophia. Jorieke was largely responsible for implementing and coordinating the study at these centers and the data management and analyses. In May 2016, she started working as a child and adolescent psychologist at the Psychosocial care unit of the Sophia Children's hospital and completed the basic course on Cognitive Behavioral Therapy to advance her development as a clinical professional. She combines this clinical work with a job as a senior researcher for the ACCEPT study, a randomized controlled trial evaluating the effectiveness of the PEERS social skills training for adolescents with ASD, which is a combined project of Yulius and the department of Child and Adolescent Psychiatry/Psychology of the Erasmus MC Sophia Children's hospital.

Publications

Duvekot, J., van der Ende, J., Verhulst, F.C., & Greaves-Lord, K. Examining bidirectional effects between the Autism Spectrum Disorder (ASD) core symptom domains and anxiety in children with ASD. *Journal of Child Psychology and Psychiatry, accepted for publication.*

Duvekot, J., van der Ende, J., Verhulst, F. C., Slappendel, G., van Daalen, E., Maras, A., & Greaves-Lord, K. (2017). Factors influencing the probability of a diagnosis of autism spectrum disorder in girls versus boys. *Autism, 21*(6), 646–658.

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PhD portfolio

Name PhD student:	Jorieke Duvekot
Erasmus MC Department:	Child and Adolescent Psychiatry/psychology
PhD period:	2010-2015
Promotor(s):	Prof.dr. F.C. Verhulst
Supervisor/co-promotor(s):	Dr. K. Greaves-Lord
Research school:	NIHES

1. PhD training	Year	Workload (ECTS)
General academic skills		
Basiscursus Regelgeving en Organisatie Klinische trials (BROK), Erasmus MC, Rotterdam, the Netherlands	2011	1.0
Research Management for PhD-students, Erasmus MC, Rotterdam, the Netherlands	2011	1.0
Research Integrity in Medical Research, Erasmus MC, Rotterdam, the Netherlands	2012	2.0
Training presentation skills, Yulius, Barendrecht, the Netherlands	2013	0.5
Biomedical English Writing and Communication, Erasmus MC, Rotterdam, the Netherlands	2013	4.0
Searching in Pubmed, Erasmus MC, Rotterdam, the Netherlands	2014	0.3
Specific research skills		
Introduction to Clinical Research, NIHES, Erasmus MC, Rotterdam, the Netherlands	2012	0.9
Diagnostic Research, NIHES, Erasmus MC, Rotterdam, the Netherlands	2012	0.9
Regression Analysis, NIHES, Erasmus MC, Rotterdam, the Netherlands	2013	1.9
Clinical training		
ADI-R training, Accare, Assen, the Netherlands	2010	1.5
ADOS training module 1&2, Accare, Assen, the Netherlands	2010	1.5

ADOS training module 3&4, Accare, Assen, the Netherlands	2010	1.5
3Di training, Erasmus MC, Rotterdam, the Netherlands	2012	0.4
UCLA PEERS training, Yulius, Barendrecht, the Netherlands	2014	1.0
Total courses		**18.4**
Workshops and Meetings		
Various presentations about the project and (early) results at participating centers	2010-2017	2.0
Research Work Meetings at the department of child and adolescent psychiatry/psychology, Erasmus MC, Rotterdam, the Netherlands	2010-2016	1.0
(Inter)national conferences and symposia		
10e Nationaal Autisme Congres, Rotterdam, the Netherlands	2010	0.3
Symposium Neuroimaging, Genetics and Endophenotypes: Development and Psychopathology, Rotterdam, the Netherlands	2010	0.3
NVA Congres, Utrecht, the Netherlands	2010	0.3
11e Nationaal Autisme Congres, Rotterdam, the Netherlands	2011	0.3
Symposium Standardized assessment of Child Psychopathology, Erasmus MC, Rotterdam, the Netherlands	2011	0.3
Congres Kracht van Autisme, Yulius, the Netherlands	2011	0.3
NVA Autisme Congres, Utrecht, the Netherlands	2011	0.3
CPO Symposium, Erasmus MC, Rotterdam, the Netherlands	2011	0.3
Congres Hogrefe: diagnostiek en behandeling van (jonge) kinderen met ASS, Amersfoort, the Netherlands (oral presentation: *Screening for ASD in young children*)	2012	1.0
CPO Symposium, Erasmus MC, Rotterdam, the Netherlands	2013	0.3

14e Nationaal Autisme Congres, Rotterdam, the Netherlands (poster presentation: *Using parent and teacher ratings on the social responsiveness scale (SRS) to screen for ASD in clinically referred children*)	2014	1.0
International Meeting for Autism Research (IMFAR), Atlanta, USA (poster presentation: *Validation of the parent- and teacher-report Social Responsiveness Scale (SRS) in the Netherlands*)	2014	2.0
International Conference on Child Development in School & Community Settings (CDSCS, Yulius), Rotterdam, the Netherlands	2014	0.3
European Association for Behavioural & Cognitive Therapies (EABCT) Congress, The Hague, the Netherlands, (oral presentation: *Relationships between parents' and children's ASD and anxiety symptoms*)	2014	2.0
Nederlandse Vereniging voor Psychiatrie (NVvP) Voorjaarscongres, Maastricht, the Netherlands (oral presentation: *Relationships between parents' and children's ASD and anxiety symptoms*)	2015	1.0
15e Nationaal Autisme Congres, Rotterdam, the Netherlands (winner best poster prize: *Associations between ASD and anxiety symptoms among parents and children*)	2015	1.0
Congres Autisme: transities in de sociale context, Capelle ad IJssel, the Netherlands (oral presentation: *Autism in the family – results from the Social Spectrum Study*)	2016	1.0
Total congresses, seminars, presentations		**15**

2. Teaching		
Supervising practicals medical students	2011-2013	1.0
Supervising Review medical students	2011	1.0
Supervising Master's theses:	2010-2013	18.0
- Mette Offerhaus (Medicine, Erasmus MC): *The validity of the Dutch Social Responsiveness Scale for parents and teachers*		
- Iris Bonnema (Medicine, Erasmus MC): *The relationship between social stress vulnerability and autistic symptoms*		
- Suzanne Gerritsen (Psychology, Leiden University): *Predictive validity and utility of the M-CHAT for Autism Spectrum Disorder screening in the Netherlands*		
- Romi Bos (Psychology, Leiden University): *The reliability and validity of a screening instrument for Autism Spectrum Disorders: the Dutch Social Responsiveness Scale (SRS)*		
- Daisy van 't Land (Psychology, Utrecht University): *The validation of three screening instruments for toddlers and preschoolers to detect children with Autism Spectrum Disorders*		
- Kristel den Dubbelden (Psychology, Leiden University): *The potential of the CBCL and SRS in differentiating between ASD and non-ASD in Dutch clinically referred children*		
DISC training	2011	1.0
	Total teaching	**21**
	Total ECTS	**54.4**

1 ECTS (European Credit Transfer System) is equal to a workload of 28 hours.

Dankwoord

"A journey is best measured in friends rather than miles."
- Tim Cahill

Dit is het eindproduct van mijn promotieonderzoek waar ik jarenlang aan heb gewerkt. Ook al ben ik trots en blij dat het nu klaar is, gaat het met zoals de meeste dingen in het leven niet om het eindpunt maar om de reis ernaartoe. Een cliché, maar waar. En die reis heb ik niet alleen gemaakt. Daarom hierbij een woord van dank aan een aantal mensen die mij tijdens deze reis hebben vergezeld, gesteund en begeleid.

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"Begin at the beginning," the King said, very gravely, "and go on till you come to the end: then stop."
- Lewis Carroll, Alice in Wonderland

"Don't worry about the future; or worry, but know that worrying is as effective as trying to solve an algebra equation by chewing bubblegum. The real troubles in your life are apt to be things that never crossed your worried mind; the kind that blindside you at 4pm on some idle Tuesday."
- Baz Luhrmann, Everybody's Free (To Wear Sunscreen)