Heterogeneity in Autism Spectrum Disorders: Clarifying Core and Co-occurring Characteristics, Correlates and Course.

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Heterogeneity in Autism Spectrum Disorders: Clarifying Core and Co-occurring Characteristics, Correlates and Course.

Heterogeniteit bij autismespectrumstoornissen: op zoek naar de samenhang tussen kernsymptomen, comorbide symptomen, onderliggende kenmerken en beloop

Proefschrift

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General introduction

INTRODUCTION

Short background, general aims

The general aim of the current thesis is to contribute to the clarification of the heterogeneity within Autism Spectrum Disorder (ASD). ASD is a heterogeneous disorder at the phenotypical level, but also at the endophenotypical and the genotypical level (Waterhouse, 2011).

The phenotype can be defined as the composite of all observable characteristics of an individual. At the phenotypical level, ASD is characterized by a broad range and variation in the core symptoms of social interaction problems, communication problems and repetitive behaviors and restricted interests (Hus, Pickles, Cook et al., 2007). Besides that, individuals with ASD show a large variation in the levels of co-occurring psychiatric symptoms, like anxiety, attention problems, externalizing behavior and this results in an overlap between ASD and other disorders (Leyfer, Folstein, Bacalman et al., 2006; De Bruin, Ferdinand, Meester et al., 2007; Simonoff, Pickles, Charman et al., 2008).

The genotype can be defined as the sum total of genes, transmitted from parent to offspring. At the level of the genotype, heterogeneity in ASD is caused in the first place by the presence of multiple gene variants, each exerting a small effect on the phenotype (Rutter & Thapar, 2014; Jeste & Geschwind, 2014). Copy number variations (CNV) constitute a second source of genetic heterogeneity in ASD. CNV's are unique for each person; 70% of CNV's in ASD concern de novo mutations and CNV's result in milder or more severe symptoms (Jeste & Geschwind, 2014). Single Nucteotide Polymorfisms (SNP) constitute a third source of genetic heterogeneity and from Genome Wide Association Studies (GWAS) we know that SNP's in ASD are not only located in the coding regions (exons) of genes, but also in the noncoding or regulatory regions (introns) (Abrahams & Geschwind, 2008; Waterhouse, 2011; Rutter & Thapar, 2014.

Endophenotypes (or intermediate phenotypes or vulnerability markers) can be defined as internal, not directly observable characteristics, which can be detected by biochemical tests, brain imaging or neuropsychological tests. The concept of endophenotypes was introduced in order to bridge the gap between the considerable genetic and phenotypical variability (Gottesman & Gould, 2003). Positioned between the genetic disposition of the individual and the phenotype, endophenotypes were considered to offer a gateway to clarify the complex interplay of genetic factors and life experiences that finally give rise to the phenotype (Gottesman & Gould, 2003; Persico & Sacco, 2014). At present, many different endophenotypes for ASD have been proposed, most of which show insufficient specificity and sensitivity

(Persico & Sacco, 2014) and hence the level of endophenotypes is also characterized by heterogeneity.

In this introduction, first general aspects of ASD and sources of phenotypical heterogeneity within ASD will be discussed. Next, as a frame of interpretation, general aspects of endophenotypes will be described, and subsequently, particular neuropsychological and social cognitive endophenotypes in ASD relevant for this thesis will be addressed in more detail. Finally, the research questions and sample in the chapters of this thesis will be discussed and an overall outline will be provided.

General aspects of ASD

As for the definition of ASD, both the Diagnostic Statistical Manual (DSM)-IV-TR (APA, 2000) classification will be described - because it was used in this thesis - as well as the classification according to DSM 5 (APA, 2013), because it incorporates important changes compared to DSM-IV-TR based on insights from research findings.

In the current DSM 5 (APA, 2013), ASD is defined as a neurodevelopmental disorder with persistent deficits across multiple social contexts on two domains of symptoms: 'social communication & social interaction' (SCI) and 'restricted, repetitive patterns of behaviour, interests, or activities' (RRBI). The term neurodevelopmental implicates that symptoms are present early in live, that these same symptoms exert their influence upon further development and that altered brain processes govern this atypical development. As a consequence, the symptoms of ASD should be present in early childhood during the second year of life (12-24 months of age), but they may not fully manifest themselves until social demands exceed limited capacities (APA, 2013) or they may be seen earlier than 12 months if developmental delays are severe.

In the DSM-IV-TR the overarching category of Pervasive Developmental Disorder (PDD) was introduced and this overarching category included multiple classifications, ranging from the classification of Autistic Disorder (AD) with strict criteria and severe symptoms on each of the symptom domains, to categories with more lenient criteria. The categories of Asperger's Syndrome (AS) and Pervasive Developmental Disorder -Not Otherwise Specified (PDD-NOS) were characterized by more lenient criteria, i.e. less symptoms on the different domains (APA, 2000). The presumed category of AS in DSM-IV-TR differed from AD in its relatively normal language development, in the high level of cognitive functioning and in the relatively mild communication impairment (APA, 2000; Toth & King, 2008). The classification of PDD-NOS in DSM-IV-TR could be applied to a child who showed symptoms within all three domains of ASD, but did not reach the threshold for a full diagnosis of AD, or to a child who only showed symptoms above threshold in one or two domains of ASD (APA, 2000; Happé & Ronald, 2008). Thus, children with PDD-NOS constituted a

very heterogeneous group with considerable variation in the number and severity of ASD symptoms.

In the DSM 5, the overarching category of PDD was replaced by ASD. ASD is conceptualized as a spectrum disorder, without a further sub classification into distinct component disorders. In order to qualify for the diagnosis ASD the symptoms must cause clinically significant impairment in social, occupational, or other important areas of functioning. A diagnosis of ASD can be made in the presence of three manifestations of SCI and at least two manifestations of RRBI (DSM 5; APA, 2013).

Nowadays, approximately 1 out of 100 individuals meets criteria for ASD (e.g. Maenner, Rice, Arneson et al., 2014). The assumed rising prevalence rates of ASD might have to do with the broadening of the ASD concept in the former versions of the DSM IV and DSM IV-TR (Fombonne, 2009), it may be due to increased awareness in the medical, psychiatric and psychological community (Rutter, 2005) or there may be a true increase in the frequency of ASD in Western countries (Grether, Rosen, Smith et al., 2009; DSM 5, APA, 2013).

Heterogeneity within the ASD phenotype

In this section, four different aspects of phenotypical heterogeneity in ASD will be discussed:

a. the arrangement of different symptoms in symptom domains;
b. the subdivision of the autism spectrum into several distinct disorders;
c. the presence of co-occurring symptoms and syndromes (comorbidity);
d. the influence of intelligence on the manifestation of symptoms

Ad a. Symptom domains: In the former DSM-IV and DSM IV-TR versions of the DSM, ASD used to be diagnosed on the basis of a triad of impairments in three different symptom domains: Social Impairments (SI), Communication Impairments (CI), and Restricted, Repetitive Behaviours and Interests (RRBI). Factor analytic evidence (e.g. Gotham, Risi, Pickles, et al. 2007; Gotham, Risi, Dawson, et al. 2008) has shown that the triad of autistic symptoms should be replaced by a dyad, comprising of persistent deficits in social communication and interaction (SCI) and restricted, repetitive behaviors (RRB). Therefore in the DSM 5 a dyad of symptom domains was introduced instead of a triad (APA, 2013).

Ad b. Subclassifications of ASD: Serious doubts have been raised whether clinically defined categorical subtypes of the DSM IV-TR (i.e. AD, AS, PDD) can be validly distinguished (e.g. Kamp-Becker, Smidt, Ghahreman, et al. 2010; Walker, Thompson, Zwaigenbaum, et al. 2004; Stevens, Fein, Dunn, et al. 2000). Recent research has challenged the validity of the existing symptom domains and subtypes (e.g. Mandy, Charman, Skuse, 2012; Frazier, Youngstrom, Speer, et al. 2012; Mandy, Charman, Gilmour, et al. 2011), and has underscored the need

for a more empirically based conceptualization. Evidence that DSM-IV-TR categorical subtypes of AS and PDD-NOS cannot be distinguished reliably (Lord, Petkova, Hus, et al. 2012b) and are similar in terms of prognosis and treatment needs (Witwer & Lecavalier, 2008; Lord, Risi, Dilavore, et al. 2006) has led to the merging of these subtypes into a single ASD category in the DSM-5 (APA, 2013). This unitary approach conceptualizes autistic traits on a continuous dimension, with mild symptoms of the so called broader autism phenotype at one side of the spectrum and classic autism with severe symptoms at the other end of the spectrum. Distinct categories of disorders within the autism spectrum are dismissed and quantitative differences, regarding symptoms, level of functioning, intelligence are incorporated.

Categorical and dimensional models of conceptualizing diseases both have their limitations. Categorical models, like the DSM-IV-TR model of ASD, tend to "carve nature at the joints" and ignore transitional states between two conditions with autistic features. Dimensional models, when based on one measure, for instance blood pressure, are clarifying and user friendly. Multi-dimensional models based on two or more measures, while describing a complex reality more validly, have the inherent problem that it is difficult to locate an individual patient within these dimensions. This creates difficulties for both clinicians and researchers, and raises issues of user acceptability (First, 2005). The current DSM 5 model of ASD constitutes a mixed categorical/dimensional model: categorical in the sense that cut-off points between ASD and non-ASD are used and dimensional in the sense that no categories are discerned within the autism spectrum.

Ad c. Co-occurring symptoms: High rates of psychiatric comorbidity have been found in children with ASD, with 70 to 80 % of the patients having at least one comorbid disorder. This holds for clinical samples (De Bruin, De Nijs, Verheij, et al., 2007a), for population based samples (Simonoff et al, 2008) and across the different sub classifications of DSM-IV-TR (Leyfer et al., 2006). The most prevalent comorbid diagnoses in ASD are anxiety disorders, Oppositional Defiant Disorder (ODD) and Attention Deficit and Hyperactivity Disorder (ADHD) (De Bruin et al, 2007b; Simonoff et al, 2008; Leyfer et al, 2006). In different studies, the percentage of comorbid DSM-IV-TR anxiety disorders varied from 42 to 55% (Simonoff et al., 2008; De Bruin et al., 2007b; for an overview: White, Oswald, Ollendick, et al. 2009a). An inverse relation exists between anxiety and autistic symptom severity; anxiety being more prevalent in PDD-NOS as compared to AD (e.g. Szatmari, Bartolucci, Bremner et al., 1989; Gadow, Devincent, Pomeroy et al., 2005; Pearson, Loveland, Lachar et al., 2006; Mazurek, Kanne, 2010; Snow, Lecavalier, 2011). Scores of children with PDD-NOS on the Child

Behavior Checklist (CBCL) Attention Problems Scale were as high as the scores of children with ADHD, suggesting that attention problems are as common in PDD-NOS as in ADHD (Luteijn et al., 2000b). An inverse relation exists between ADHD and autistic symptom severity; ADHD being more prevalent in PDD-NOS as compared to AD (Yoshida & Uchiyama, 2004).

Ad d. Intelligence: Numerous studies have shown that intelligence level is associated with the manifestation of autism symptoms (i.e. Waterhouse, Morris, Allen, et al., 1996) and on the long term prognosis and course (Billstedt, Gillberg, Gillberg, 2005; Howlin, Goode, Hutton, et al., 2004). Low IQ's are associated with more severe manifestations of autism, whereas higher IQ's are associated with the milder manifestations like PDD NOS or Asperger's syndrome (Billstedt, et al., 2005; McGovern & Sigman, 2005). A higher level of cognitive functioning during childhood was associated with better functional outcome in adulthood (Howlin et al., 2004; Billstedt et al., 2005; Billstedt, Gillberg, Gillberg, 2007) and with a better clinical outcome during adolescence and adulthood (Billstedt et al., 2005; McGovern & Sigman, 2005).

In this thesis, we studied whether the variation in ASD core symptoms reflects different underlying diagnostic categories or a dimensional distribution of symptoms (Chapter 2). We also investigated how co-occurring symptoms were associated with variations in core symptoms (Chapter 2) and we investigated the association of IQ, quality of social relations, and co-occurring anxiety on ASD symptom severity (Chapter 3).

Endophenotypes in ASD

Efforts to connect single gene variants to specific psychiatric disorders have proven unsuccessful. Only weak relationships have been found between specific gene variants and specific psychiatric disorders. Endophenotypes should represent simpler clues to genetic underpinnings than the symptoms of the disorder, promoting the view that psychiatric diagnoses can be decomposed or deconstructed, which can result in more straightforward and more successful genetic analyses (Gottesman & Gould, 2003). Furthermore, endophenotypes may help to reduce heterogeneity, help to bridge the gap between genotype and phenotype and supply explanations for causes, symptoms and course of a disorder. An endophenotype may be neurophysiological, biochemical, endocrinological, immunological, neuroanatomical, cognitive or neuropsychological (Gottesman & Gould, 2003). The biochemical, hormonal and immunological endophenotypes operate on a microbiological level and are more closely connected to the genotype, whereas the neuropsychological endophenotypes operate on a behavioral level, in vicinity of the phenotype. A wide range of putative endophenotypes for ASD were introduced, such as elevated blood

serotonin levels (Anderson, Horne, Chatterjee et al., 1990), macrocephaly between 6 months and four years (Courchesne, Pierce, Schumann et al., 2007), and hypoactivation of the fusiform gyrus in reaction to the vision of human movement (Kaiser, Hudac, Schultz et al., 2010). An endophenotype for a psychiatric disorder must meet five criteria: it must be heritable; it is associated with the disorder in the population; it must be state independent (the endophenotype can be detected even if the disorder is in remission); within families the disorder and the endophenotype co-segregate; and the endophenotype is found in non-affected family members at a higher rate than in the general population (Persico & Sacco, 2014). Endophenotypes differ from biomarkers in the sense that biomarkers are state dependent, not necessarily genetic and not necessarily familial (Persico & Sacco, 2014). Ideally, the use of endophenotypes holds promise for finding more reliable genotype-phenotype correlations in autism research, for dissecting clinical subgroups of ASD patients with relatively homogeneous genetic and pathophysiological underpinnings, for aiding clinicians in early diagnosis, and for predicting developmental trajectories or treatment response. Sensitivity and specificity of each single endophenotype has proven to be at best moderate (Persico & Sacco, 2014); and therefore combining several endophenotypical parameters each belonging to different biological domains (for instance biochemical, brain imaging, electrophysiological and neuropsychological) might be the best strategy for diagnosing ASD (Persico & Sacco, 2014). Recently, it was stated that psychiatric research should focus on certain "behavioral domains", which coincide with cognitive and neuropsychological endophenotypes and it was proposed that psychiatric research should abandon its focus on symptoms and diagnostic categories (Insel, Cuthbert, Garvey et al. 2010; Cuthbert & Insel, 2013; Insel, 2014). These authors propose to study relations between genetic data, data from brain imaging on brain circuitry and data from behavioral domains or endophenotypes, thereby assigning an important role to these behavioral domains (Cuthbert & Insel, 2013).

Five potential domains of cognitive endophenotypes and their presumed neurobiological underpinnings are summarized in table 1.1 (adapted from Dawson, Webb, McPartland et al., 2005a and in accordance with Cuthbert and Insel, 2013).

In the current thesis, only three very specific presumed social cognitive and neuropsychological endophenotypes were tested for their capacity to predict future course and development in a longitudinal study. The underlying idea was that the presence of these presumed endophenotypes, which are by definition associated with ASD and which represent an underlying mechanism of the disorder, may have an important influence on further development and future course. It is considered an ideal demonstration of causality, when an endophenotype measure at T1 pre-

Table 1.1: Relations between social cognitive and neuropsychological endophenotypes; their presumed underlying dysfunctional brain circuitry and the psychological function or test, which is involved in this endophenotype.

Endophenotype/behavioral domain	Presumed Dysfunctional Brain Circuitry	Presumed test or psychological function
Affiliative behavior/ social reward	Ventro-medial prefrontal cortex Amygdala	Theory of Mind. (Social cognition)
Language and phonological processing	Superior temporal gyrus Temporoparietal cortex Broca's area	Language development Formal Thought Disorder** (chapter 4)
Face processing	Fusiform face area Inferior temporal gyrus right Amygdala	Face and emotion recognition** (Social cognition; chapter 5)
Executive function/planning/ flexibility	Prefrontal cortex	Executive tests like Wisconsin Card Sorting. (Neuropsychological)
Central Coherence; detail-focused cognitive style	Reduced long distance tracts and increased local circuitry	Disembedding performance; visuo-spatial tasks** (Neuropsychological; chapter 6)

(** plus chapter: endophenotype, which is studied in this thesis.)

dates the emergence of certain symptoms or pathological behavior at T2 (De Geus & Boomsma, 2001; Viding & Blakemore, 2007).

We focused on three potential social cognitive and neuropsychological endophenotypes, thus endophenotypes that operate on a behavioral level, in relative vicinity of the phenotype. These endophenotypes are formal thought disorder (FTD) in the language and communication domain (Chapter 4), FR and IFE in the social cognitive domain (Chapter 5), and detail-focused cognitive style in the non-social, neuropsychological domain (Chapter 6).

Formal Thought Disorder (FTD), which was studied in chapter 4, is viewed as an endophenotype in the linguistic domain by some investigators and as an endophenotype in the domain of communication and social cognition by others (Dochtery, McCleery, Divilbiss et al., 2013). The social cognition perspective bears certain advantages: speech is measured in its functional way, namely its capacity to convey meaning and furthermore this approach is easier to integrate with other findings on social cognition (Dochtery et al, 2013). Individuals with ASD show striking peculiarities in the domain of language and communication. Formal Thought Disorder (FTD) is a disruption in the organisation and flow of thoughts, which is inferred from the disorganization of spoken language (Caplan, 1994; Bearden, Wu, Kaplan et al., 2011). Disordered speech, or formal thought disorder is an important symptom of severe mental illnesses like schizophrenia (Bleuler, 1950; Andreasen,

1979; Caplan, 1994; Caplan, Guthrie, Tang et al., 2001; Dochtery, 2012) and ASD (Solomon, Ozonoff, Carter et al., 2008).

FTD was also selected to examine its predictive properties as an endophenotype, because of the interesting link with psychosis as well as with ASD.

Facial Recognition (FR) and Identification of Facial Emotions (IFE), which were studied in chapter 5, constitute examples of potential social cognitive endophenotypes in ASD. Deficits in facial recognition (FR) have been reported in ASD (e.g. Klin, Sparrow, De Bildt et al., 1999; Joseph & Tanaka, 2003; Wolf, Tanaka, Klaiman et al., 2008), as well as deficits in the identification of facial emotions (IFE) (e.g. Pelphrey, Sasson, Reznick et al., 2002; Lindner & Rosen, 2006; Wright, Clarke, Jordan et al., 2008; overviews: Harms, Martin, Wallace, 2010; Uljarevic & Hamilton, 2013). Underlying dysfunctional brain mechanisms of FR and IFE in ASD have been studied with event related potentials (ERP) and with fMRI scans. ERP studies found evidence for N170 and N300 abnormalities, both interpreted as an aberrant salience for human faces (Dawson et al., 2005a; Dawson, Webb, Wijsman et al., 2005b; Jeste & Nelson, 2009) and fMRI studies found dysfunctions in the fusiform face area (Schultz, Gaulthier, Klin et al., 2000; Pierce, Muller, Ambrose et al., 2001;Weigelt, Koldewyn, Kanwisher, 2012; for an overview Harms et al., 2010). FR and IFE were chosen to examine their predictive properties as endophenotypes, because of these promising results in brain imaging and neurophysiological studies and because of the direct association with symptoms of ASD like gaze avoidance, lack of reciprocity.

Weak central coherence (WCC), which was studied in chapter 6, constitutes an example of a neuropsychological endophenotype for ASD. Weak Central Coherence implies that a local and detailed-focused style of information processing is usually favored by individuals with ASD, rather than a global or integrative cognitive style (Happé & Frith, 2006; Happé & Booth, 2008). Individuals with ASD show an equal or even superior performance, compared to individuals without ASD on tasks that favor local, detail-focused processing (Bolte, Holtmann, Poustka et al., 2007). Central coherence or detail-focused cognitive style was chosen to examine its predictive properties as an endophenotype, because it represents a non-social endophenotype, which may be linked to RRBI behaviours in ASD (Chen, Rodgers, McConachie, 2009).

For each of these linguistic, social cognitive and neuropsychological endophenotypes we studied longitudinally whether their presence in childhood predicted more severe symptoms seven years later in adolescence.

Research questions

Based upon the state-of-the art of the ASD literature discussed above, the general aims of the current thesis are twofold. The first aim of this thesis is to gain more

insight in the phenotypical variance of core and co-occurring symptoms of ASD. The specific research questions concerning this first aim are:

1. Do symptom profiles on core ASD symptoms support a categorical view with different underlying diagnostic categories or do they reflect a dimensional distribution of ASD symptoms (Chapter 2)?
2. How are co-occurring symptoms associated with severity of core ASD symptoms (Chapter 2)?
3. What is the influence of quality of social relations, ASD symptom severity and IQ on the manifestation of co-occurring anxiety in ASD (Chapter 3)?

The second aim of this thesis is to determine whether presumed endophenotypical correlates of ASD predict future symptom severity of this condition. The particular research questions concerning this second aim are:

1. Does FTD in school aged children with ASD predict a higher symptom severity of ASD in adolescence over and above the ASD symptom severity in childhood ? Or does FTD better predict prodromal symptoms of psychosis in adolescence? (Chapter 4)
2. Does poor performance on indices of social cognition, namely Facial Recognition and Identification of Facial Emotions in childhood predict higher symptom severity of ASD in adolescence over and above the ASD symptom severity in childhood ? (Chapter 5)
3. Does a detail-focused cognitive style in childhood, operationalized as superior disembedding performance on a visuo-spatial test, predict higher symptom severity of RRBI symptoms in adolescence over and above the RRBI symptoms in childhood (Chapter 6)?

Sample and study design

The selection of the individuals participating in respectively the cross-sectional (part 1) and the longitudinal part of this thesis (part 2) are described in the current section. A clinical cohort was retrieved from consecutive referrals for psychiatric evaluation to the outpatient clinic of the Department of Child and Adolescent Psychiatry/psychology of the Erasmus MC-Sophia in Rotterdam. Between July 2002 and September 2004, all parents of 6-13 year old children whom were referred to this outpatient clinic (n=503, de Bruin et al., 2007a; de Bruin et al., 2007b) completed the Child Social Behavior Questionnaire [(CSBQ; (Hartman, Luteijn, Serra et al., 2006)]. Children were eligible for the study if their referral complaints consisted of problems in social interaction and/or communication and if these social and communication

problems were above the threshold (n=234) (Figure 1). The cross-sectional study on the heterogeneity in core and co-occurring symptoms (chapter 2) was performed on this sample of 234 children, aged 6-13 years old, who were diagnosed with autism spectrum disorder (n=139) or who belonged to the broader autism phenotype (n=95). Of this sample, 139 children received a DSM-IV-TR classification within the autism spectrum (n=16 Autistic Disorder, n=11 Asperger Syndrome, n=112 PDD-NOS). A group of 95 individuals did not fulfil the full DSM-IV-TR criteria for a diagnosis of ASD, although children in this group did show certain ASD traits at referral (broader autism phenotype).

The sample of the cross-sectional study on correlates of anxiety (chapter 3) consisted of 134 children with a DSM-IV-TR classification of ASD, aged 6 to 13 years (n=15 Autistic Disorder, n=10 Asperger Syndrome, n=109 PDD-NOS). In 61.2% (n=82) this clinical diagnosis was confirmed with an ADOS, module 3 classification within the autism spectrum. In 43% (n=58) of this sample an anxiety disorder, according to DISC-IV was present.

A second assessment wave took place approximately seven years later between June 2009 and May 2011 (mean follow-up time of 6.9 years, SD = .7) in the same group of participants, which were at that time adolescents aged between 12-19 years. There was no selective attrition (please see Chapter 3 for details). Within this cohort, the ADOS was assessed both in childhood (wave 1) and in adolescence (wave 2).

The sample of the longitudinal study on formal thought disorder (Chapter 4) consisted of 91 individuals (n=134 were diagnosed with ASD on the ADOS, module 3 at T1; n=114 returned at T2; n=91 had complete data at T2). The missing data in 23 participants at T2 were caused by the Prodromal Questionnaire, a self-rating scale, which was not complete in 23 cases.

The sample of the longitudinal studies on facial recognition (chapter 5) and detail oriented cognitive style (chapter 6) consisted of 87 individuals (n=134 were diagnosed with ASD on the ADOS, module 3 at T1; n=114 returned at T2; n=87 had an IQ >=70 and complete data at T2).

Outline of the thesis:

The current studies were performed, using cross-sectional as well as longitudinal data. In the first part of this thesis, cross-sectional data were used, and we studied the profiles of - and interrelations among - the core and co-occurring phenotypic characteristics (Chapter 2, 3). In Chapter 2 we investigated core symptoms and symptom domains of ASD without a theoretical a priori perspective in order to find empirically based classifications. In Chapter 3 we investigated how anxiety - an im-

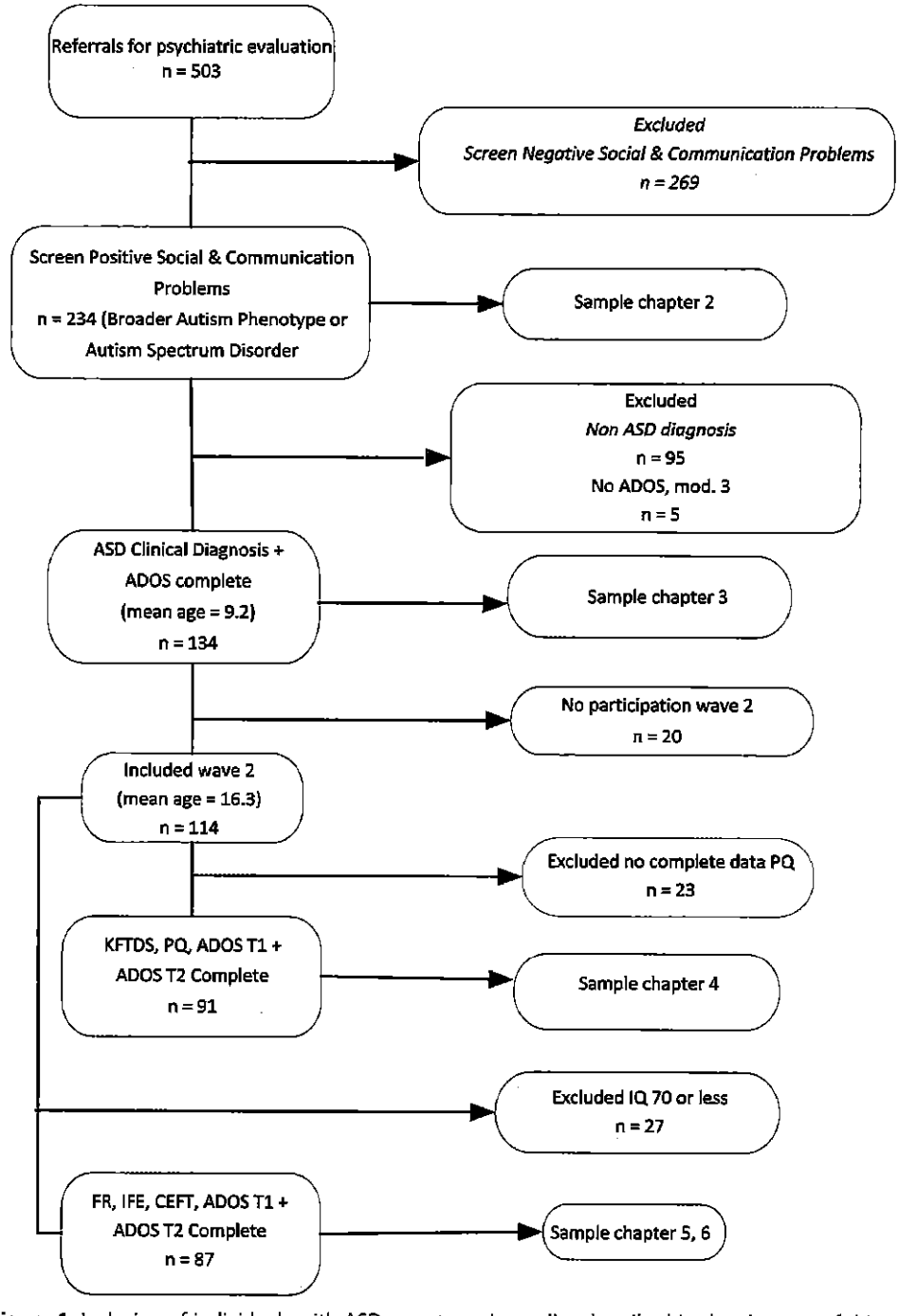

Figure 1. Inclusion of individuals with ASD symptoms in studies described in the chapters of this thesis.

portant co-occurring characteristic in ASD - is related to relevant correlates, namely ASD symptom severity, IQ and quality of social relations.

In the second part of this thesis, longitudinal data were used, and we explored the role of certain potential endophenotypes in the course of ASD symptoms (chapter 4, 5 and 6). More particularly, in this second part, it was studied whether symptoms of formal thought disorder (chapter 4), indices of social cognition (face and emotion recognition, chapter 5), and indices of non-social cognition (detail-focused cognitive style, chapter 6) as assessed in childhood (age 6-12) predicted a greater social and/or non-social ASD symptom severity seven years later in adolescence (age 12-19). Finally, in Chapter 8 the main findings and conclusions of the studies presented in the foregoing chapters are presented and discussed. Research and clinical implications and recommendations for future studies are given.

Chapter 2

Profiles of core autistic symptoms and relations with co-occurring internalizing and externalizing problems

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(Has been submitted)

ABSTRACT

The current study investigated relations among core autistic traits and co-occurring internalizing and externalizing problems. Firstly, we detected profiles within the core symptom domains of Autism Spectrum Disorders (ASD), as assessed with the Autism Diagnostic Observation Schedule (ADOS) in 234 clinically referred 6-13 year old children with varying degrees of autistic traits. Subsequently, we examined whether groups with different ASD symptom profiles differed regarding co-occurring internalizing and externalizing problems. Latent profile analyses revealed three classes that showed low, moderate versus high scores on all ADOS domains. Children with moderate ASD symptom profiles - often classified as PDD-NOS - showed relatively high levels of co-occurring internalizing and externalizing problems. Therefore, clinical attention is warranted for co-occurring problems in individuals at the less extreme end of the autism spectrum.

KEY WORDS

Autism Spectrum Disorders; Internalizing Problems; Externalizing Problems; Latent Profile Analyses

INTRODUCTION

In the proposed DSM-V, the current diagnostic subtypes of 'Autistic Disorder (AD)', 'Asperger Syndrome' and 'Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS)' will be abandoned, and a dimensional approach -in which ASD is regarded as a continuum of traits and symptoms- will have a much more prominent role (www.dsm5.org/proposed revisions/autistic disorder). This more dimensional approach towards ASD has indeed been supported by a number of studies both in clinical as well as general population samples (Constantino, Przybeck, Friezen et al., 2000; Constantino, Gruber, Davis et al., 2004; Fein, Stevens, Dunn et al., 1999; Kamp-Becker, Smidt, Ghahreman et al., 2010; Waterhouse, Morris, Allen et al., 1996).

A large body of research has demonstrated that within individuals with ASD there is a large variation in the level of severity of core ASD symptoms, as well as in the patterning of the different types of core symptoms (Constantino et al., 2000; Szatmari, Merette, Bryson et al., 2002; Van Lang, Boomsma, Sytema et al., 2006; Georgiades, Szatmari, Zwaigenbaum et al., 2007; Gotham, Risi, Dawson et al., 2008; Ronald, Happé, Bolton et al., 2006; Happé & Ronald, 2008).

Besides this variation in level and profile of core ASD symptoms, there is also a lot of variation in the level of co-occurring internalizing and externalizing problems (De Bruin, Ferdinand, Meester et al., 2007b). For instance, Pearson and colleagues (2006) compared the levels of co-occurring internalizing and externalizing problems between children with AD and children with PDD-NOS and found that one out of three children with AD versus one out of two children with PDD-NOS showed clinically significant anxiety levels. Gadow and colleagues (2005) reported higher levels of anxiety in Asperger Syndrome as compared to AD and postulated an inverse relationship between the level of ASD symptoms and the level of anxiety symptoms. As for externalizing problems, higher rates of co-occurring Attention Deficit Hyperactivity Disorder (ADHD) problems were found in children with PDD-NOS as compared to children with AD (Yoshida & Uchiyama, 2004). However, previous studies determined the relationship between DSM-IV defined ASD categories and levels of other type of psychopathology, and did not use a more empirically based dimensional approach towards the taxonomy of ASD.

To clarify the relation between patterning of core ASD symptoms and co-occurring internalizing and externalizing problems, the current study investigated how groups with separate ASD profiles as assessed with the Autism Diagnostic Observation Schedule (ADOS) (Lord, Rutter, Dilavore et al., 1999) differed regarding co-occurring internalizing and externalizing problems in a large sample of clinically referred children aged 6 to 13.

METHODS

Participants

The current sample consisted of 234 children, aged 6-13, who were consecutively referred to the outpatient clinic of the Erasmus MC, the Netherlands between July 2002 and September 2004. Children were eligible for the study if their referral complaints consisted of problems in social interaction and/or communication. Furthermore, to be included in the study, the level of language development had to be sufficient to administer module 3 of the ADOS and the Wechsler's Intelligence Scale for Children-Revised (WISC-R Projectgroep, 1986; Wechsler, 1974).

Clinical diagnostic assessment consisted of a parental interview on the child's early developmental history, the child's medical history, and the child's current functioning, psychiatric observations of the child during a semi-structured interview, an IQ test and school information. Integrating all this information, a multidisciplinary team reached consensus on a clinical diagnosis based on DSM-IV-TR criteria. For the purpose of this study, the clinical diagnosis was derived independently from ADOS evaluation (see below). Of the total sample, 139 children received a DSM-IV-TR classification within the autism spectrum (n = 16 Autistic Disorder, n = 11 Asperger Syndrome, n = 112 PDD-NOS). A group of 95 individuals did not fulfil the full DSM-IV-TR criteria for a classification of ASD, although children in this group did show subsyndromal ASD traits at referral. Of these 95 patients, 42 fulfilled DSM-IV-TR criteria for an externalizing disorder (ADHD/Oppositional Defiant Disorder (ODD), 26 fulfilled DSM-IV-TR criteria for an internalizing disorder (anxiety/depression), six patients had another developmental disorder, six patients had an adjustment disorder and 15 patients received no axis I disorder.

Prior to participation in the study all parents/caretakers had signed informed consent forms. Children of 12 years old signed the consent forms themselves as well. The Medical Ethics Committee of the Erasmus Medical Centre approved the study.

Measures

Autism Diagnostic Observation Schedule (ADOS)

The ADOS module 3 (Lord et al., 1999) was used to assess ASD symptoms. The ADOS is considered a "gold standard" diagnostic tool, and provides a standardized context for elaborate observation and scoring of ASD symptoms. The ADOS ASD symptom domains are divided into Language and Communication (LC), Reciprocal Social Interaction (RSI), and Stereotyped Behaviors and Restricted Interests (SBRI). The items of each domain are scored on a 3-point scale from 0 (no evidence of abnormality related to autism) to 2 (definite evidence of abnormality). Some items include

a code of 3 to indicate particularly severe abnormalities. When using the original ADOS algorithm, such scores of 3 are converted to 2.

The ADOS has good psychometric properties (Lord et al., 1999). We used the ADOS domain scores in a dimensional way as proposed by Volkmar and colleagues (2009). Problems in quantifying ADOS scores (Gotham, Risi, Pickles et al., 2007) could be avoided, since all our participants underwent module 3. The ADOS was performed and scored by trained and certified clinicians, who were blind for the clinical diagnosis. ADOS classifications and ADOS calibrated severity scores were computed to provide clinicians with an impression of the overall severity of ASD. ADOS classifications include non-ASD, ASD and AD. The ADOS calibrated severity scores (Gotham, Pickles, Lord, 2009) transform the raw ADOS scores into a decimal score (0-10), which represents severity of ASD.

Child Behavior Checklist (CBCL)

To assess co-occurring internalizing and externalizing problems, the Child Behavior Checklist/ 4-18 (CBCL) (Achenbach, 1991) was completed by the mother. The CBCL has 118 problem items and two open-ended items that are scored on a three-point scale (0 = not true, 1 = somewhat or sometimes true, 2 = very true or often true). Items are scored on six DSM-oriented scales: Affective Problems, Anxiety Problems, Somatic Problems, Attention Deficit Hyperactivity Problems, Oppositional Defiant Problems and Conduct Problems (Achenbach & Rescorla, 2001). The good psychometric qualities of the CBCL (Achenbach, 1991) were confirmed for the Dutch translation (Verhulst, Van der Ende, Koot, 1996). Krol and colleagues (2006) showed good predictability of the DSM-oriented scales to DSM-IV diagnosis in a Dutch clinical sample.

Wechsler's Intelligence Scale for Children-Revised (WISC-R)

To assess the full scale intelligence quotient (FSIQ), the Dutch version of the WISC-R was administered (WISC-R Projectgroep, 1986; Wechsler, 1974). Like the original version, the Dutch version has good reliability and validity (WISC-R Projectgroep, 1986). Newer versions of the WISC-III were not administered since at the time of this study these versions were not fully available.

Statistical analyses

ADOS LC, SRI, and SBRI domain scores were computed in accordance with the ADOS algorithm by adding the item scores. To improve comparability of scores across these domains, mean weighted domain scores were computed for each domain by adding the item scores (0, 1, 2, or 3) of all items from one domain on the ADOS (8 items for LC; 10 items for SRI and 5 items for SBRI) and subsequently dividing these

sum scores by the number of items in that domain. To detect groups with separate profiles on the three ASD domains (LC, RSI, SBRI), Latent Profile Analysis (LPA) was performed, using Mplus version 4.21 (Muthén & Muthén, 2007). In contrast to factor analysis, which yields information on the co-occurrence of symptoms, LPA is a technique that tests whether groups of individuals with similar responses on a serie of items can be identified. The primary objective of LPA in our study was to find the smallest number of classes of individuals with distinct endorsement profiles of ASD symptoms. Models that fit a one class model, a two class model, a three class model, and so on, were analyzed in a stepwise fashion until the model did not improve any further. To identify the model with the according (number of) classes that best fitted the data, the log likelihood value, Bayesian Information Criterion (BIC) (Kass & Wasserman, 1995), the Akaike Information Criterion (AIC), the entropy, and the results of the Vuong-Lo-Mendell-Rubin-Likelihood ratio tests were evaluated. When considering LPA, the BIC is considered to be superior to the other information criteria (Nylund, Asparouhov, Muthén, 2007). In general, models with more classes have more parameters and can therefore provide a better fit for the data. This is reflected in lower log-likelihood values for models with more classes. The information criteria BIC and AIC give penalties to models with more parameters and therefore protect against unnecessary model complexity. These information criteria do not necessarily favour the same model as the log likelihood values. After examining the fit of the general model, sex, age, and full scale IQ, were separately included in the model as a covariate to investigate whether adding one of these factors improved the fit of the model (Dayton & Macready, 1988). For descriptive purposes, classes revealed within the best fitting model were compared regarding sex, DSM-IV-TR classification, ADOS classification, IQ, age, calibrated ADOS severity scores and weighted ADOS domain scores.

To investigate whether classes with separate ASD profiles differed regarding co-occurring internalizing and externalizing problems, CBCL descriptives were computed and the classes were compared on the CBCL DSM-oriented scales using ANCOVAs. We assumed statistical significance at the $<.05$ level. As an estimate of effect sizes, the percentage of explained variance ($\eta 2$) was calculated when comparing the classes on continuous variables.

RESULTS

Latent profiles

As shown in table 1, the latent profile analyses showed that the log likelihood, BIC and AIC parameters pointed in the same direction, favoring a three-class model.

Table 1: LPA Fit indices

# of latent classes	Loglikeli-hood	# of parameters	BIC	Adjusted BIC	AIC	S	p LRT
1 (LC, RSI, SBRI)	-1,416.44	6	2,865.61	2,846.59	2,844.88		
2	-1,318.89	10	2,692.34	2,660.64	2,657.78	0.92	0.03
3	-1,272.45	14	2,621.27	2,576.90	2,572.90	0.90	0.10
4	NC						
2 (covariate sex)	-1,318.15	11	2,696.30	2,661.44	2,658.29	0.91	0.06
2 (covariate age)	-1,312.14	11	2,684.30	2,649.43	2,646.29	0.89	0.25
2 (covariate IQ)	-1,163.21	11	2,385.99	2,351.13	2,348.42	0.81	< 0.01
3 (covariate IQ)	-1118.51	16	2,323.68	2,272.97	2,269.02	0.86	0.06
4 (covariate IQ)	NC						

Note: # = Number, BIC = Bayesian Information Criterion, Adjusted BIC = Sample Size Adjusted BIC, AIC = Akaike Information Criterion, S = Entropy, p LRT = significance level from the Vuong-Lo-Mendell-Rubin Likelihood ratio tests, LC = Language and Communication, RSI = Reciprocal Social interaction, SBRI = Stereotyped Behaviors and Restricted Interests, NC = Not Convergent

Using sex or age as a covariate did not improve the model fit. However, adding IQ as a covariate improved the fit. Based on these results, the three-class model including IQ was selected. As illustrated in figure 1, three classes were discerned: a 'high' class, with high scores on all three domains (10 % of the total sample, n = 23); a 'moderate' class, with moderate scores on all domains (43 % of the total sample, n = 101); and a 'low' class, with low scores on all domains (47 % of the total sample, n = 110). The Average Latent Class Probability, an indicator of latent profile distinctive-

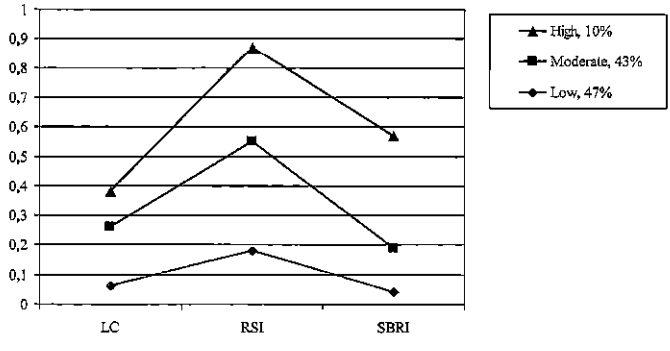

Figure 1. ASD symptom profiles of the three classes

Note: Y axis: average weighted domain score, X-axis: LC = Language and Communication, RSI = Reciprocal Social Interaction, SBRI = Stereotyped Behaviours and Restricted Interests. High = class with relatively high scores on all domains n=23 (10%), Moderate = class with moderate scores on all domains n=101 (43%), Low = class with relatively low scores on all domains n=110 (47%).

ness in this model, was 0.94 for the high class; 0.93 for the moderate class and 0.94 for the low class; which exceeds the value of 0.80 that is considered adequate.

Based on the ADOS classification, 65 % in the high class had AD, in the moderate class 64 % had ASD, and in the low class 100 % had a non-ASD diagnosis ($\chi 2$ (4) = 203.41, $p < 0.001$). The calibrated ADOS scores further illustrated the level dif-

Table 2. Descriptive statistics on the three ASD classes

		High n=23 (10%)	Moderate n=101 (43%)	Low n=110 (47%)	p η2
Boys:girls	%	90: 10	92: 8	66: 34	0.00**
AD:AS:PDDNOS: No (DSM-IV TR)	%	30: 10: 60: 0	3: 7: 68: 22	1: 2: 32: 65	0.00**
AD: ASD: No (ADOS)	%	65: 35: 0	7: 64: 29	0: 0: 100	0.00**
FSIQ	mean (SD)	81.8 (17.9)	93.9 (18.7)	91.1 (15.9)	0.02*
	range	48-108	56-144	48-120	
Age	mean (SD)	8.4 (1.5)	9.2 (2.0)	9.9 (1.7)	0.00**
	range	6.0-11.0	6.0-13.0	6.0-13.0	
ADOS calibrated	mean (SD)	8.00 (1.34)	4.69 (1.6)	1.44 (0.75)	0.00**
severity score	range	6.0- 10.0	1.0-8.0	1.0-4.0	74%
LC	mean (SD)	0.38 (1.27)	0.26 (0.08)	0.06	0.00**
	range	0.22-0.67	0.00-0.56	0.00-0.22	68%
RSI	mean (SD)	0.87 (0.24)	0.54 (0.20)	0.18 (0.16)	0.00**
	range	0.40-1.20	0.10-1.00	0.00-0.60	60%
SBRI	mean (SD)	0.57 (0.18)	0.19 (0.16)	0.04 (0.08)	0.00**
	range	0.20-0.80	0.00-0.60	0.00-0.40	56%
ADHD	mean (SD)	1.06 (0.47)	1.20 (0.51)	1.23 (0.53)	0.46
	range	0.29-1.71	0.00-2.00	0.00-2.00	0.8%
ODD	mean (SD)	0.77 (0.51)	0.99 (0.54)	1.14 (0.52)	0.11
	range	0.00-1.80	0.00-2.00	0.00-2.00	4.5%
CD	mean (SD)	0.19 (0.25)	0.34 (0.29)	0.38 (0.31)	0.05*
	range	0.00-0.82	0.00-1.18	0.00-1.76	3%
ANX	mean (SD)	0.44 (0.37)	0.84 (0.46)	0.93 (0.48)	0.00**
	range	0.00-1.33	0.00-2.00	0.00-1.83	7.8%
AFF	mean (SD)	0.26 (0.24)	0.47 (0.29)	0.93 (0.48)	0.01*
	range	0.00-0.85	0.00-1.15	0.00-1.46	6.4%
SOM	mean (SD)	0.19 (0.26)	0.27 (0.30)	0.35 (0.33)	0.19
	range	0.00-1.00	0.00-1.29	0.00-1.43	1.6%

Note: DSM-IV-TR diagnoses: AD=Autistic Disorder; AS=Asperger Syndrome; PDD-NOS=Pervasive Developmental Disorder Not Otherwise Specified; No=Non Autism Spectrum diagnosis.
ADOS diagnoses: AD=Autistic Disorder; ASD=Autism Spectrum Disorder; Non-Sp.=Non Spectrum diagnosis. IQ=Intelligence Quotient. ADOS domains: LC=Language and Communication; RSI=Reciprocal Social Interaction; SBRI=Stereotyped Behaviours and Repetitive Interests. CBCL DSM-oriented scales: ADHD=Attentional Deficit Hyperactivity Problems, ODD=Oppositional Defiant Problems, CD=Conduct Problems, ANX=Anxiety Problems, AFF=Affective Problems, SOM=Somatic Problems. SD=Standard deviation; *=p<0.05; **=p<0.01; η2=percentage of explained variance.

ferences between the classes with the high class having a mean score of 8.00, the moderate class having a mean score of 4.69 and the low class 1.44 ($F(2, 221) = 321.7$, $p < 0.001$). With respect to DSM-IV-TR classifications, the most cases of AD were in the high class, the most cases of PDD-NOS and AS were in the moderate class and the most non-ASD cases were in the low class ($\chi2(6) = 81.94$, $p<0.001$). As shown in table 2, the mean IQ in the high class was significantly lower than in the moderate and low class ($p = 0.02$). The children in the high class were also significantly younger as compared to the moderate and low classes ($p < 0.001$). The low class included significantly more girls as compared to the high and moderate classes ($p < 0.001$). Therefore, in the subsequent ANCOVAs, we included IQ, age and gender as covariates.

Comparison on internalizing and externalizing problems

As indicated in figure 2, ANCOVAs revealed that the level of internalizing and externalizing problems was higher in the low and moderate ASD classes than in the high ASD class. Scores in the low class were higher than scores in the high class for Oppositional Defiant Problems ($p = 0.002$), Conduct Problems ($p = 0.006$), Anxiety Problems ($p = 0.01$) and Affective Problems ($p = 0.011$). Scores in the moderate class were higher than scores in the high class for Anxiety Problems ($p = 0.005$) and for Conduct Problems ($p = 0.049$).

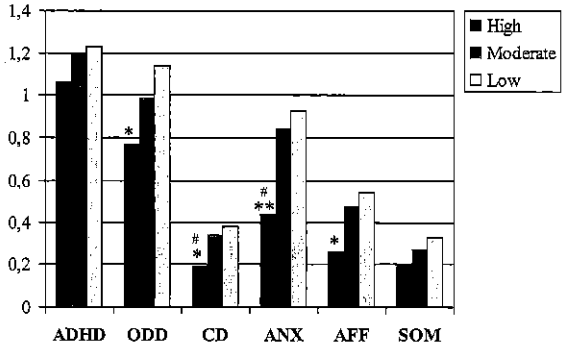

Figure 2 Weighted scores on the CBCL DSM-oriented scales for each of the classes.
Note: Y-axis: mean weighted score (Range = 0-2), X-axis: CBCL DSM-oriented scales; ADHD = Attentional Deficit Hyperactivity Problems, ODD = Oppositional Defiant Problems, CD = Conduct Problems, ANX = Anxiety Problems, AFF = Affective Problems, SOM = Somatic Problems. * = significant difference between high and low class at $p < 0.05$, ** = significant difference between high and low class at $p < 0.01$, # = significant difference between high and moderate class at $p < 0.05$.

DISCUSSION

The aim of the current study was to investigate whether children with different ASD symptom profiles differed concerning co-occurring internalizing and externalizing problems. Three classes of children were distinguished within our sample: one class with high levels of symptoms in all three ASD symptom domains, a second class with moderate levels of symptoms in all three ASD symptom domains, and a third class with low levels of symptoms in all three ASD symptom domains. Thus, latent profile analyses revealed mainly level differences across all three of the ADOS domains and we did not find a class of children scoring high on one domain and much lower on the other two domains. Interestingly, children with low and moderate levels of ASD symptoms showed significantly higher levels of co-occurring internalizing and externalizing problems than children with high levels of ASD symptoms. In other words, when considering internalizing and externalizing problems, children with moderate ASD symptoms (mainly PDD-NOS cases) were more similar to children with fewer ASD symptoms (mainly children with internalizing and externalizing disorders) than to children with severe ASD symptoms (AD, Asperger Syndrome or severe PDD-NOS), as indicated with an # in Figure 2. Differences were particularly found regarding anxiety and conduct problems, thus children with moderate ASD especially showed problems in regulating their emotions and behavior. An inverse relationship between severity of autistic symptoms and co-occurring psychiatric symptoms has also been found by other authors who compared children with DSM-IV-TR defined AD with those with Asperger Syndrome (Gadow et al., 2005) or AD versus PDD-NOS (Pearson et al., 2006). Our findings extend these earlier findings by using an empirical, more dimensionally oriented approach based on standardized assessments to classify children according to the severity and patterning of their ASD symptoms and relating this to the severity of a broad range of psychiatric problems.

Our findings have important clinical implications stressing that, clinically referred children with moderate ASD symptoms ('mild, high functioning ASD') often have many other behavioral and emotional problems, like anxiety and conduct problems, which warrant clinical attention and specifically aimed treatment. Therefore, to obtain a comprehensive picture of the functioning of children with ASD problems, it is not only important to describe or to plot the core ASD symptoms as stressed by Ronald and colleagues (2005), it is equally important to assess a broad range of behavioral and emotional problems, in addition to cognitive and adaptive functioning.

Strengths and limitations

In this study, we used a sample of clinically referred children who showed considerable variation in the amount of ASD symptoms, as assessed with a gold standard instrument, the ADOS. The relatively large sample enabled us to perform LPA without being limited by sample size. Unfortunately, no Autism Diagnostic Interview-Revised (ADI-R) data were available. Also, our sample mainly consisted of children with PDD-NOS with a normal to high IQ. Therefore, the constitution of our sample is not representative of all ASD cases, thus conclusions are confined to higher functioning children at the milder end of the autism spectrum.

CONCLUSIONS AND FUTURE RESEARCH

Taken together, children with low and moderate ASD symptoms show higher levels of co-occurring internalizing and externalizing problems as compared to cases with more severe ASD symptoms. Thus, charting internalizing and externalizing problems in children at the milder end of the autism spectrum is valuable both for a complete diagnostic picture as well as for deciding on specifically aimed treatment.

The behavioral phenotype of ASD should be further investigated, also examining other behavioral, neuropsychological, and biological characteristics. Longitudinal studies are needed to reveal the developmental trajectories of the different manifestations of ASD from childhood into adolescence and adulthood. Research should be performed on precise symptomatology and need for care of children at the lower end of the autism spectrum.

Chapter 3

The association of quality of social relations, symptom severity and intelligence with anxiety in children with Autism Spectrum Disorders

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ABSTRACT

Limited quality of social relations, milder symptom severity, and higher intelligence were shown to account for higher anxiety levels in autism spectrum disorders (ASD). The current study replicated and extended earlier findings by combining these three determinants of anxiety in ASD in one study. The sample consisted of 134 school aged children with ASD, of whom 58 (43%) had a comorbid anxiety disorder according to the Diagnostic Interview Schedule for Children-Parent version (DISC-P). In this sample we tested associations between these determinants and anxiety univariately and multivariately to clarify the unique contribution of all determinants. Since we hypothesized that the association between limited quality of social relations and anxiety would be amplified by low symptom severity and/or high intelligence, we additionally tested for moderating effects. We found that higher anxiety levels were associated with a lower quality of social relations and lower symptom severity. In this mainly high-functioning sample, intelligence was not related to anxiety levels. No moderation effects were found. Since lower quality of social relations and lower symptom severity are associated with higher anxiety levels in children with ASD, therapeutic interventions aimed at reducing anxiety in ASD should pay attention to improving social relations, and presumably children with a lower symptom severity could benefit most from such interventions.

KEYWORDS

ASD, anxiety, social relations, symptom severity, intelligence.

INTRODUCTION

Recently, scientific interest for anxiety in Autism Spectrum Disorder (ASD) and interest in interventions, aiming at diminishing anxiety for these children, has increased enormously, as witnessed by the amount of publications on this topic in the last few years (e.g. Sukhodolsky, Scahill, Gadow et al., 2008; White, Oswald, Ollendick et al., 2009a; Mazurek & Kanne, 2010; Van Steensel, Bogels, Perrin, 2011). Anxiety is a very common phenomenon among children and adolescents with ASD, percentages of comorbidity rates varying from 42 to 55% (Simonoff, Pickles, Charman et al., 2008; De Bruin, Ferdinand, Meester et al., 2007b). When using cut-offs on dimensional symptom scales, the prevalence rates for elevated anxiety problems in ASD varied from 11% to 84%, depending on the cut-off levels chosen (for an overview, please see White et al., 2009a). Co-occurring anxiety has a large impact on the everyday functioning of individuals with ASD. Anxiety related concerns are among the most common presenting problems for school-age children and adolescents with ASD in clinical settings (Ghaziuddin, 2002). Anxiety can be debilitating, and is often associated with isolation (Tantam, 2000). When ASD and anxiety co-occur, the symptoms of both conditions may negatively influence each other (Van Steensel et al., 2011).

The core features of ASD may not be amenable for treatment (Billstedt, Gillberg, Gillberg, 2007), thus treating co-occurring anxiety problems may be a fruitful approach to the improvement of everyday functioning of children with ASD (De Bildt, Blijd-Hoogewys, Dijkstra et al, 2007). In fact, treatment studies revealed that anxiety in ASD can be decreased (Chalfant, Rapee, Caroll, 2007). Developing effective treatments might be facilitated by the identification of relevant determinants. This study therefore investigated several factors that have been shown to be related to anxiety in ASD in recent previous research, namely the quality of social relations, ASD symptom severity and intelligence (e.g.: Mazurek & Kanne, 2010; Snow & Lecavalier, 2011; Sukhodolsky et al., 2008). Since quality of social relations might be a suitable candidate for therapeutical interventions, the focus is on this factor, and moderating influences of the other two factors will be explored. The goal of the current study was to replicate and extend earlier findings by combining these three determinants of anxiety in ASD in one study and establishing the relative contribution of each of these factors. In doing so, we aimed to furnish an empirical starting point for further development of targeted interventions.

Quality of social relations and anxiety

Anxiety levels were shown to be higher in children with ASD who were less likely to initiate contact with peers (White & Roberson-Nay, 2009 b). Also, levels of anxiety were higher among children with ASD who had one or more friends, but whose

friendships were limited in terms of responsiveness or reciprocity (Mazurek & Kanne, 2010). It was concluded that children with ASD, who are able to engage in friendships, but who have difficulties in maintaining them or whose friendships are limited in quality, might be more aware of their social deficits, and thus feel more anxious (Mazurek & Kanne, 2010).

ASD symptom severity and anxiety

An inverse association between severity of core ASD symptoms and co-occurring anxiety has been suggested in several studies. In studies where the categories of autistic disorder and PDD-NOS were compared with regard to anxiety, anxiety was more prevalent in PDD-NOS (e.g. Szatmari, Bartolucci, Bremner et al., 1989; Gadow, Devincent, Pomeroy et al., 2005; Pearson, Loveland, Lachar et al., 2006; Mazurek & Kanne, 2010; Snow & Lecavalier, 2011). Moreover, Pearson and colleagues (2006) found that 38 % of the children with autism showed clinically significant anxiety levels, whereas 52 % of the children with PDD-NOS showed these levels of anxiety. Several explanations for this inverse relationship between symptom severity and anxiety have been brought forward. ASD children with milder impairments might be placed in more challenging social situations because of their perceived higher social abilities which could have an increased level of anxiety as a result (Pearson et al., 2006). A second explanation is that the awareness of ones own social deficits and the confrontation with social failure may contribute to anxiety in children with high functioning forms of ASD (Bellini, 2004; Chamberlain, Kasari, Rotheram-Fuller, 2007). This mechanism has more provocatively been called "ignorant bliss" or "happy obliviousness" (Chamberlain et al., 2007). In severe cases of ASD poor emotional understanding and worse perspective-taking skills may act as a buffer against developing anxiety symptoms (Mazurek & Kanne, 2010).

Intelligence and anxiety

In several studies, a higher intelligence quotient (IQ) in children with ASD was associated with more severe anxiety (Gadow, et al., 2005; Weisbroth, Gadow, Devincent et al., 2005; Witwer & Lecavalier, 2010; Sukhodolsky et al., 2008), whereas other studies found that lower mean IQ's were associated with higher rates of anxiety (White & Roberson-Nay, 2009b). Differences in the IQ distribution of the samples, assessment tools used, methods of operationalisation of anxiety disorder and intellectual (dis)ability probably account for these seemingly contradicting findings. For instance, the study of White et al. (2009b) used a self-report measure for anxiety in a relatively small sample, whereas most of the other studies used parent report measures. Sukhodolsky et al. (2008), in a sample with a high percentage of intellectually disabled children, found that children with ASD and IQ scores higher than

70 showed significantly more anxiety than children with ASD and IQ scores below 70. A recent meta-analysis found that the relation between anxiety and IQ might in fact not be linear, but rather quadratic, with especially children in the IQ range between 70 (2 SD's below average) and 87 (1 SD below average and the mean level across all the studies in the meta-analysis) being most anxious (Van Steensel et al., 2011). Furthermore, a body of literature indicates, that intelligence is related to ASD symptom severity (e.g: Stevens, Fein, Dunn et al., 2000; Witwer & Lecavalier, 2008; Eagle, Romanczyk, Lenzensweger, 2010; Bradley, Ames, Bolton, 2011).

All in all, the relationship between IQ and anxiety in ASD has not been settled definitively.

The current study

As described above, anxiety may be more outspoken in children with ASD with limited and non-reciprocal social relations, anxiety seems to be inversely related to ASD symptom severity, and may be more prominent in the more intelligent children with ASD. Previous studies usually focused mainly on one or two of these factors, but did not combine them in one model, accounting for their complex mutual associations. Therefore, the aim of the present study was to investigate the mutual role of these three important determinants of anxiety in children with ASD. We combined these three factors into one multivariate model to investigate which of these factors contributed most to the manifestation of anxiety in children with ASD. Furthermore, we tested whether ASD symptom severity or intelligence moderated the relation between quality of social relations and anxiety in children with ASD. Based on the existing literature, we hypothesized that higher levels of anxiety are associated with a lower quality of social relations, lower symptom severity and to a higher intelligence level. Regarding moderating effects, we hypothesized that low ASD severity and /or high intelligence moderate(s) the influence of quality of social relations on anxiety. In other words, children with relatively mild ASD symptoms and/or cognitively high functioning children with ASD would be more vulnerable to low quality of social relations, which would in turn increase their anxiety levels.

METHODS

Participants and procedure

The current sample consisted of 134 children with a DSM-IV-TR classification of ASD, aged 6 to 13 years, who were referred to the outpatient department of Child and Adolescent Psychiatry of the Erasmus Medical Center in Rotterdam, the Netherlands in the period between July 2002 and September 2004. This center is specialized in

diagnosing children with suspected ASD, presenting with milder or atypical symptoms, and with average to high intelligence.

Diagnostic evaluation took place by a multi-disciplinary team through elaborate assessment of early development, interviews carried out with parents or caretakers, psychiatric observation of the child in a one-to-one situation, psychological assessment, information about medical history and school, which resulted in a clinical consensus diagnosis according to DSM-IV-TR research criteria (APA, 2000). Clinicians were blind to the ADOS classification, but otherwise they had access to all past and present information about the child. The participating 134 children received a DSM-IV-TR diagnosis within the autism spectrum (n=15 Autistic Disorder, n=10 Asperger Syndrome, n=109 PDD-NOS). Module 3 of the Autism Diagnostic Observation Schedule (Lord, Rutter, DiLavore et al., 1999) was administered by independent raters. Only 5 children were assessed using ADOS module 2, whereas 134 children were assessed using ADOS module 3. For the sake of homogeneity and comparability within the dataset, we decided to only include the children with ADOS module 3 data. All participants received an ADOS and in 61.2% (n=82) of the cases the clinical diagnosis was confirmed with an ADOS classification within the autism spectrum. According to the Diagnostic Interview Schedule for Children, parent version (DISC-IV-P, Shaffer, Fisher, Lucas et al., 2000) 43% (n=58) of the current sample fulfilled full criteria for an anxiety disorder (for more detailed information on the sample and diagnostic procedures, please see De Bruin, et al., 2007b). The Wechsler's Intelligence Scale for Children-Revised (WISC-R: Van Haasen, 1986; Wechsler, 1974) was available for all the children in the sample (Mean score= 91.4; SD= 17.4; Range: 48 – 124).

Measures

Anxiety levels

To obtain a continuous measure of anxiety levels, the Child Behaviour Checklist 4/18 (CBCL, Achenbach, 1991) was completed by the mother. The CBCL covers 118 problem items that are scored on a three-point scale (0=not true, 1=somewhat or sometimes true, 2=very true or often true). The DSM-oriented scale 'Anxiety Problems' (Achenbach & Rescorla, 2001) was used as dependant variable. The DSM oriented anxiety scale consists of six items (dependant, worries about future or family, (specific) fears, fears for school, nervousness, general fearfulness). Mean weighted scores per item were computed by adding the item scores (0, 1, or 2) of all items belonging to the Anxiety Problems scale and subsequently these sum scores were divided by six, yielding scores ranging between 0 and 2. Krol and colleagues (2006) showed good predictability of CBCL scale scores to DSM-IV diagnosis in a Dutch clinical sample. The psychometric quality of both the original instrument and the

Dutch translation has been well established (Achenbach, 1991; Verhulst, van der Ende, Koot, 1996).

In the current sample, the correlation between the DSM oriented Anxiety Problems scale and the original factor generated CBCL anxious-depressed scale was high ($r=0.74$, $p<0.01$), and the correlation of the DSM oriented Anxiety Problems scale and the DISC-P classification was moderate (Spearman's rho= 0.41, $p<0.01$).

Quality of social relations.

The 'social relationships' subscale of the Children's Communication Checklist (CCC; Bishop, 1998) was used to obtain an overall measure of quality and number of social relations. The CCC is a parent based 70 item scale. Each item describes an aspect of the child's behavior and it can be scored as 0 =does not apply, 1= applies somewhat, 2= definitely applies or 9=unable to judge. The scale contains nine subscales: five subscales for pragmatic use of language, two scales assess formal language and the remaining two scales pertain on non- language domains, namely unusual and restricted interests and social relationships. For the purpose of this study only the social relationships subscale was used. This subscale consists of 10 items, which describe either positive aspects of social relationships (for instance: is popular with other children, has one or two good friends) or negative aspects of social relationships (for instance: tends to be teased or bullied, is deliberately aggressive to other children, is perceived as odd by other children). Positive aspects of social relations like social support or having friends are scored positive in the social relations subscale of the CCC and negative aspects of social relations, like bullying and peer rejection are scored negative; so the sum score on this subscale is a composite score of positive social influences, negative social influences, social support and social isolation. High scores represent a higher number and quality of social relations. The reliability of this scale has shown to be good (Bishop, 1998).

ASD symptom severity.

The ADOS module 3 (Lord et al., 1999) was used to assess ASD symptom severity in all participants. The observation of the children was performed by trained and certified clinicians who were blind for the clinical diagnosis. The ADOS items are scored on a 3-point scale from 0 (no evidence of abnormality related to autism) to 2 (definite evidence of abnormality). Some items include a code of 3 to indicate particularly severe abnormalities. In the ADOS scoring algorithm, these scores of 3 are converted to 2. The ADOS is considered the "gold standard" diagnostic tool and provides a standardized context for an elaborate observation and scoring of ASD symptoms in the domains of Language and Communication, Reciprocal Social Impairments, and Stereotyped behaviours and Restricted Interests. Lord and col-

leagues (1999) showed that the psychometric properties of the ADOS are good with an excellent internal consistency. ADOS calibrated severity scores (Gotham, Pickles, Lord, 2009) were used as an index for ASD symptom severity. These scores can range from 1 to 10. To post-hoc explore the associations with the separate ADOS domains of Language and Communication, Reciprocal Social Impairments, and Stereotyped behaviours and Restricted Interests, mean weighted scale scores were computed by adding the item scores (0, 1, or 2) of all items belonging to the domain, and subsequently dividing these scores by the total number of items completed within that domain; thus yielding scores ranging between 0 and 2 (Volkmar, State, Klin, 2009). In the current sample, when considering the clinical diagnosis according to DSM-IV-TR as the reference standard, the ADOS reached a specificity of 100 % and a sensitivity of 61.2 %. This sensitivity of around 60% is similar to the values found by other authors when investigating module 3 in samples with relatively many PDD NOS patients (Gotham, Risi, Dawson et al., 2008).

Intelligence.

To assess the general intelligence quotient (IQ), the Dutch version of the Wechsler Intelligence Scale for Children-Revised (WISC-R) was administered (WISC-R Projectgroep, 1986; Wechsler, 1974). The WISC-R is composed of several verbal and performance subtests: Information, Similarities, Arithmetic, Vocabulary, Comprehension, Digit Span, Picture Completion, Picture Arrangement, Block Design, Object Assembly, Coding and Mazes. Like the original version, the Dutch version has good reliability and validity (WISC-R Projectgroep, 1986). The newer version, WISC-III (or even WISC-IV) was not administered since at the time of study issues with respect to translation and psychometric properties of the Dutch version were not fully solved yet. We used Full Scale IQ to get an overall picture of global cognitive functioning.

Statistical analyses.

For descriptive purposes, means and standard deviations were computed for anxiety, quality of social relations, ASD symptom severity, IQ and age. In addition, the gender ratio was calculated. Bivariate correlations (2-tailed; Spearman's correlations in case of categorical measures, and Pearson's correlations in case of continuous measures) were computed between anxiety, quality of social relations, symptom severity, IQ, age and gender. Since the relation between IQ and anxiety levels might be quadratic instead of linear (Van Steensel et al., 2011), we also tested whether anxiety levels differed between children with an IQ below 70, between 70 and 87, or above 87.

To test how quality of social relations, symptom severity and IQ together explained anxiety levels in children with ASD, we used multiple linear regression analysis with

level of anxiety as the dependent variable and quality of social relations and symptom severity as independent variables. Since the preliminary bivariate correlations showed that IQ, age and gender were not significantly related to the dependent and independent variables, these factors were no longer regarded in this multiple linear regression model.

We tested for moderating effects of symptom severity on the association between quality of social relations and anxiety by in a final step adding the interaction term of social relations X symptom severity to the regression model. A similar analysis was performed to investigate the moderating effect of IQ.

Post-hoc analyses were performed to gain further insight in the specific relations with the separate symptom domains of ASD.

RESULTS

Descriptives and correlations

Descriptive information on the sample and correlations are depicted in Table 1.

A small, but significant negative association was found between social relations and anxiety levels ($r = -0.21$, $p = 0.02$), indicating that worse social relations go along with more anxiety. Also, a medium significant negative correlation between symptom severity and anxiety levels ($r = -0.30$, $p<0.01$) was found, indicating that anxiety

Table 1. Descriptives and correlations of anxiety, quality of social relations, symptom severity, IQ, age and gender

	Mean	SD	Anxiety level	Social relations	Symptom severity	IQ	Age	Gender
1. Anxiety level	0.84	0.47						
2. Social relations	25.98	3.73	-0.21 p=0.02					
3. Symptom severity	4.64	2.62	-0.30 p<0.01	0.02 p=0.87				
4. IQ	91.84	17.44	0.14 p=0.12	-0.07 p=0.44	-0.14 p=0.13			
5. Age	9.22	0.46	0.14 p=0.14	-0.05 p=0.61	-0.23 p<0.01	0.09 p=0.29		
6. Gender	88% males		-0.30 p=0.74	-0.11 p=0.21	-0.13 p=0.13	-0.78 p=0.38	-0.09 p=0.32	

Note:
Anxiety level: Weighted score per item (range 0-2) on CBCL syndrome scale for anxiety;
Social relations: Total score on social relations subscale of the CCC;
Symptom severity: ADOS calibrated severity scores (range 1-10)

levels are higher when symptom severity is low. No significant relation was found between IQ and anxiety levels (p>.05). When a quadratic relation was explored, a somewhat higher mean level of anxiety was found in the group with an IQ ranging from 70-87 (0.92) than in the group with an IQ lower than 70 (0.72) or the group with an IQ above 87 (0.83), but this group difference also did not reach significance (F=0.97, df=2, p=0.38). Because of this non-significant association between IQ and anxiety levels, IQ was no longer considered in the subsequent multivariate analysis. Moreover, since age was only significantly correlated with symptom severity (r=-0.23; p<0.01), age and gender were also not considered as covariates in the subsequent multiple linear regression.

Multiple linear regression analyses

As shown in Table 2, in the multiple linear regression model, the independent variables quality of social relations (p=0.02, ΔR^2=4.6 %) and symptom severity (p<0.01, ΔR^2=9.4 %) contributed significantly to the variation in anxiety levels.

Moderating effects

Table 2.
Results of the multiple linear regression analyses with anxiety levels as the dependent variable

	Unstandardized B	95% CI	t value	P	ΔR^2
Quality of Social relations	-0.026	-0.047 — -0.005	-2.40	0.02	4.6 %
Symptom severity	-0.055	-0.086 — -0.023	-3.46	<0.01	9.4 %

Note: ΔR^2 = percentage explained variance for this particular variable.

No significant moderation effect of ASD symptom severity on the association between quality of social relations and anxiety levels was found (B=-0.002 [CI:-0.010-0.006], t=-0.468, p=0.64, ΔR^2=0.2%). Moreover, no significant moderation effect of IQ on the association between quality of social relations and anxiety levels was found (B= 0.002 [CI:0.00-0.004], t=1.850, p=0.07, ΔR^2=2.7%).

DISCUSSION

This study investigated the relationship between quality of social relations, symptom severity and IQ with anxiety levels in children with ASD. The first hypothesis, that a better quality of social relations would be associated with less anxiety, was supported by the current results. This is in line with earlier findings in non-ASD

samples, that signs of poor social relations, like being bullied or other forms of negative peer interactions, were associated with more anxiety (La Greca & Lopez, 1998; Ginsburg, La Greca, Silverman, 1998). Furthermore, our findings parallel the already mentioned findings of White et al. (2009b), indicating that more anxiety was found in ASD patients who tend to initiate less social contact.

The second hypothesis, that low ASD symptom severity would be related to higher anxiety levels, was also supported by the current results. This finding replicates findings of others (i.e. Szatmari et al., 1989; Gadow et al., 2005; Pearson et al., 2006; Mazurek & Kanne, 2010), and extends these previous findings by showing that global ASD symptom severity in a multivariate model has the strongest impact on anxiety in ASD as compared to other factors such as quality of social relations and IQ. In fact ASD symptom severity has a medium effect size, whereas quality of social relations has a small effect size. In addition, we found that the explained variance of ASD symptom severity on anxiety was 9.4% which indicates that besides the determinants we currently investigated, many other genetic, biological and psychological factors probably also play a role in the emergence of anxiety in ASD. Associations between anxiety levels and ASD symptom severity might be different when specific symptoms or symptom domains are considered (e.g. Hallet, Ronald, Rijsdijk et al., 2010). We explored this idea in a post-hoc analysis and found that the scores on each of the three core ASD symptom domains of the ADOS showed a significant negative association with anxiety levels. Thus, the relation we found between 'global' ASD symptom severity and anxiety scores is not restricted to one or two domains, but holds true for all three domains as assessed with the ADOS.

The third hypothesis, that higher IQ would be related to more anxiety, was not supported by the current results. This is in contrast to the findings of Sukhodolski et al. (2008), which is probably due to differences in sample characteristics. In the study of Sukhodolsky et al. (2008), only 13% of the study population had an IQ in the normal range (above 85), the mean IQ was far below 70 and their sample consisted mainly of children with autistic disorder (88%). In contrast, our sample consisted mainly of children with an IQ within the normal range (mean IQ=91.8; range= 48-128; 69% FSIQ above 85) and 74% of the sample had a diagnosis of PDD-NOS. Our findings indicate that within the normal IQ range (roughly one standard deviation below and above average) and in children with less severe autistic symptoms, IQ level does not explain differences regarding anxiety. Also when a quadratic relation was explored, with individuals in the IQ range between 70 and 87 having highest anxiety levels (Van Steensel et al 2011), the group difference did not reach statistical significance.

Our hypothesis regarding moderating effects of symptom severity and/or IQ on the association between quality of social relations and anxiety was refuted. Our data

did not demonstrate that children with low ASD severity and/or high intelligence were more vulnerable to worse quality of social relations and thus to increased levels of anxiety.

The fact that more anxiety was present in individuals with mild ASD symptom severity seems to support the idea that being aware of one's own functioning leads to more anxiety in children with ASD. Also awareness of one's own social deficits and the legacy of social failure may amplify anxiety in children with high functioning forms of ASD, as suggested in earlier studies (Bellini, 2004; Chamberlain et al., 2007). 'Awareness' might be indexed by ASD symptom severity or intelligence, however, in the current study, we did not find a relation between higher intelligence and anxiety and no moderating effects on ASD symptom severity and IQ on the relation between quality of social relations was found. The concept 'awareness' is however complex. It seems straightforward that children with ASD have impairments in awareness (i.e Hobson, Chidambi, Lee et al., 2006; Iacoboni, 2006; Mazurek & Kanne, 2010) yet, when taking a closer look, the concept of 'awareness' is hard to operationalize, as it holds several aspects, such as emotional components (i.e. self-awareness), cognitive components (i.e. intellectual ability) and social components (i.e. insight in others, social situation, "theory of mind"). Recently, Rieffe, Oosterveld, Terwogt et al. (2011) used a more sophisticated measure of certain aspects of emotion awareness and found that the ability to differentiate between emotions was related to the tendency to internalizing symptoms, such as worry and rumination. Using such in-depth measures of awareness will help to further clarify the relation between awareness and anxiety in children with ASD.

Strengths and limitations

In this study, we included a relatively large sample of clinically referred children who showed considerable variation in anxiety, quality of social relations, symptom severity and IQ. By using the social relations subscale of the CCC we were able to score the quality of social relations in a dimensional way. This social relations score takes into account number of friendships or parental support, and negative social experiences like peer rejection and being bullied. The total score thus represents an overall rating of the amount and quality of social relations. Studies into correlations between anxiety and IQ, friendships and symptom severity in ASD have been performed before, but this is the first time to our knowledge that these determinants are studied simultaneously and that interaction effects of these factors were examined.

We should however emphasize, that our participants were referred to a specialized university outpatient department for child and adolescent psychiatry. In order to be included in the study, the level of language and cognitive development had

to be sufficient to administer module 3 of the ADOS and the WISC-R, and the child had to be between 6 to 13 years old. As a consequence, our sample mainly includes school-aged children with ASD, whose intelligence lies within the normal range and whose verbal development is sufficient to interact with others. Therefore, the findings and conclusions should be confined to this particular subpopulation of children with ASD. Since this is a group of children often seen by many professionals who are faced with many complexities concerning diagnosis and therapy in this group, we feel the current findings are however relevant to a substantial group of professionals.

Furthermore, in the assessment of anxiety different tools can be used, all targeted to measure different aspects of anxiety. In our study the CBCL DSM oriented scale was used to assess anxiety levels. Advantages of using the CBCL to assess anxiety in an ASD population include the fact that it is a well-validated, broadly used, standardized measure and, more importantly, that it is a parent report questionnaire, therefore issues concerning the inherent difficulties of self-report in individuals with ASD (Kanne, Abbacchi, Constantino, 2009) could be avoided. Since the empirically derived internalizing scales of the CBCL contain items on withdrawn behaviour, thus creating an overlap with the symptoms of ASD, in this study the DSM-oriented anxiety scale was used, which focuses more specifically on anxiety. A disadvantage of the use of CBCL might be that it generates a general measure of anxiety, and it does not assess the various aspects of anxiety separately, as for instance social anxiety versus generalized anxiety versus phobic symptoms.

Clinical implications and future research

Since we found an inverse relation between anxiety and ASD symptom severity, anxiety problems are most prominent in milder cases of ASD with symptom levels just above the diagnostic threshold of the DSM-IV-TR. Therefore, it is important in these milder, atypical ASD cases, to explicitly diagnose the comorbid anxiety disorder in order to facilitate treatment that focuses not only on the social and communication impairments, but also on treating the co-occurring anxiety. In addition, we found that a better quality of social relations was related to less anxiety. Thus, social relations should be an important aspect in preventive or intervention programs aimed at reducing anxiety in children with ASD. As we did not find a significant relation between ASD symptom severity and quality of social relations ($r= -0.064$, $p=0.48$), nor did we find a moderation effect of ASD symptom severity on the relation between quality of social relations and anxiety, this means that ASD symptom severity and quality of social relations are largely independent. Also when post-hoc exploring relations between the separate ASD subdomains and CCC social relations, no significant associations between specific ASD symptoms and quality

of social relations were found ($r \leq 0.1$, $p > 0.25$). Thus, interventions can be directed at improving quality of social relations without intervening effects of ASD symptom severity, and influencing quality of social relations in a positive way may be a helpful approach for all children with ASD. In suggesting so, we are aware of the fact that our finding needs to be replicated and that the found explained variance of social relations on anxiety was modest. Still, it seems worthwhile to assess the balance between protective social factors, like supportive relations and aggravating social factors, like being bullied or teased in children with ASD. Based on this, parents, siblings, peers and teachers could be trained to enhance protective social factors and to counteract unfavourable social factors. Social relations with parents and sibs could be influenced by family based interventions and social relations at school could be improved by psycho-education for teachers and class programs against bullying, buddy projects, or social skills training.

Existing individual or group treatment programs against anxiety can be administered in a slightly adapted way in children with milder forms of ASD. Chalfant et al. (2007) showed that high functioning ASD children benefited from cognitive behavioural therapy against anxiety, which was adapted to the more concrete learning style of these children, focussing on exercises and practise instead of talking, and in which children were allowed to choose their helping thoughts from a list of possible alternatives. The effects of cognitive behaviour anxiety therapy in children with ASD are supported by a small, but growing body of evidence (Chalfant et al., 2007; Reaven, Blakeley-Smith, Nichols et al., 2009; Van Steensel et al., 2011).

We conclude that anxiety is a prevalent and severe problem in children with relatively milder ASD symptoms and in children facing adverse social relations. Longitudinal studies are needed to investigate whether low ASD symptom severity and low quality of social relations in children with ASD are predictive of anxiety or other psychopathology later in life. More research is needed to establish the efficacy of targeted interventions aimed at reducing anxiety in children with moderate levels of ASD symptoms.

Chapter 4

Formal Thought Disorder in Autism Spectrum Disorder predicts future symptom-severity, but not psychosis prodrome.

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ABSTRACT

Objectives: Formal Thought Disorder (FTD) is a disruption in the flow of thought, which is inferred from disorganization of spoken language. FTD in Autism Spectrum Disorders (ASD) might be a precursor of psychotic disorders or a manifestation of ASD symptom severity. The current longitudinal study is a seven-year follow-up of 91 individuals aged 5-12 years with ASD. We tested 1) whether childhood FTD predicted prodromal symptoms of psychosis in adolescence, and 2) whether childhood FTD was associated with greater ASD symptom severity in adolescence.

Methods: ASD symptom severity was assessed in childhood (T1) and seven years later (T2), using the Autism Diagnostic Observation Schedule (ADOS). At T1, the Kiddie-Formal Thought Disorder rating Scale (KFTDS) was used to measure symptoms of FTD. At T2, the Prodromal Questionnaire (PQ) was used to assess prodromal symptoms of psychosis.

Results: FTD at T1 did not predict prodromal symptoms of psychosis at T2 in children with ASD. FTD symptoms at T1, namely illogical thinking, predicted ASD symptom severity at T2 and this effect remained significant after controlling for T1 ASD symptom severity.

Conclusions: In children with ASD, illogical thinking predicts severity of ASD symptoms in adolescence, but FTD does not predict prodromal symptoms of psychosis.

KEYWORDS

Autism spectrum disorder-longitudinal study-psychotic symptoms-thought disorder-psychopathology.

INTRODUCTION

Disordered speech is an important symptom of severe mental illnesses like schizophrenia and autism (Docherty, McCleery, Divilbiss, et al., 2013). Disordered speech in these conditions can reflect a linguistic impairment, a cognitive impairment, or an abnormal integration of these functions for communication as in formal thought disorder (FTD) (Docherty et al., 2013). FTD has been defined as a disruption in the organisation and flow of thoughts, which is inferred from the disorganization of spoken language (i.e. as assessed using the Kiddie-Formal Thought Disorder rating Scale (KFTDS) (Caplan, 1994; Bearden, Wu, Caplan, et al., 2011).

FTD has been viewed as an impaired ability to apply goal directed behaviour in the language domain (Ozonoff, Pennington, Solomon, 2006). It has been established that FTD is associated with a wide variety of neuropsychological dysfunctions, including dysfunctions in sustained attention, working memory and sequencing (Docherty et al., 2013; Docherty, 2012). This association explains why FTD has been found in severe mental illness and in Attention Deficit and Hyperactivity Disorder (ADHD), as well as in neurological diseases like epilepsy (Caplan, Guthrie, Komo, et al., 2002). Originally, based on Andreasen's scale (Andreasen, 1979) four types of FTD symptoms were discerned: illogical thinking, loose associations, poverty of content of speech and incoherence (Caplan, Guthrie, Fish, et al., 1989). Later, based on empirical studies, two of these types of FTD remained to be valid: loose associations and illogical thinking (Caplan, Guthrie, Tang, et al., 2000). Loose associations were rated when the child changed the topic of conversation to a new and unrelated topic without preparing the listener for this change. Illogical thinking was rated when the child used causal utterances in an inappropriate way, and presented the listener with unfounded and inappropriate reasoning in non-causal utterances or when the child contradicted him/herself.

FTD is regarded as a hallmark for childhood or adult onset schizophrenia (Caplan, 1994; Docherty, 2012; Andreasen, 1979; Caplan et al., 2000; Bleuler, 1950) and as a marker of abnormal neurodevelopment in schizophrenia, indicated by the fact that school-aged children with schizophrenia show persistent high levels of illogical thinking and loose associations, whereas in typically developing school-aged children there is a considerable decline of illogical thinking and loose associations (Caplan, 1994). FTD is also regarded as a manifestation of the genetic vulnerability to schizophrenia, which was underscored by the finding that subtle forms of FTD were present in first degree relatives of patients with schizophrenia (Docherty & Gottesman, 2000; Docherty, 2005).

However, FTD is not restricted to patients who might develop psychosis, but it is also a symptom of Autism Spectrum Disorders (ASD) (Solomon, Ozonoff, Carter, et

al., 2008). Some older studies showed that certain forms of FTD (i.e. neologisms, idiosyncratic language or lack of cohesion) were very common in ASD (Volden & Lord, 1991; Baltaxe & D'Angiola, 1992. Moreover, high levels of FTD, as assessed by KFTDS, have been found in ASD, and were related to language abnormalities (Solomon et al., 2008; Van der Gaag, Caplan, Van Engeland, et al., 2005). In one study, half of the ASD participants showed two or more illogical utterances, and 30% showed two or more loose associations (Solomon et al., 2008). It was found that the amount of loose associations correlated positively with total scores on the Autism Diagnostic Observation Schedule (ADOS) (Solomon et al., 2008).

The relationship between ASD and schizophrenia is complicated. Historically, some authors have considered autism and schizophrenia as two independent disorders (Kanner, 1943; Rutter, 1972; Volkmar & Cohen, 1991), whereas others have considered autism as an early precursor of schizophrenia (Bender, 1947). Nowadays, ASD is considered to be a developmental disorder without a relation to schizophrenia or other psychotic disorders, although this remains a point of debate.

There are clear differences between core autism and core schizophrenia and the rate of comorbidity is very low (King & Lord, 2011; Rapaport, Chavez, Greenstein, et al., 2009). However, within the broader defined autism spectrum some children go on to develop psychosis or broader defined schizophrenia spectrum disorder. For instance, longitudinal studies revealed that six to 29% of individuals diagnosed with ASD in childhood developed schizophrenia later in life (Wolff, 1991; Wolff & McGuire, 1995) and it was found that ASD was present before onset of the psychotic disorder in 25% of a cohort of children diagnosed with early onset schizophrenia (Sporn, Addington, Gogtay, et al., 2004). A distinct subgroup of children with ASD characterized by the presence of FTD and a high vulnerability to develop schizophrenia spectrum disorder has been suggested, referred to as Multiple Complex Developmental Disorder (MCDD). Follow-up of children, diagnosed with MCDD into adulthood demonstrated that 17% developed schizophrenia and 58% schizotypal personality disorder (Van der Gaag, Buitelaar, Van den Ban, et al., 1995; Van Engeland & Van der Gaag, 1994).

In the last decade, there has been an impressive increase of research into the developmental aspects of psychosis and more specifically research aimed at the definition of criteria to identify young people at immanent risk for developing psychosis. Yung and McGorry (2007) distinguished three groups, comprising children with "ultra high-risk" (UHR) for psychosis, namely 1) a vulnerability group, defined as having schizotypal personality disorder or a first-degree relative with psychotic disorder, accompanied by a significant deterioration in social functioning in the last year; 2) a group with attenuated psychotic symptoms (APS) and 3) a group with brief, limited intermittent psychotic symptoms. This UHR approach has resulted in

measures, including the Prodromal Questionnaire (PQ) (Loewy, Bearden, Johnson, et al., 2005), and the Composite Assessment of At Risk Mental States (CAARMS) (Yung, Yuen, McGorry, et al.,2005). The latter predicts the outbreak of psychosis with probabilities of 22% within one year and 36% within three years (Fusar-Poli, Bonoldi, Yung, et al., 2012). The incidence rate of first episode psychosis in the general population is about 0.09% per year (Yung, Phillips, Yuen, et al., 2003; Yung, Phillips, Yuen et al., 2004), and therefore it can be concluded that these UHR patients have a 405-fold risk of becoming psychotic within a year relative to an average boy or girl from the same age (Cannon, Cadenhead, Cornblatt, et al., 2008). Recently, it was shown that UHR patients, who converted to psychosis showed higher rates of FTD before the onset of psychosis than a group UHR patients, who did not convert to psychosis and this latter group showed higher rates of FTD than a group of typically developing controls (Bearden et al., 2011). Using the KFTDS (Caplan et al., 2002) as a measure for FTD, illogical thinking predicted conversion to psychosis in 70.5% of the cases, whereas the scale of prodromal symptoms predicted only 35% of the cases (Bearden et al., 2011). In other words: FTD may be an early and reliable predictor for later psychosis in UHR patients.

The presence of FTD both in ASD and in individuals, who will develop schizophrenia and the fact that some ASD patients develop psychotic disorders, raises the question, whether FTD symptoms in ASD are a sign of impending psychosis or a manifestation of language and thought problems inherent to ASD. Summarizing, FTD can be a precursor of psychosis, a symptom of ASD and might be predictive of the development of psychosis in adolescence in children with ASD.

Aims of the study

The current study is a seven-year follow-up of 91 individuals, aged 6-12 years old, diagnosed with ASD at T1, with the aims to determine whether: 1) childhood FTD predicted prodromal symptoms of psychosis in adolescence, and 2) childhood FTD was associated with ASD symptom severity in adolescence. Moreover, the effects of age, IQ, and comorbid psychopathology were explored.

METHOD

Participants and Procedure

At the first assessment (T1) participants visited the outpatient's department of Child and Adolescent Psychiatry of Erasmus University Medical Center Rotterdam in the Netherlands. The inclusion criteria were (a) a clinical DSM-IV-TR (APA, 2000) classification of ASD, and (b) parents were able to communicate in the Dutch lan-

guage. Exclusion criterion was (a) the presence of severe neurological or physical problems (e.g. blindness) (De Bruin, De Nijs, Verheij, et al., 2007a). A total of 142 children received a DSM-IV-TR (APA, 2000) clinical diagnosis of ASD, obtained by a multi-disciplinary team based on elaborate assessment of early development, semi-structured interviews and parental questionnaires, psychiatric observation of the child in a one-to-one situation, psychological assessment, medical history, and school information (De Bruin et al., 2007a). Seventeen individuals (12%) met DSM-IV-TR criteria for Autistic Disorder, 11/142 (7.7%) met criteria for Asperger Syndrome, and 114/142 (80.3%) received a diagnosis of Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS); n=142; mean age= 8.9 years, SD= 1.81 years; Boys: 88.1%; mean IQ= 91.2, S.D= 18. How these DSM-IV-TR PDD classifications relate to the DSM 5 classification of ASD still needs to be further clarified (e.g. Mandy, Charman, Skuse, 2012; Skuse, 2012). To connect to the DSM 5 recommendations as closely as possible, we combined all PDD sub classifications into one category of ASD.

Comorbid diagnoses were assessed, using the Diagnostic Interview Schedule for Children (DISC) (Shaffer, Fisher, Lucas, et al., 2000). The most common comorbid disorders were anxiety disorders (n=40; 44%); ADHD (n=30; 33%); Oppositional Defiant Disorder (ODD) (n=20; 22%) and Mood Disorder (n=8; 8.8%).

All participants with a clinical diagnosis of ASD at T1 (n=142) were eligible for the follow-up study (T2). Participants were then 12-19 years old. The average time to follow-up was 7.17 years. For these children KFTDS and ADOS data on T1 were available. To assess prodromal symptoms of psychosis at T2, the PQ was completed by the participants and when they scored above the cut-off score (>=18), a complete CAARMS was performed. The ADOS was administered again to assess ASD symptoms at T2. In total 114 children agreed to participate in the follow-up study (response rate= 80.3%) and 91 children had complete data at T2 (64.1%).

Ethical aspects

At T1, parents/caretakers of the participating children signed informed consent forms prior to participation in the study. At Time 2 both parents and adolescents signed the informed consent forms. The Medical Ethics Committee of the Erasmus Medical Centre approved this study.

Materials

Formal thought disorder at T1

The KFTDS is considered as a reliable measure of FTD in children aged 7-18 years (Caplan et al., 1989; Caplan et al., 2000). The validity of the KFTDS has been estab-

lished in children with ASD (13), with schizophrenia spectrum disorders (Caplan, 1994; Caplan et al., 2000) and in children with ADHD (Caplan, Guthrie, Tang, et al., 2001). Loose associations and illogical thinking have the highest clinical significance for childhood psychopathology, because they appear at high base rate in ASD and childhood-onset schizophrenia and at a much lower base rate in controls (Ozonoff et al., 2006).

Children were presented two audio taped stories for which they were asked to answer questions in a standardized, structured way (i.e., "what did you like about this story?" or "do you think this a true story?"). Subsequently, the child was asked to make up his/her own story about one of four given topics (the incredible hulk, a witch, a disobedient child or an unhappy child). During this part of the test session, the investigator mainly made encouraging remarks, but could pose extra open ended questions (i.e. "can you tell more?") when for instance the child was only giving limited or very short verbal responses, or when the child was hesitating to carry on. This took approximately 20 to 30 minutes, during which the speech samples were videotaped. A blind rater established the number of FTD signs. A total raw score was derived by summing frequency counts for illogical thinking and loose associations. To correct for the variability of speech elicited in different children, raw scores were divided by the number of utterances per minute, which yielded the final corrected Loose Associations and Illogical Thinking scores. Signs of FTD were scored according to KFTDS guidelines (Caplan et al., 1989).

Caplan et al. (1989) determined clinical cut-off scores with optimal sensitivity and specificity. Scores above the cut-off point reflect a higher likelihood of pathology (Caplan et al., 1989). We used these dichotomized scores for the regression analyses, because the dimensional variables Loose Associations and Illogical Thinking were not normally distributed. Continuous KFTDS scores were dichotomized as falling above or below the cut-off point. These cut-off scores are not available for children younger than seven years, because below this age illogical thinking and loose associations appear at a much higher base rate and therefore these measures cannot be used to discriminate between normality and pathology (Caplan et al., 1989; Caplan et al., 2000). The inter-rater reliability was good: Caplan and colleagues (1989) reported a kappa of 0.77 for the total KFTDS score and in the present study the kappa for the total KFTDS score was 0.78. One of the authors (EdB) was trained in KFTDS ratings by R. Caplan.

Prodromal symptoms at T2:

The PQ (Loewy et al., 2005) is designed to assess the presence and the severity of prodromal symptoms of psychosis using self-report and it serves to identify young people, with a minimum (mental) age of twelve years, at UHR for psychosis in an

early stage. The PQ sums up 92 true or false statements about symptoms, which may manifest in the prodromal phase of psychosis. The PQ consists of a positive scale, measuring symptoms like ideas of reference, delusional ideas and perceptual illusions and a negative scale, measuring symptoms like decline in social functioning, passivity and withdrawn behaviour. A threshold of 18 on the PQ total score (positive and negative symptoms of psychosis) predicted UHR status with 90% sensitivity and 38% specificity (Loewy et al., 2005) and a threshold of 14 on the PQ positive score predicted UHR status with 71% sensitivity and 81% specificity (Loewy et al., 2005). These thresholds were used in this study to describe severity of UHR symptoms. The PQ was also used as an outcome measure at T2 and for that goal dimensional scores on the PQ positive scale were assessed. We used the PQ positive scale, because 12 out of the 17 questions that pertain to the PQ negative scale bear crucial similarities with symptoms of ASD, leading to overrating of presumed prodromal symptoms (and loss of specificity) when using the PQ total score or the PQ negative score in an ASD population. Because scores of the PQ were not normally distributed, we used a root transformation, which resulted in a normal distribution. Participants with incomplete PQ data (n=23; 21%) were excluded from these analyses.

When the PQ total score exceeded or equalled 18, the CAARMS (Yung et al., 2005) was administered. The CAARMS, which is validated for children from 14 years onwards, uses strictly defined quantitative criteria to distinguish between full threshold psychosis, attenuated psychosis and no UHR. In this study mean age of the participants, who completed the CAARMS was 15.8 years, S.D=1.8 years; range: 13.0 to 19.6 years. In the CAARMS psychotic symptoms are described under four main headings: unusual thoughts, non-bizarre ideas, perceptual disturbances and cognitive disorganisation.

ASD severity at T1 and T2:

The ADOS (Lord, Rutter, DiLavore et al., 1999) was administered at both time points. The ADOS provides a standardized context for an elaborate observation of ASD related behaviors in the domains of social interaction, communication, and stereotyped behaviors and restricted interests. Lord and colleagues (1999) showed that the psychometric properties of the ADOS are good with an excellent internal consistency. In the current study, at T1 ADOS module 3 was used and at T2 ADOS, module 4 was administered. The items are scored on a 3-point scale from 0 (no evidence of abnormality related to autism) to 2 (definite evidence of abnormality). We used the ADOS scores in a dimensional way as proposed by Volkmar and colleagues (2009). Mean weighted scores were computed by adding all item scores (0, 1, or 2), and subsequently dividing these scores by the total number of items; thus yielding scores ranging between 0 and 2. We did not use ADOS calibrated severity scores,

because at T2 module 4 of the ADOS was administered in a substantial number of cases and currently, there are no guidelines to translate module 4 scores into ADOS calibrated severity scores. The ADOS at T1 and at T2 were performed and scored by trained and certified clinicians and researchers, who were blind for the clinical diagnosis.

Putative covariates

Age, sex, IQ, co-occurring attention problems, anxious/depressed problems and the use of anti-psychotic medication were taken into account as possible confounding covariates. Age was taken into account as a covariate, because developmental aspects play a pivotal role in the manifestation of FTD and therefore FTD scores could correlate with age. Age was included as a possible confounder since prodromal symptoms of psychosis emerge in middle or late adolescence and therefore older adolescents are more often affected with prodromal symptoms of psychosis than younger adolescents (Klosterkotter, Hellmich, Steinmeyer, et al., 2001). Intelligence Quotient (IQ) was taken into account as possible covariate, because FTD might be more prominent in children with lower IQ's. At T1 IQ was measured with the Wechsler's Intelligence Scale for Children-Revised version (WISC-R, Van Haasen, De Bruyn, Pijl, et al., 1986) and at T2 with the Wechsler's Abbreviated Scale for Intelligence (WASI). Co-occurring attention problems and anxious/depressed problems were assessed with the Child Behavior Checklist (CBCL) (Achenbach, 1991). Attention Problems and the Anxious/ Depressed Problems subscales. This was done because comorbid attention problems (Gadow 2012) or internalizing problems could increase the chance of developing psychosis for a youngster with ASD. The CBCL / 6 -18 (Achenbach 1991), problem items are scored on a three-point scale (0=not true, 1=somewhat or sometimes true, 2=very true or often true), and were completed by the mother. The CBCL, Attention Problems subscale consists of ten items, the Anxious-Depressed scale consists of 13 items. The psychometric qualities of the CBCL have been well established (Achenbach, 1991; Verhulst & Van der Ende, 2013).

The DISC (Shaffer et al., 2000) was used to assess correlations between DISC- diagnoses of ADHD, ODD, Anxiety disorders, Depression and the outcome variables of ADOS total scores at T2 and the PQ positive scale.

To investigate whether use of medication between Time 1 and 2 influenced the development of prodromal symptoms in adolescence, an additional health care questionnaire was used (Amone-P'Olak, Ormel, Oldehinkel, et al., 2010). At T2 parents were asked if their adolescents had used medication in the past two weeks. Antipsychotics use was taken into account.

Statistical analyses

To check for the effects of attrition differences in age, sex, ASD subtype and mean IQ were calculated between the group at T1 (n=142) and at T2 (n=91) and between the group with complete data on the PQ (n=91) and the part of T2 group without PQ data (n=23).

For descriptive purposes, means, ranges and standard deviations were calculated at T1 and T2 for age, IQ, weighted ADOS total scores and PQ scores. KFTDS scores and CBCL, Attention Problems subscale scores were only assessed at T1 and PQ scores were only assessed at T2. To provide further descriptive information regarding psychotic symptoms at T2, frequencies of CAARMS scores were computed. For children participating on PQ and/or CAARMS complete age, intelligence range and mental age were calculated, because we used these measures in relatively young children.

To check which putative covariates needed to be included in the models, correlations were computed between each of these covariates (age; sex; IQ; CBCL: Attention Problems, Anxious/Depressed Problems; DISC sections: ADHD, Anxiety Disorders, Mood Disorders; use of antipsychotic medication) and the outcome variables (PQ and ADOS symptom severity). If one of these putative covariates showed a significant correlation with the predictor and with the outcome variable, we included this covariate in the subsequent multiple linear regression.

To investigate whether FTD during childhood predicted prodromal symptoms of psychosis during adolescence (Aim 1), multiple linear regression analyses were performed with the dichotomous KFTDS loose associations and illogical thinking scores as predictors and the PQ positive symptoms scale as the outcome variable.

To investigate whether FTD during childhood was associated with higher ASD symptom severity in adolescence (Aim 2), multiple linear regression analyses were performed with the dichotomous scores regarding loose associations and illogical thinking on the KFTDS as the predictors and the ADOS symptom severity score at T2 as the outcome.

RESULTS

Descriptives:

No statistically significant differences were found between participants at T1 and T2, regarding initial age, sex and ASD subtype. The mean IQ at T1 was 94.4 (S.D=16.9), range 56-128. Nine participants scored below 70 at T1. The mean IQ at T2 was 100.6 (S.D=17.0), range 58-135. Four participants scored below 70 at T2. Mean IQ of at T2

was higher than mean IQ of this group at T1 (mean IQ T1=94.4 (SD=16.9), mean IQ T2=100.6 (SD=17.0), mean difference=6.2; t=-5.69; df=73; p< .01).

An attrition analysis was performed, in which the participants who did not have complete PQ data at T2, were compared to the participants with complete PQ data at T2 on several features. The groups with and without complete PQ data at T2 did not differ significantly on age, sex, IQ, ADOS, or KFTDS scores (p>.05). On the KFTDS 55/91 (60.4%) of the sample scored above the diagnostic threshold for illogical thinking at T1 and 15/91 (16.5%) scored above the threshold for loose associations.

With regard to the PQ, in 32/91 (35.2%) of the subjects the total score equalled or exceeded 18 and subsequently the CAARMS was administered. In 22/91 (24.2%) of the subjects the PQ positive score scored equalled or exceeded 14 (all of the subjects with PQ positive scores above 14 scored also more than 18 on the PQ total

Table 1: Descriptive information of the total sample at T1 and at T2 (n=91)

	N=91	
	N/%	
Male	82 (90.1%)	
ASD subtype: AD	9 (9.9%)	
ASD subtype: AS	7 (7.7%)	
ASD subtype PDD-NOS	75 (82.4%)	
T1 KFTDS, Total score above threshold	63/91 (69%)	
T1 KFTDS, loose associations above threshold	15 (16.5%)	
T1 KFTDS, illogical thinking above threshold	55 (60.4%)	
T2 PQ, total score >=18	32/91 (35.2%)	
T2 PQ, positive score >=14	22/91 (24.2%)	
T2 Use of anti-psychotics	18 (19.8%)	
	Mean (SD)	Range
T1 Chronological age (years)	8.82 (1.84)	5.08-12.64
T2 Chronological age (years)	16.03 (1.97)	12.85-20.87
Total IQ T1	94.4(16.91)	56-128
Total IQ T2	100.58 (16.95)	58-135
ADOS T1 raw total scores	9.67 (5.04)	0-31
ADOS T2 weighted score per item	.73 (.39)	.14-1.93
PQ total score T2	20 (16.69)	1-75

Abbreviations: AD= autistic disorder; ADOS raw total scores = Autism Diagnostic Observation Schedule, total raw scores of the sum of social affect and restricted repetitive behaviour domain of module 3; ADOS, weighted score= total raw scores of the ADOS divided by the number of items on module 3 and module 4; AS= Asperger Syndrome; IQ = Intelligence quotient; KFTDS=Kiddie Formal Thought Disorder Scale; PDD-NOS=Pervasive Developmental Disorder not Otherwise Specified; PQ=Prodromal Questionnaire; SD = standard deviation.

scores). On the CAARMS two patients met the criteria for attenuated psychosis, high risk state, but none of these 32 patients with high PQ scores met the criteria for full threshold psychosis. These 32 patients however showed quite serious attenuated psychotic symptoms. Perceptual disturbances were present in 14 of these 32 subjects, unusual thought content in 13 subjects and non-bizarre ideas in 12 subjects. Eighteen participants (19.8%) used anti-psychotic medication at T2.

Correlations with putative covariates

The predictor variables illogical thinking and loose associations did not show significant bivariate correlations with any of the comorbid DISC classifications (Illogical Thinking with depression (ρ=.04; p=.76), with anxiety disorder (ρ=.06; p=.60), with DISC ADHD (ρ=.15; p=.22) and Loose Associations with depression (ρ=.13; p=.31), with anxiety disorder (ρ=.08; p=.53), with DISC ADHD (ρ=.23; p=.07)).

Only the use of anti-psychotic medication showed a significant correlation with the outcome variable PQ positive scale at T2 (r=.27; p<.01), whereas age (r=-.05 ; p=.69), sex (ρ=.15, p=.16), IQ (r=.05, p=.67), CBCL Attention Problems (r=.05; p=.67), CBCL anxious-depressed (r=.01; p=.90), DISC depression (ρ=.12; p=.28), DISC anxiety disorder (ρ=.02; p=.85), DISC ADHD (ρ=.09; p=.43) did not show a significant correlation with the PQ positive scale at T2. Use of anti-psychotic medication at T2 did not show a significant correlation with the predictor loose associations (r=.08; p=.52) or illogical thinking (r=.19, p=.11). Therefore, in the multiple linear regression analysis with the PQ positive scale at T2 as outcome measure and KFTDS illogical thinking and loose associations as predictors, the use of anti-psychotic medication was not taken into account as a covariate.

The putative covariates sex (ρ=<.01; p=.97), IQ (r=.17; p=.13), comorbid CBCL attention problems (r=-.07; p=.57), CBCL anxious-depressed (r=-.18; p=.11), DISC depression (ρ=-.09; p=.43), DISC anxiety disorder (ρ=.15; p=.16), DISC internalizing disorder (ρ=-.19; p=.07), DISC ADHD (ρ=.19; p=.08) did not show a significant correlation with the ADOS symptom severity score at T2, whereas age did (r=-.21; p=.03). Moreover age was negatively correlated with the dichotomous predictor illogical thinking (ρ= -.29; p=.01), and with loose associations (ρ =-.30; p=.01). Therefore, in the multiple regression analyses with the ADOS symptom severity score at T2 as the outcome variable, age was entered as a covariate.

Main effects: FTD as a predictor of prodromal symptoms

As shown in Table 2, KFTDS scores on illogical thinking (t=.48, p=.63) and loose associations (t=.67, p=.51) did not significantly predict scores on the PQ positive scale. Excluding the nine participants for whom the use of PQ was not validated due to a mental age at T2 lower than 12 years old, did not change the results. As found in the

total sample, illogical thinking (t=.06, p=.95) and loose associations (t=.53, p=.60) did not significantly predict scores on PQ positive scale in this subsample.

When taking the covariate, use of anti-psychotics into account this covariate did predict scores on PQ positive scale (t=2.54;p=.01; 95%CI: .03- .27).

Table 2: Multiple regression using scores on Prodromal Questionnaire (PQ) positive symptoms scale at T2 as outcome measure and illogical thinking/ loose associations as predictors. (N=69)

Variable	B	SE	t value	CI-L	CI-U	p	R2
Model						.66	.04
Illogical	.03	.06	.48	-.09	.15	.63	
Loose Ass.	.04	.07	.67	-.09	.18	.51	

Abbreviations: Regression coefficient (B), standard error (SE), t-test value (t), 95% Confidence interval lower bound (CI-L) and upper bound (CI-U), significance value (p), multiple correlation coefficient squared (R2).

Main effects: FTD as a predictor of ASD severity

As shown in Table 3, illogical thinking at T1 significantly predicted a higher total score on the ADOS symptom severity score at T2 seven years later (t=2.91; p<.01; 95% CI: .09 - .46). Other factors, in particular loose associations did not significantly predict ADOS symptom severity scores at T2.

Table 3: Multiple regression with total score on ADOS at T2 as outcome measure; illogical thinking and loose associations as predictors and age as a covariate. (N=67)

Variable	B	SE	t value	CI-L	CI-U	p	R2
Model						.02	.15
Illogical	.28	.10	2.91	.09	..46	<.01	.13
Loose Ass.	-.05	.11	-.47	-.27	.17	.64	
Age T1	-.02	.03	-.87	-.07	.03	.39	

Abbreviations: Regression coefficient (B), standard error (SE), t-test value (t), 95% Confidence interval, lower bound (CI-L) and upper bound (CI-U), significance value (p), multiple correlation coefficient squared (R2).

Illogical thinking correlated positively with ADOS total score at T1 (r=.27; p=.01) and with ADOS total score at T2 (r=.22; p=.03). Loose associations did not correlate significantly with ADOS total scores at T1 (r=.13; p=.19) or with ADOS total score at T2 (r=.06; p=.59). As expected ADOS T1 total scores correlated significantly with ADOS T2 total scores (r=.44; p<.01). ADOS T1 total scores were added to the multiple regression models in order to evaluate whether illogical thinking predicted ADOS T2 total scores independent of ADOS T1 total scores. It turned out that illogical

thinking predicted ADOS T2 total scores significantly (p=.<01) even if the ADOS T1 total scores (p<.01) were taken into account (table 4). Illogical thinking and ADOS T1 scores together accounted for 26% of the total variance in the ADOS T2 scores and illogical thinking accounted for 13% of the total variance. Cohen's f2 was .15, which represents a medium effect size.

Table 4: Multiple regression with total score on ADOS at T2 as outcome measure and ADOS score at T1 and illogical thinking as predictors. (N=73)

Variable	B	SE	t-value	CI-L	CI-U	P	R2
Model						<.01	.26
Illogical thinking	.26	.09	2.90	.08	.44	<.01	.13
ADOS T1	.02	.01	2.90	.01	.04	<.01	

Abbreviations: Regression coefficient (B), standard error (SE), t-test value (t), 95% Confidence interval, lower bound (CI-L) and upper bound (CI-U), significance value (p), multiple correlation coefficient squared (R2).

DISCUSSION

This study showed that illogical thinking and loose associations as forms of FTD in children with ASD did not predict prodromal symptoms of psychosis seven years later. The presence of illogical thinking predicted the severity of autistic symptoms seven years later, whereas loose associations did not. FTD in ASD may not be an early sign of psychosis, but it may rather be a manifestation of the social communication difficulties that are part of ASD.

These data provide evidence for the hypothesis that FTD, especially illogical thinking, in children with ASD predicts a higher future severity of ASD. The fact that illogical thinking had a significant influence on ADOS T2 severity scores, even when the ADOS scores on T1 were taken into account, underscores the importance of illogical thinking as a predictor for the future severity of ASD independent of the severity of ASD at baseline. For theoretical reasons, we also examined whether illogical thinking predicted ADOS T2 scores over and above IQ. Adding IQ at T1 to the model did not change the findings, indicating that illogical thinking predicted ADOS T2 scores over and above ADOS T1 and IQ. Thus, FTD seems to be a predictor of future ASD severity rather than a predictor of positive prodromal symptoms.

A note of caution needs to be made concerning our findings that illogical thinking and loose associations do not predict (prodromal state of) psychosis. From the fact that at T1 60.4% of this sample scored above the threshold for illogical thinking and 16.5% for loose associations, it can be concluded that FTD is very common in childhood ASD. However, the fact that FTD is so common among ASD subjects and later conversion to psychosis is so rare, has a negative impact on the predictive value of

FTD. Furthermore, FTD also does not seem to influence the chance of developing psychotic symptoms.

We chose not to study the predictive value of FTD on negative prodromal symptoms, because of the close resemblance between autistic symptoms and negative symptoms.

However, recent research has pointed out that negative symptoms and cognitive disorganization may both play an important role in the transition to psychosis (Demjaha, Valmaggia, Stahl et al., 2012). Moreover, it is assumed nowadays that autism and psychosis share common pathophysiological mechanisms (Sporn et al., 2004) and negative symptoms may well be the common ground for the two disorders.

The results and the design of the present study bear important similarities and also differences with the Bearden et al. study (2011). In their study FTD was assessed in clinically referred or UHR adolescents, who were followed-up for conversion to psychosis during a mean period of 14.8 months. In the present study FTD was assessed in ASD children, who were followed-up for seven years, using prodromal symptoms of psychosis as outcome measure. In the Bearden et al. (2011) study illogical thinking and lack of cohesion predicted transition to psychosis. In our ASD sample illogical thinking did not predict prodromal symptoms. In both studies loose associations did not predict prodromal symptoms or transition to psychosis. These different findings may be due to the inclusion of different age groups (adolescents versus children), to differences in initial diagnosis (UHR versus ASD) or to differences in the outcome measure (psychosis versus psychosis prodromal state). The percentage of adolescents on anti-psychotic medication was almost equal in both studies and in our sample this was an important covariate, whereas use of medication at baseline in their study did not differ between those who converted to psychosis and those who did not. The use of anti-psychotic medication may have masked symptoms of emerging psychosis. We found a significant positive association between use of anti-psychotics and scores on the PQ positive scale, indicating that subjects on medication showed significantly more positive symptoms of psychosis even after the administration of anti-psychotics. Whether use of anti-psychotics in this study has resulted in lower numbers of subjects with Attenuated Psychotic Symptoms (APS) or lower numbers with full threshold psychosis remains object of speculation and should be clarified in further research.

The factors age and comorbid attention problems or internalizing problems are relevant for the interpretation of our results. The average age at first episode psychosis is 19 years for men and 22 years for women; prodromal symptoms emerge about two years earlier (Amenteros & Davies, 2006). Therefore, the younger part of the adolescents in our T2 sample (ages between 12.8 and 16 years) may still be

too young to display prodromal symptoms of psychosis and they might develop prodromal symptoms in the next five years. However, in bivariate correlations we did not find a correlation between age and PQ scores.

Other authors (Gadow, 2012) found that FTD and attenuated psychotic experiences in samples of ASD children were associated with the presence of comorbid attention problems. However, we observed no relationship between attention problems at T1 and FTD at T1 and prodromal signs at T2, nor did we find a correlation between attention problems and illogical thinking or between attention problems and loose associations. Because a relation between anxiety and FTD has been demonstrated (Ozonoff et al., 2006), we examined the putative influence of comorbid anxiety and depression on our outcome measures, but we found no significant effect.

The choice to take prodromal symptoms of psychosis as an outcome measure raises three methodological issues. Firstly, when identifying individuals at risk for psychosis, the threshold should not be set too low in order not to compromise specificity and to avoid "false positives". Psychotic experiences are rather common in adolescents, with rates varying from 15-20% (Van Os, Hanssen, Bijl, et al., 2001; Poulton, Caspi, Moffitt, et al., 2000; Arango, 2011). The empirically based thresholds (Loewy et al., 2005) we used (PQ total >18 and PQ positive>14) are far beyond the level of having one psychotic like experience ever and therefore specificity is not compromised. In our analyses we used the PQ positive score in a dimensional way, thereby avoiding the problem of the proper cut-off.

The second issue concerns the specificity of prodromal symptoms with respect to impending psychosis or to put it simply: prodromal symptoms are not always followed by a psychotic episode. A recent meta-analysis revealed that the transition rate from UHR to psychosis is 22% over one year and 36% over three years (Fusar-Poli et al., 2012) and preliminary evidence suggests that the transition rate to psychosis is slightly lower in adolescents as compared to adults (Ziermans, Schothorst, Sprong, et al., 2011). In the present study, based on the CAARMS, a rather large proportion of adolescents with ASD had quite serious attenuated psychotic symptoms, but none of the participants had made the transition to full psychosis yet. This may be due to the relatively low age of the sample and to the possibility that these participants might be in an early prodromal stage.

The third methodological issue concerns the minimum age for using the PQ. At T2, nine of our participants had a mental age below 12 years (i.e. calculated as IQ divided by 100 multiplied by chronological age). We decided not to exclude them since re-analysing results with these subjects excluded did not change the findings.

The fact that illogical thinking in this study predicted severity of autistic symptoms at T2 seven years later with a medium effect size is in line with earlier findings. In a cross-sectional study Solomon and colleagues (2008) found medium effect size

relationships between illogical thinking and scores on the Social Communication Questionnaire (SCQ) and medium to large effect size relationships between loose associations and ADOS symptom severity scores. We found a negative correlation between age and illogical thinking or loose associations, which is in line with the findings of Van der Gaag and colleagues (2005), who concluded that FTD reflects immature verbal skills and processing. Furthermore, our conclusions are in line with the general conclusions of the Solomon and colleagues (2008) and the Van der Gaag and colleagues (2005) studies, indicating that FTD in ASD in not an early sign of psychosis, but rather a manifestation of pragmatic language abnormalities in ASD. The contribution of the present study is that these findings are replicated and extended using long term follow-up data.

Limitations of the study:

The fact that at follow-up about twenty percent of the participants used anti-psychotics may have influenced the results on the prediction of prodromal symptoms of psychosis, because the use of these compounds may mask or mitigate symptoms of psychosis.

The second limitation concerns the age of the participants at follow-up. Although this study encompasses a follow-up period of seven years, the adolescents who were younger than 16 years at T2 may still be too young to display prodromal symptoms of psychosis.

Furthermore, at T2 114/ 142 (80.3%) children agreed to participate in the follow-up study and 91 children had complete data at T2 (64.1%). In 23 (15.8%) children the data on the Prodromal Questionnaire (PQ) were not complete.

CONCLUSIONS AND IMPLICATIONS

Childhood FTD, namely illogical thinking, predicted more severe symptoms of ASD in adolescence, up and above the effect of ASD symptom severity in childhood. Because illogical thinking constitutes a significant and independent contribution to future ASD severity, it is advisable to assess illogical thinking in school-aged ASD children in order to get an impression of future course.

FTD does not predict prodromal symptoms of psychosis in ASD children. Although FTD in non-ASD samples predicts (prodromal symptoms of) psychosis, we could not demonstrate a clear cut relation between FTD and prodromal symptoms of psychosis in this ASD sample. FTD is common among ASD subjects and later conversion to psychosis is rare, and this negatively impacts the predictive power of FTD for psychosis in ASD children. The presence of illogical thinking seems to have an

important psychopathological impact and therefore these symptoms might invite to be cautiously followed up to see the evolution of the disorder.

Future research

It would be interesting to follow-up samples of children with ASD, especially children with PDD-NOS, for a longer period of time, long enough to enclose the total period of transition to psychosis, which lasts roughly until the age of 25. The goal of such studies would be to identify sub-categories or predictors of later psychosis in samples of children with complex developmental disorders.

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Chapter 5

Childhood facial recognition predicts adolescent symptom severity in autism spectrum disorder

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ABSTRACT

Objectives: To evaluate the predictive value of facial recognition (FR) and the identification of facial emotions (IFE) for future symptom severity in a seven-year follow-up study of 87 children with autism spectrum disorders (ASD). Methods: FR and IFE were assessed in 87 children with ASD during childhood (T1: age 6-12) using the Amsterdam Neuropsychological Tasks (ANT). Symptom severity was assessed using the Autism Diagnostic Observation Schedule (ADOS) at T1 and again seven years later during adolescence (T2: age 12-19). Multiple regression analyses were performed to investigate whether T1 FR and IFE predicted T2 ADOS severity, while controlling for T1 ADOS severity.

Results: More accurate FR significantly predicted lower T2 ASD symptom severity scores ($\Delta R^2 = .09$), even when controlling for T1 ASD symptom severity. IFE was not a significant predictor of T2 ASD symptom severity.

Conclusions: In ASD, the accuracy of FR is a relevant predictor of symptom severity in adolescence. Test results on FR in children with ASD may have prognostic value regarding later symptom severity.

KEYWORDS

autism spectrum disorder- social cognition-facial recognition-identification of facial emotions-follow-up study

INTRODUCTION

Deficits in facial recognition (FR) and the identification of facial emotions (IFE) have been associated with the social communication deficits of individuals with Autism Spectrum Disorder (ASD), namely with reduced social interest, attention and motivation to social stimuli (e.g. Dawson, Webb, McPartland, 2005a; Begeer, Koot, Rieffe et al., 2008; Faja, Aylward, Bernie et al, 2008). According to the enactive mind theory, young children with ASD do not adequately attend to social stimuli, which is reflected by a lack of reciprocity, a lack of joint attention and atypical gaze behaviour (e.g. Klin, Jones, Schultz et al, 2005). As a consequence, children with ASD fail to develop expertise regarding the processing of social stimuli, resulting in an atypical way of recognizing faces and processing facial emotions (Schultz, Gauthier, Klin et al., 2000; Pierce, Muller, Ambrose et al., 2001; Dawson, Carver, Meltzhoff et al., 2002).

Facial recognition (FR)

FR has been shown to be limited in accuracy and speed in ASD (e.g. Klin, Sparrow, de Bildt et al., 1999; Joseph &Tanaka, 2003; Wolf, Tanaka, Klaiman et al., 2008), although some studies could not confirm these deficits (e.g. Celani, Battacchi, Arcidiacono, 1999). Across different tests for FR, children with ASD seem to use a more time-consuming, attention demanding strategy than age-matched typically developing children, which may partly be due to problems with the memory of faces (Serra, Althaus, de Sonneville et al., 2003; Weigelt, Koldewyn, Kanwisher, 2012). A comprehensive review of studies on face recognition in ASD indicated poorer performance on FR tasks in children with ASD as compared to typical developing children (Weigelt et al., 2012). In previous literature, differences between children with ASD and typically developing children have mainly been found regarding quantitative indices of accuracy and speed of face recognition. In contrast, few differences have been found between children with ASD and typically developing children regarding more qualitative indices of face perception, such as the recognition of outer versus inner face parts, parts of faces versus whole faces, or inverted versus non-inverted faces. Weigelt et al. 2012 provide a detailed review of this mixed literature. Recently, it has been found that FR difficulties in ASD are process specific (i.e. involving face memory but not face perception) and domain specific (i.e. involving faces but not objects, Weigelt, Koldewyn, Kanwisher, 2013). In contrast with this finding, it has been postulated that difficulties in FR in ASD are part of a more general pervasive perceptual atypicality, which also affects non-face stimuli rather than a selective and disproportionate defect in particularly the processing of face stimuli (Ewing, Pellicano, Rhodes, 2013). The first view (Weigelt et al., 2013) is in line with the social

motivation theory, while the latter view (Ewing et al., 2013) opposes the social motivation theory, as it suggests more general perceptual atypicalities.

Pattern recognition (PR)

In contrast to this poorer performance on FR tasks, an equal or even superior performance of ASD children compared to typically developing children has been found on pattern recognition (PR) tasks (Serra et al., 2003), suggesting that a specific deficit in the recognition of faces may be characteristic of ASD (Weigelt et al., 2013).

Identification of Facial Emotions (IFE)

Deficits in IFE with respect to speed and accuracy have been reported in ASD (e.g. Pelphrey, Sasson, Reznick et al., 2002; Lindner & Rosen, 2006; Wright, Clarke, Jordan et al., 2008; overviews: Harms, Martin, Wallace, 2010; Uljarevic & Hamilton, 2013), although some studies could not confirm these deficits (e.g. Castelli, 2005). Previous studies comparing IFE between children with ASD and typically developing children have yielded mixed results (Harms et al., 2010). However, studies also incorporating brain imaging, eye tracking or event related potentials in their design, have found evidence for differences in the processing of IFE stimuli between typically developing children and ASD children and suggest differences in the underlying neurobiological processes involved in IFE between typically developing children and children with ASD (Harms et al., 2010). Thus, although at the behavioral level children with ASD may sometimes perform similarly to age-matched typically developing controls, they may use a more time-consuming, attention demanding strategy involving different neurobiological substrates than controls (Serra et al., 2003; Weigelt et al., 2012). It has been hypothesized, that in ASD there is no generalized deficit in the recognition of all emotions, but rather a specific difficulty in the recognition of one or more negative emotions, such as fear (Pelphrey et al, 2002; Humphreys, Minshew, Leonard et al., 2007) or sadness (Boraston, Blakemore, Chilvers et al., 2007). Blair (2003) in a review noted that IFE differences disappeared once groups were matched on mental age.

Most previous studies compared FR and IFE between children with ASD and typically developing children, while fewer studies focused on correlates of FR and IFE within samples of children with ASD. By comparing FR and IFE within samples of ASD children, it could be elucidated whether any differences in FR and IFE reflect the severity of ASD symptoms. In an earlier study, we demonstrated FR differences among children with ASD (Herba, de Bruin, Althaus et al., 2008). Children with the diagnosis of Pervasive Developmental Disorders Not Otherwise Specified (PDD NOS) processed faces less accurately and more slowly than children with the presumed sub-classification of Multiple Complex Developmental Disorder (MCDD). Recently it

was found that FR difficulties in ASD children showed a borderline significant correlation with autism severity (Weigelt et al., 2013). Only a few studies have focused on the relationship between IFE and ASD symptom severity. Using the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore et al., 2002) it was found that higher levels of global impairment on IFE tests for four basic emotions correlated with poorer scores on social interaction as evaluated by the ADOS (Boraston et al., 2007). Another study found that poorer identification of fear correlated with higher scores on the communication domain of the ADOS (Humphreys et al., 2007).

Previous studies focused on cross-sectional associations between FR and IFE with ASD symptom severity. To date, longitudinal research aimed at determining the prognostic significance of FR and IFE in ASD has not been carried out. Investigating the longitudinal associations of atypicalities in FR and IFE may be important for two reasons: theoretically, to determine whether differences in FR and IFE really reflect an underlying core deficit in ASD and clinically, to determine whether FR and IFE findings may predict future severity of the disorder.

If indeed, insufficient attention to social stimuli is at the core of ASD, and if abnormalities in the recognition of faces and emotions are close derivatives of this core deficit, tests assessing FR and IFE might have prognostic value regarding the future symptom severity of children with ASD. In the current longitudinal study participants with ASD were followed up from childhood into adolescence to determine whether tests on FR and IFE yield valuable prognostic information with regard to later symptom severity of ASD. Therefore, the predictive value of childhood FR and IFE for later ASD symptom severity was studied, using the Amsterdam Neuropsychological Tasks (ANT version 2.1; De Sonneville, 1999) and the ADOS both in childhood and seven years later in adolescence. We hypothesized that poorer childhood performance on FR and IFE tests would predict more severe ASD symptoms in adolescence. For PR we did not expect to find a relationship between performance and future ASD symptom severity.

METHODS

Participants

Participants were 87 individuals with a clinical DSM-IV-TR classification of ASD in childhood (T1: age 6-12; Eussen, Van Gool, Verheij et al., 2013) who were followed to adolescence (T2: age 12-19). The average time between the two assessment waves was 6.88 years (SD = .66).

Initially, all individuals were referred for psychiatric evaluation to the outpatient Department of Child and Adolescent Psychiatry/psychology, Erasmus Medical Cen-

ter Rotterdam, the Netherlands, specialized in diagnosing individuals, presenting with milder or atypical symptoms of ASD with an average intelligence. In total, 503 children between 6 and 13 years of age were referred between July 2002 and September 2004 (T1; De Bruin, Ferdinand, Meester et al., 2007b). Of these 503 children, 114 children met the inclusion criteria for the current study, which were (a) a clinical DSM-IV-TR classification of ASD, (b) total IQ >=70 (c) absence of severe neurological or physical problems (e.g. blindness), and (d) parents were able to communicate in the Dutch language (De Bruin et al., 2007b). The clinical DSM-IV-TR classification was obtained by a multi-disciplinary team on the basis of elaborate assessment of early development, semi-structured interviews carried out with parents or caretakers, psychiatric observation of the child in a one-to-one situation, psychological assessment, CSBQ (Children's Social Behaviour Questionnaire; Luteijn, Luteijn, Jackson et al., 2000a), medical information and school information (Eussen et al., 2013; Greaves-Lord, Eussen, Verhulst et al., 2013). Of the 114 children meeting the inclusion criteria, 8 (7.0 %) met DSM-IV TR criteria for Autistic Disorder; 10 patients (8.8 %) met criteria for Asperger Syndrome and 96 patients (84.2 %) received the diagnosis PDD-NOS.

During the second assessment wave (T2), 87 (76.3%) of the 114 initially selected children agreed to participate in the follow-up study. These 87 participants did not differ from the 27 adolescents who did not participate at T2 with regard to gender, initial age, IQ, scores on the Children's Social Behaviour Questionnaire (CSBQ), an ASD symptom inventory, and on ADOS total score at T1.

Ethics

At T1, parents/caretakers of the participating children signed informed consent forms prior to participation in the study. At T2 both parents and adolescents signed the informed consent forms. The Medical Ethics Committee of the Erasmus Medical Centre approved the study.

Procedure

At T1, after finishing the diagnostic assessment and the ADOS, tests of social cognition were performed on two occasions, separated by a week, in a quiet room and always in the morning to minimize effects of fatigue and to maximize concentration. On the first occasion, the Wechsler's Intelligence Scale for Children (WISC-R, 1986) was administered. During the second visit, subtests of the computerized ANT, version 2.1 (De Sonneville, 1999) were administered. The ANT is an elaborate neuropsychological test battery, covering a broad range of neuropsychological functions like attention, memory, encoding, arithmetic and impulse-inhibition. In the current study FR, IFE, PR and baseline speed were included. These tasks of FR

and PR involved sequential presentation: the target was shown for 2500 milliseconds and after a delay of 500 milliseconds the display set of four possible solutions appeared (Serra et al., 2003). In the IFE task the target was shown for 2500 msec and subsequently the subject had to indicate whether this target did or did not show one specific emotion (Serra et al., 2003).

At T2, approximately seven years later, the ADOS (see below) was again administered to assess ASD symptom severity.

Materials

Facial recognition (FR)

The FR task of the ANT (ANT 2.1; De Sonneville, 1999) was selected to measure the speed and accuracy of recognizing neutral faces. A target face with a neutral face expression was presented for 2.5 seconds in 40 trials. Following the presentation of this target face, a set of four photographs of neutral faces were presented and the children was required to indicate (using a two key response panel) whether or not the target face appeared in the set of four photographs. In half of the trials the target face did appear in the set of four and the child was required to press a "yes" key (target condition) and in half of the trials the target face did not appear in the set of four and thus the child was required to press a "no" key (non-target condition). Reaction time (RT) and accuracy were calculated for target trials and non-target trials. In our analyses we used the target trials only, because the non-target trials involve more general and complex cognitive processing (Serra et al., 2003), while the target trials more specifically tap into face perception and memory for faces.

Pattern recognition (PR)

A subtest of the ANT battery, assessing pattern recognition was administered. Children were asked to respond as to whether a certain visuo-spatial pattern was identical to one of four patterns in a display set. The task consisted of an easy condition, containing dissimilar visuo-spatial patterns, which are easy to distinguish and a complex condition, containing similar patterns, which are very difficult to distinguish. Accuracy and RT were calculated for target trials. In our study we used the results of the complex condition, because ASD participants perform relatively better on the complex condition than typically developing subjects and therefore the complex condition may provide more useful information for distinguishing subjects within the autism spectrum (Herba et al., 2008).

Baseline Speed (BS)

A simple reaction time task was employed to obtain a baseline measure for speed (BS) of a child's response to the response key (ANT 2.1, De Sonneville, 1999). This was done to ensure that the child understood how to use the response key and to make sure that relations between FR, PR, IFE and ASD severity were not explained by differences in baseline speed. The child was required to press a key with the index finger of their dominant hand when a square was presented. Thirty-two trials were administered. The total baseline speed and the standard deviation (SD) of the BS were calculated. The SD provides a measure of the variability of performance, a higher SD being indicative of loss of attention during the task.

Identification of Facial Emotions (IFE)

The Identification of Facial Emotions (IFE) subtest of the ANT 2.1 was employed to probe emotion processing. Children were asked to respond as to whether a face displayed a particular target emotion or not. Four conditions were administered (happy, sad, anger, fear). For each condition, the child had to respond whether the face showed that particular emotion or not, by pushing the button. Each emotion condition consisted of 40 trials and the target emotions were present in half of the trials. Accuracy and RT were calculated for target and non-target conditions as previously conducted by Herba and colleagues (2008). In our analyses, we specifically included the scores on the target trials for anger, fear, sad and happy, to be able to particularly examine IFE. Similar to our approach for the FR task, we did not include the scores on non-target trials in our analyses, since these scores reflect more general neuropsychological processes, such as perception, memory, decision making, inhibitory control (i.e. also including non-social cognition, such as executive functioning), while our focus was on explaining the underlying social cognition processes of symptom severity in ASD.

Autism Diagnostic Observation Schedule (ADOS)

The ADOS was used to assess ASD symptom severity at T1 and T2. The ADOS is considered to be a "gold standard" diagnostic tool and provides a standardized context for observation and scoring of ASD symptoms in the domains of Language and Communication, Reciprocal Social Impairments, and Stereotyped Behaviours and Restricted Interests. Lord and colleagues (2002) showed that the psychometric properties of the ADOS are good with an excellent internal consistency. The ADOS comprises four age appropriate modules (Lord et al., 2002). At T1 the ADOS module 3 was used (Lord et al., 2002; Gotham, Risi, Pickles et al., 2007; Gotham, Pickles, Lord, 2009). At T2 ADOS module 4 was used and in nine children module 3 was used. The observation of the children was performed by trained and certified clini-

cians who were blind to all previous diagnostic information. In the ADOS scoring algorithm items are scored on a 3-point scale from 0 (no evidence of abnormality related to autism) to 2 (definite evidence of abnormality related to autism). We computed ADOS severity scores as proposed by Volkmar and colleagues (2009), i.e. by computing a total score of all item scores and subsequently dividing these sum scores by the total number of items; thus yielding scores between 0 and 2. We did not use the ADOS calibrated severity scores (Lord, Rutter, DiLavore et al., 2012a; De Bildt, Greaves-Lord, De Jonge, 2013), as our participants completed module 4 of the ADOS at T2 and the calibrated severity scores for module 4 are not yet available.

Wechsler Intelligence Scale for Children-Revised (WISC-R)

To assess intelligence, the Dutch version of the Wechsler Intelligence Scale for Children-Revised (WISC-R) was administered at T1 (WISC-R Projectgroep, 1986). The WISC-R is composed of several verbal and performance subtests: Information, Similarities, Arithmetic, Vocabulary, Comprehension, Digit Span, Picture Completion, Picture Arrangement, Block Design, Object Assembly, Coding and Mazes. Like the original version, the Dutch version has good reliability and validity (WISC-R Projectgroep, 1986). Since it was shown that performance IQ (PIQ) versus verbal IQ (VIQ), as well as Full Scale IQ (FSIQ) might be differentially related to emotional processing ability in individuals with ASD (Harms et al., 2010), we considered FSIQ, PIQ as well as VIQ separately as putative covariates.

Statistical analyses

For descriptive purposes, means and standard deviations or frequencies were calculated for age, sex, FSIQ, PIQ, VIQ, baseline speed and ADOS severity scores at T1 and T2. Means and standard deviations were also calculated for the experimental variables FR time, FR accuracy, PR time, PR accuracy, IFE time for four basic emotions: anger, fear, sad, happy and IFE accuracy for these four basic emotions. Indices of reaction time/accuracy were assessed separately for each of the four basic emotions, in order to determine whether the identification of a specific emotion was most predictive of later ASD symptom severity.

Statistical analyses were conducted in three main steps: 1) identification of relevant predictor variables; 2) identification of relevant covariates; and 3) multiple regression analysis examining whether FR and IFE measures in childhood are predictive of ADOS severity in adolescence.

Step 1) To identify which predictor variables should be included in the main multiple linear regression analysis, bivariate correlations were calculated between all putative predictor variables (i.e. FR, PR and IFE measures) and the outcome variable (ADOS T2). To avoid multicollinearity, and given that the FR and IFE time measures

Table 1: Descriptives of the sample.

	Mean (S.D)	Range	
Sex	89.6% boys		
Age at T1	9.23 (1.85)	6.54-13.02	
ADOS weighted scores T1	.50 (.28)	.00-1.08	
ADOS raw scores T1	7.1 (3.7)	1-18	
ADOS classification T1:			
Non-ASD	39.1%		
ASD	21.8%		
Autism	39.1%		
IQ at T1	95.8 (14.4)	70-128	
PIQ at T1	98.3 (15.4)	61-129	
VIQ at T1	97.0 (14.1)	65-144	
Baseline speed at T1	400.6 (108.5)	249.0-781.1	
ADOS weighted score T2	.56 (.25)	.07-1.32	
ADOS raw scores T2	8.0 (4.3)	1-20	
ADOS classification T2:			
Non-ASD	36.8%		
ASD	24.1%		
Autism	32.2%		
FR time (msec) at T1	2058 (617)	972-4037	66.7%*
FR accuracy at T1	86% (11.6%)	60-100%	34.5%*
PR time at T1	2995 (697)	1001-4364	NA
PR accuracy at T1	78% (20%)	15-100%	NA
IFE angry time at T1	1195 (463)	428-3735	52.4%*
IFE fear time at T1	1344 (550)	602-3722	48.2%*
IFE sad time at T1	1345(469)	436-2978	50.0%*
IFE happy time at T1	953(291)	498-2302	64.3%*
IFE angry accuracy at T1	90% (13%)	35-100%	14.9%*
IFE fear accuracy at T1	82% (18%)	0-100%	56.6%*
IFE sad accuracy at T1	80% (19%)	25-100%	22.6%*
IFE happy accuracy at T1	94% (9%)	40-100%	48.2%*

Caption Table 1: ADOS severity weighted at T1 and at T2: mean score per item on the ADOS for all domains of the ADOS. Baseline speed at T1: mean time in milliseconds on reaction time tasks. IQ at T1: FSIQ as measured by WISC-R. FR time: time in milliseconds needed to recognize neutral faces. FR accuracy: percentage of correct answers on 20 trials of the FR task. PR time: time in milliseconds needed to recognize complex patterns. PR accuracy: percentage of correct answers on 20 trials of the PR task. Identification of Facial Emotions (IFE) angry time: time in milliseconds needed to identify angry faces. IFE fear time: time in milliseconds needed to identify fearful faces. IFE sad time: time in milliseconds needed to identify sad faces. IFE happy time: time in milliseconds needed to identify happy faces. IFE angry accuracy: percentage of correct answers on 20 trials of the IFE angry faces task. IFE fear accuracy: percentage of correct answers on 20 trials of the IFE fearful faces task. IFE sad accuracy: percentage of correct answers on 20 trials of the IFE sad faces task. IFE happy accuracy: percentage of correct answers on 20 trials of the IFE happy faces task. *=Percentage of participants scoring at least one standard deviation below control group of typical developing children of the same age (Greimel et al., 2014). NA=Non-Available.

could be interrelated, only significant correlates of ADOS T2 were included as predictors in the subsequent multiple regression analysis. Step 2) Identification of relevant covariates: To examine which variables needed to be included as covariates in the multiple regression analyses, bivariate correlations between putative covariates (i.e. age, sex, FSIQ, PIQ, VIQ and baseline speed) the outcome measure (ADOS weighted scores at T2), and the selected predictor variables were calculated using Pearson's correlations in the case of continuous variables or Spearman's correlations in the case of ordinal variables. Covariates were retained in the subsequent multiple regression analyses if a covariate significantly correlated with the predictor as well as the outcome variable. Step 3) A multiple linear regression analysis was performed to examine the longitudinal association between our predictor variables of interest (as resulted from step 1: FR time, FR accuracy and IFE fear time) and our main outcome variable (ADOS T2). Our goal was to directly compare the relative predictive power of time and the accuracy measures of FR and IFE and therefore we included these measures in one model. To make sure there was no multicollinearity among these remaining predictor variables, we tested for multicollinearity, using the Variance Inflation Factor (VIF) and eigenvalues. To obtain a valid estimation of the prediction of ADOS T2 scores, we accounted for baseline levels (i.e. ADOS T1). In other words, we tested whether FR and IFE measures were predictive of ADOS T2 scores over and above the association with ADOS T1 scores. A backward regression procedure was followed to isolate the most powerful predictors of the ADOS T2 scores. For all analyses, we used SPSS software (Version 20.0). All analyses were two-tailed, and the alpha was set at 0.05.

RESULTS

Descriptives

Table 1 provides descriptive information on demographic characteristics, putative covariates, autism symptom severity and measures of social cognition.

Step1: Identification of relevant predictor variables

As shown in table 2, the variables FR time, FR accuracy, and IFE fear time showed a significant bivariate correlation with the outcome variable ADOS T2. Therefore, these variables were included as predictors in the subsequent multiple regression model. Since measures of PR and the IFE measures angry, happy, sad, did not show significant correlations with the outcome variable ADOS T2, these variables were not included as predictors in the multiple regression model.

Step 2: Identification of relevant covariates

Table 2 also shows the correlations between the putative covariates, the outcome and the predictor variables. Several significant correlations were found, including negative correlations between age and the reaction time measures of FR and IFE, and positive correlations between baseline speed and the reaction time measures of FR and IFE.

PIQ was negatively correlated with the reaction time measures on PR and on IFE fear, sad, and happy. Furthermore PIQ correlated significantly with the accuracy measures on FR and IFE fear. A significant negative correlation was found between VIQ and ADOS T2 scores.

However, since none of these variables significantly correlated with the outcome variable as well as the predictor variables, none of the putative covariates were included in the subsequent regression analyses.

Table 2: Bivariate correlations between putative covariates, measures of social cognition and outcome variable ADOS T2

Bivariate correlations (r,p))	FR time	FR acc.	PR time	PR acc.	IFE angry time	IFE fear time	IFE sad time	IFE happy time	IFE angry acc	IFE fear acc	IFE sad acc	IFE happy acc	ADOS T2
Sex	.06	-.31	-.14	-.52	.10	-.03	-.06	-.02	-.07	-.02	-.14	-.01	-.02
	.62	<.01**	.30	<.01**	.38	.85	.59	.87	.53	.85	.22	.90	.87
Age	-.54	-.14	-.50	-.22	-.40	-.43	-.24	-.32	-.09	.04	.77	.24	-.09
	<.01**	.27	<.01**	.07	<.01**	<.01**	.05*	<.01**	.48	.79	.54	.05*	.42
IQ	.00	.17	-.24	.11	.04	-.11	-.01	-.17	.04	.18	.01	-.03	-.15
	.97	.13	.02*	.32	.72	.34	.95	.11	.72	.10	.95	.81	.17
Baseline Speed	.62	-.22	.47	-.23	.45	.51	-.52	.46	-.36	-.10	-.26	-.07	.21
	<.01**	<.01**	<.01**	.04*	<.01**	<.01**	<.01**	<.01**	.01*	.39	.02*	.55	.07
ADOS T1	.04	-.16	.19	.09	.12	.02	.06	-.07	-.27	-.20	-.05	.00	.33
	.71	.16	.09	.40	.27	.90	.58	.54	.01*	.07	.62	.98	<.01
ADOS T2	.27	-.26	.09	.09	.21	.25	.18	-.08	-.02	-.16	-.07	-.06	
	.02*	.02*	.42	.45	.06	.03*	.12	.49	.99	.17	.57	.62	

Table 2: Baseline Speed: average reaction time on a simple reaction time test. FR time: time in milliseconds needed to recognize neutral faces. FR accuracy: number of correct answers on 20 trials of the FR task. PR time: time in milliseconds needed to recognise complex patterns. PR accuracy: number of correct answers on 20 trials of the PR task. Identification of Facial Emotions (IFE) angry time: time in milliseconds needed to identify angry faces. IFE fear time: time in milliseconds needed to identify fearful faces. IFE sad time: time in milliseconds needed to identify sad faces. IFE happy time: time in milliseconds needed to identify happy faces. IFE angry accuracy: number of correct answers on 20 trials of the IFE angry faces task. IFE fear accuracy: number of correct answers on 20 trials of the IFE fearful faces task. IFE sad accuracy: number of correct answers on 20 trials of the IFE sad faces task. IFE happy accuracy: number of correct answers on 20 trials of the IFE happy faces task.
r= Pearson correlation between two variables.
p=significance. *correlation significant at 0.1<p<0.5 and **: correlation significant at p<.01 level.

Step 3: Multiple regression analyses

The multiple regression model shown in Table 3 included FR time, FR accuracy, IFE fear time and ADOS T1 scores as predictors and ADOS T2 scores as the outcome measure. Multicollinearity diagnostics, including the variance inflation factor (VIF) and eigenvalues indicated that there was no multicollinearity. In the backward regression procedure, the variables FR time and IFE fear time were excluded from the model in the first and second step of the procedure, because these variables were no longer significant in combination with the other predictors (i.e. FR accuracy, ADOS T1). The final model thus included ADOS T1 scores and FR accuracy as significant predictors. The model characteristics were good ($F(2,75) = 14.7$; $R^2=.29$; $p<.01$). FR accuracy significantly predicted ADOS T2 scores, explaining 9 % of the variance ($p= .01$; $\beta = -.26$; 95% CI= -.05- -.01, $\Delta R^2=.09$; Table 3).

Because there were important null findings, we performed a post-hoc power analysis to calculate the minimum effect size that we were able to detect. Setting the α at .05 and the β at .80 and given our sample size of n=78, we were able to find in our study an f2=.08 (Cohen, 1988), corresponding to $R^2=.07$, indicating 7% explained variance. Thus, an effect larger than 7% explained variance could be detected in our sample.

Table 3: Multiple linear regression analyses, using ADOS total scores at T2 as outcome variable, scores on social cognition tests as predictors and ADOS total scores at T1 as a covariate. (n=84)

	β	t	P	95% CI	ΔR2
Model			<.01**		.29
FR accuracy	-.26	-2.6	01**	-.05- -.01	.09
ADOS T1 total	.45	4.6	<.01**	.27- .68	.20

Table 3: FR accuracy: number of misses on 20 trials of the FR task. ADOS T1 total: mean score per item (weighted score) on all items of the ADOS at T1.
B= Standardized Beta. t= T value. P=significance. 95% CI= 95 percent confidence interval. ΔR^2 = percentage explained variance for this particular variable.
*: correlation significant at 0.1<p<0.5 level and **: correlation significant at p<.01 level.

DISCUSSION

Within the context of a longitudinal investigation of 87 children with ASD, we studied the predictive value of FR, IFE and PR for ASD symptom severity seven years later in adolescence. It was hypothesized that poorer performance on the (1) FR and the (2) IFE tasks in childhood would predict higher ASD symptom severity scores during adolescence, while (3) performance on PR tasks would not be associated with later ASD symptom severity. Our first hypothesis was supported. We found that less accurate FR at T1 predicted significantly higher ASD symptom severity scores at T2.

The effect of the FR accuracy on the outcome seven years later remained significant after adjusting for T1 symptom severity. Results did not provide support for our second hypothesis, that childhood IFE scores would be associated with later ASD symptom severity. Finally, as hypothesized, PR scores did not significantly predict higher symptom severity scores at T2.

Longitudinal studies focusing on the prognostic significance of tests of social cognition in ASD are scarce. One study investigated the predictive value of different aspects of cognition, namely executive functioning, theory of mind and central coherence (Pellicano, 2010). However, to our knowledge, this is the first study to find longitudinal associations between social cognition tests in children with ASD and symptom severity in adolescence. The fact that FR accuracy predicted the ADOS T2 scores even after adjusting for ADOS T1 scores in the model indicates that these atypicalities in face processing do not merely reflect ASD symptom severity, but may have a specific additional prognostic value.

Our findings are consistent with the theory of the enactive mind (Klin et al., 2005). We demonstrated that less accurate processing of faces at school age (T1) predicted a higher ASD severity seven years later. The enactive mind hypothesis posits that an altered way of processing faces is the outcome of an underlying difference in the attention towards social stimuli that may in turn influence gaze behaviour. A decline in the fixation on the eyes of other people between the age of two to six months has been demonstrated in infants who later received a diagnosis of ASD (Jones & Klin, 2013) and the correlation between lack of eye-fixation and level of social disability has been established in 2-year old children (Jones, Carr, Klin, 2008). The early lack of eye-fixation in ASD possibly results in an altered way of processing and recognizing faces, as indicated, for instance, by the performance on FR tests.

Also the social motivation theory (Dawson et al., 2005 a; Chevallier, Kohls, Troiani et al., 2012) provides an interesting theoretical framework for our findings. The social motivation theory conceives ASD as an extreme case of diminished social motivation, i.e. the humans' intrinsic drive to seek social acceptance and avoid social rejection. This theory posits that in ASD, early-onset impairments in social attention foster developmental processes that reduce the child's opportunity for adequate social learning experiences. This further alters the development of social skills and cognition, and in turn, social interactions become less rewarding, resulting in diminished display of social maintenance behavior. The current findings on FR indicate that atypical face processing is indeed present in some individuals with ASD and may influence future symptom severity. Earlier alterations in social attention may result in disruptions in social cognition processes, such as less accurate FR in childhood. This less accurate FR in childhood may in turn impact further social development, possibly resulting in a higher ASD severity in adolescence. Although

the social motivation theory focuses on an inborn tendency already present very early in life, it also describes the subsequent atypical social cognitive developmental processes that may also occur later on in life, i.e. between childhood and adolescence. We hypothesize that - given the close interaction between maturation of the brain and the interactions with the social environment - social cognitive processes may undergo developmental changes throughout the life span. This would possibly explain the intriguing finding that lower accuracy in FR in childhood predicted an increase in ASD symptoms towards adolescence. In our view, increasing demands on social skills from the social environment (e.g. from peers, participation in school and broader society) between childhood and adolescence result in an increasing challenge upon social cognition in general and perhaps on FR in particular. With such an increasing challenge from the social environment, subtle dysfunctions in social cognition (i.e. FR) already present in childhood might evolve into a stronger expression of this underlying dysfunction throughout development, and thus in the more explicit manifestation of ASD symptoms (i.e. socially maladapted behaviors) in adolescence. The current prospective findings thus add to the previous cross-sectional literature regarding the putative underlying neurobiological mechanisms of ASD.

Our second hypothesis, that IFE performance predicts later ASD symptom severity was not supported, which is in line with the rather mixed results in the literature. Two recent cross-sectional studies failed to find differences on IFE tests between individuals with high functioning ASD and typically developing individuals (Jones, Pickles, Falcaro et al., 2011; Reinvall, Voutilainen, Kujala et al., 2013). Therefore in this longitudinal study, where associations between predictors and outcome measures tend to become weaker over time, the stronger association between FR and ASD symptom severity probably remained, whereas the weaker association between IFE and ASD symptom severity vanished. Possibly, ceiling effects may have masked relations between the IFE measures and ASD severity in adolescence. As shown in Table 1, the overall proportions of accurate trials concerning IFE fear, IFE angry, IFE sad and IFE happy where relatively high and reached the maximum of 100% which may have compromised the sensitivity of the IFE measures. Moreover, FR and IFE operate independently in ASD, as opposed to findings in typically developing children, where it was found that information from FR is used to provide contextual meaning to IFE (Krebs, Biswas, Pascalis et al, 2011). The fact that IFE and FR seem to operate independently in children with ASD might also partly explain why we found a strong association between FR and future symptom severity, whereas such an association did not exist between IFE and future symptom severity. We should note however, that our power analysis showed that only effects with an explained variance of 7% or higher could be detected in the current dataset and therefore it

cannot be ruled out that a smaller effect of IFE on ASD symptom severity may be present. Also, although IFE in general was not a predictor of future course, there could still be significant effects on outcome for one specific emotion. In our study, we found a significant correlation between FR accuracy and IFE fear (accuracy for fear recognition), but not between accuracy on FR and any of the other emotions. A cross-sectional study by Humphreys and colleagues (2007) found a correlation between poorer identification of fear and higher scores on the communication domain of the ADOS, however in our longitudinal study, IFE fear did not predict ASD symptom severity or scores on the ADOS communication domain. Boraston and colleagues (2007) in a cross-sectional study found specific impairments for the identification of sadness in ASD and again we could not confirm this in our study, emphasizing the need for further prospective studies.

Our third hypothesis, that PR performance is not associated with later symptom severity was supported. Although no firm conclusions can be drawn from this null finding given the power of our study, our results are more in line with theories suggesting that the underlying mechanisms of ASD are specific to social information processing (e.g. Klin et al., 2005, Dawson, Webb, Wijsman et al., 2005b; Chevallier et al., 2012; Weigelt et al., 2013) and oppose more general perceptual processing difficulties in ASD (e.g. Ewing et al., 2013).

Although our study did not incorporate brain-imaging techniques, our results are consistent with the conclusions of this line of research. A considerable body of evidence reveals atypical fMRI response to faces and other social stimuli in ASD within a network of brain structures that has been termed the 'social brain' (Baron-Cohen, Ring, Wheelwright et al., 1999). The Fusiform Face Area, located within the fusiform gyrus of the occipito-temporal cortex is particularly activated by facial identity processing in controls and is greatly reduced in activation in people with autism (Harms et al., 2010; Pierce et al., 2001; Schultz et al., 2000). The exact neurological basis of the dissociation between face recognition and face memory is not yet known. Possibly, a region for face memory in the anterior temporal region near the fusiform face area is affected in ASD, or there is a disconnection between the fusiform face area and a face memory area (Weigelt et al., 2013). The processing of PR on the other hand takes place in the ventro-medial prefrontal area and this process is not affected in ASD. Emotion processing is modulated for a large part by the amygdala, a subcortical structure which shows decreased activity in some, but not all fMRI studies on ASD subjects and which is tightly connected to the fusiform face area (Dziobek, Bahnemann, Convit et al., 2010; Harms et al., 2010). The correlation between amygdala activity and recognizing emotions has been established for fearful emotions; this correlation is less clear for sadness and happiness and in the case of anger it is believed that the orbital frontal cortex takes the lead (Blair,

2003). Altogether, the recognition of emotions is a very complex process, because cortical pathways as well as subcortical pathways are involved and different emotions involve different brain structures (Blair, 2003). The less accurate FR capacities in the cases with a higher ASD severity in adolescence, could be a developmental phenotypical expression of atypical face processing in the fusiform face area (Pierce et al, 2001; Schultz et al., 2000; Harms et al., 2010). The finding that less accurate FR predicted a higher ASD symptom severity later in development might indicate that face processing capacities are a sensitive and accurate prognostic index of such underlying neurobiological processes, that may also drive phenotypical outcomes later in life.

The significant negative correlations between age and performance on IFE time dependent tests are in line with the available literature on the developmental aspects of emotion recognition (for review see Herba & Phillips, 2004). In typical development, emotion decoding improves considerably throughout childhood, whereas in ASD it is disputed whether emotion decoding develops more slowly or whether it does not improve with age (Harms et al., 2010). Our results indicate that IFE in the older children in our sample was faster and more accurate than in the younger children in the sample, which is in line with the hypothesis of an ongoing, but perhaps slower development of emotion recognition in ASD. Labelling basic emotions is worse in high-functioning ASD than in typically developing children before the age of ten and these differences between ASD and typical development in labelling basic emotions disappear after the age of twelve (Rump, Giovanelli, Minshew et al., 2009). However the recognition of subtle emotions and the processing of configural information in ASD lags behind across all ages (Rump et al., 2009). Perhaps school-aged children with ASD gradually develop compensatory mechanisms for their weaknesses in recognizing basic emotions, which become more perfected with age.

Although baseline speed was significantly correlated with the reaction time measures of FR, PR and IFE, it was not significantly correlated with ASD symptom severity at follow-up. This suggests that although slower baseline speed is associated with slower FR and IFE, it is more specifically FR time and IFE fear time that are more specifically associated with symptom severity at follow-up. Thus, dysfunctional FR reflects a specific predictor of symptom severity in ASD over and above baseline reaction time.

We did not find significant correlations between performance on FR and IFE tests and IQ, although a previous review has emphasized that IQ can have confounding effects on FR and IFE studies (Harms et al., 2010). More specifically, the influence of IQ was particularly strong in studies with very young children, in low-functioning groups and in groups with large differences between verbal and non-verbal IQ

(Harms et al., 2010). In our study, participants were generally high-functioning school-aged children (IQ > 70), which might explain why we did not find an influence of IQ.

Strengths and limitations:

The longitudinal design, including the 7-year follow-up of a large number of children with ASD is a strength of the current study. The elaborate assessment, using the ADOS, took place at both time points. However, we also faced the following limitations. Participants were referred to a single university outpatient department for child and adolescent psychiatry, specialized in diagnosing high-functioning ASD children. As a consequence, our sample mainly included verbal children with ASD within the normal intelligence range and the majority of participants were diagnosed with PDD-NOS, rather than autism or Asperger syndrome. Therefore, the findings and conclusions should be confined to this particular sub-population of children with ASD. In the FR test we used, the images of the faces had to be remembered only for 500 milliseconds. Therefore, scores should be interpreted as an index of face memory rather than face perception. However, due to the short interval, our trials tapped onto working memory, while they did not challenge long term memory for faces as arduous as the memory for faces test used by Weigelt et al. (2013). Furthermore the measures of FR and IFE were only assessed at T1 and not repeated at T2.

Directions for future research:

It would be useful to acquire more detailed information on the developmental course of ASD and the prognostic significance of FR and IFE by assessing ASD and FR/IFE measures repeatedly throughout development in individuals with ASD.

To predict future symptom severity even more accurately, it might be worthwhile to combine FR and IFE measures with fMRI measures or with measures of evoked response potentials (Campatelli, Frederico, Apicella et al., 2013).

Clinical relevance:

In children with ASD, tests on FR might be a useful assessment tool, providing additional prognostic information regarding future symptom severity. Thus, if FR is altered in childhood, this may be indicative of a worse ASD symptom severity in adolescence, although careful clinical consideration and communication towards parents and the client would be essential.

It is too early to draw conclusions on treatment issues in ASD. However, recently, it was shown that enhancing FR and IFE were crucial factors in the improvement of social skills of children with ASD using FaceSay, a computer based social skills training

program for children with ASD (Hopkins, Gower, Perez et al., 2011). Bearing in mind the results of this recent study, enhancing FR through such treatment programs aimed at improving FR and IFE could potentially have an influence upon social development and later ASD symptom severity.

Chapter 6

Superior disembedding performance in childhood predicts adolescent severity of repetitive behaviors: a seven years follow-up of individuals with autism spectrum disorder.

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ABSTRACT

Previous research suggests that individuals with autism spectrum disorder (ASD) show a detail-focused cognitive style. The aim of the current longitudinal study was to investigate whether this detail-focused cognitive style in childhood predicted a higher symptom severity of repetitive and restrictive behaviors and interests (RRBI) in adolescence.

The Childhood Embedded Figures Test (CEFT) and the Autism Diagnostic Observation Schedule (ADOS) were administered in 87 children with ASD at the age of 6-12 years old (T1), and the ADOS was re-administered seven years later when the participants were 12-19 years old (T2). Linear regression analyses were performed to investigate whether accuracy and reaction time in the complex versus simple CEFT condition and performance in the complex condition predicted T2 ADOS RRBI calibrated severity scores (CSS), while taking into consideration relevant covariates and ADOS RRBI CSS at T1. The CEFT performance (accuracy in the complex condition divided by the time needed) significantly predicted higher ADOS RRBI CSS at T2 ($\Delta R2$= 15%). This finding further supports the detail-focused cognitive style in individuals with ASD, and shows that it is also predictive of future RRBI symptoms over time.

KEYWORDS

Autism spectrum disorder - repetitive and restrictive behaviors - central coherence - detail-focused cognitive style - follow-up

INTRODUCTION

Individuals with Autism Spectrum Disorder (ASD) may show atypicalities across multiple cognitive domains (Pellicano et al., 2006), for instance central coherence, executive functioning, and theory of mind. Theories on these domains of cognition were developed in order to link the social as well as the non-social behavioral characteristics of ASD to a particular underlying cognitive style. For example, the theory on Executive Functioning (EF) was formulated mainly to elucidate the underlying mechanisms of the non-social behavioral characteristics (i.e. repetitive, restricted behaviors and interests), whereas theory of mind was formulated to explain the social and communicative behavioral difficulties in ASD.

The theory on central coherence (Frith, 1989; Happé & Frith, 2006; Happé & Booth, 2008) has been used to primarily clarify non-social (i.e. repetitive and restricted behaviours and interests; RRBI) and perceptual aspects of the ASD phenotype (Happé & Frith, 2006) in order to account for both the strengths and the weaknesses of individuals with ASD. Central Coherence (CC) refers to the ability to constitute a coherent 'picture' out of a variety of sensory input signals. In other words, being able to integrate information to 'a whole', rather than having a limited focus on the fragmented parts and details (Happé & Frith, 2006; Happé & Booth, 2008). A local and detail-focused style of information processing is usually favoured by individuals with ASD, rather than the global or integrative cognitive style that characterizes typically developing (TD) children (Happé & Frith, 2006). This preference for local aspects while processing information in individuals with ASD is regarded a cognitive style rather than a deficit (Happé & Frith, 2006; Happé & Booth, 2008). Recently, Lawson et al. (2014) adapted the central coherence theory: they described the detail-focused cognitive style in ASD as an atypical way of dealing with precision and avoiding errors in perception. In humans, a dynamic balance is kept between (top-down) integrative prior beliefs and (bottom-up) sensory evidence. In individuals with ASD, more confidence is placed in sensory input channels, whereas in TD individuals more confidence is placed in prior beliefs (Lawson et al., 2014). This reliance on concrete sensory input and high perceptual precision in ASD is bought at the price of a tendency towards sensory overload. According to this theory, the symptom of "insisting on sameness" can be explained as a protective behavior against the underlying sensory overload; and also restrictive and repetitive behaviors may serve to reduce sensory input (Lawson et al., 2014).

In the current paper, we will use "central coherence" as an overarching theoretical construct, encompassing weak integration capacities as well as strong detail focus capacities. The term "detail-focused cognitive style" will be used to describe the strong tendency of individuals with ASD to focus on local aspects of visual stimuli.

The related term "disembedding performance" will be used with regard to the performance on the particular visuo-spatial test used in our study (i.e. Child Embedded Figures Test).

With regard to the available literature, individuals with ASD show an equal or even superior performance, compared to TD children on tasks that favour local processing (Bolte et al., 2007). For instance, relatively good performance has been found on visual search tasks (O'Riordan et al., 2001), on feature discrimination tasks (O'Riordan et al., 2001) and on the Children's Embedded Figures Test ([CEFT]; Witkin et al., 1971). There are multiple reports showing that relative to TD peers, participants with ASD had equivalent (Kaland et al., 2007; Ropar & Mitchell, 2001) or even better capacities in disembedding simple shapes from complex backgrounds (Edgin & Pennington, 2005; Jarrold et al., 2005; Pellicano et al., 2005; Pellicano et al., 2006; De Jonge et al., 2006; Mitchell & Ropar, 2004 for an overview). A detail-focused cognitive style has also been demonstrated in first degree relatives of children diagnosed with ASD (Bolte & Poustka, 2006; Happé et al., 2001). It has been brought forward that an advanced capacity for visuo-spatial analysis might be a unique and highly specific endophenotype for ASD (Grinter et al., 2009), whereas other authors have questioned this high specificity of detail-focused processing in ASD compared to other neurodevelopmental disorders (Happé & Frith, 2006). Overall, it is still unresolved whether detail-focused information processing constitutes a good endophenotype of ASD. Also, which neurophysiological processes actually constitute the superior disembedding performance is under debate. The superior disembedding performance in ASD has been theoretically explained as a local bias during information processing (Mottron et al., 1999), as a combination of absent global precedence and enhanced lower level perception (Mottron et al., 2003) or as a weakened capacity to switch attention between the global and the local level (Iarocci et al., 2006).

In TD children, it has been found that superior disembedding performance in visuo-spatial tasks was associated with higher levels of restricted and repetitive behaviors, indicating a potential association between cognitive style and repetitiveness (Evans et al., 2001). An association between a detail-focused cognitive style (at the endophenotypical level) and restrictive and repetitive behaviors (at the phenotypical level) has been found in ASD children (Chen et al., 2009). Studies, comparing children within the broader autism spectrum with controls on measures of CC have yielded mixed results, probably due to the heterogeneity of ASD (De Jonge et al., 2006). A study, using dimensional scores on the Autism Quotient found an association between fast and accurate solving of the CEFT and the autism severity scores irrespective of IQ (Grinter et al., 2009). To summarize: the Chen et al. (2009) study demonstrated a cross-sectional association between weak CC and restrictive and

repetitive behaviors in ASD, and the Grinter et al. (2009) study found cross-sectional associations between weak CC and dimensional scores on autism severity.

To date, longitudinal research aimed at determining the prognostic significance of CC in ASD is scarce. One longitudinal study, investigating inter-relations between CC and EF over a period of three years, found that good CC and good EF predicted a greater progress in Theory of Mind over this period (Pellicano, 2010). However, this study did not examine the relation between these cognitive styles and phenotypical characteristics. Investigating the longitudinal relation between CC and phenotypical characteristics of ASD may be important for two reasons. First, theoretically, to determine whether a detail-focused cognitive style and superior disembedding performance reflect an underlying cognitive marker, which may partly explain the future course of phenotypical characteristics of ASD. Second, clinically, to determine whether a detail-focused cognitive style may be a potential prognostic marker that might be used to predict future symptom severity. For these reasons, the current longitudinal study investigated whether a detail-focused cognitive style (i.e. disembedding performance as assessed with the CEFT (Witkin et al.,1971) in childhood predicted ASD symptom severity in adolescence (as assessed with the Autism Diagnostic Observation Schedule ([ADOS] Lord et al., 2002; Lord et al., 2012), Calibrated Severity Scores [CCS], domain of Repetitive and Restricted Behaviors and Interests [RRBI]. Based on previous cross-sectional findings (Chen et al, 2009) it was hypothesized, that a detail-focused cognitive style in childhood, predict more severe RRBI symptoms in adolescence.

METHODS

Participants

Participants were 87 individuals with a clinical DSM-IV-TR classification of ASD in childhood (T1: age 6-12; Eussen et al., 2013) who were followed up into adolescence (T2: age 12-19). The average time between the two assessment waves was 6.88 years (SD = .66).

Initially, all individuals were referred for psychiatric evaluation to the outpatient Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Centre Rotterdam, the Netherlands, specialized in diagnosing individuals, presenting with milder or atypical symptoms of ASD with an average intelligence. In total, 503 children between 6 and 13 years of age were referred between July 2002 and September 2004 (T1; De Bruin et al., 2007b) and these children were screened on eligibility for the current study. Of these 503 children, 114 children met the inclusion criteria for the current study, which were (a) a clinical DSM-IV-TR

classification of ASD, (b) total IQ >=70 (c) absence of severe neurological or physical problems (e.g. blindness), and (d) absence of difficulties with the Dutch language in the parents (De Bruin et al., 2007b). The other 389 participants were not eligible for the study, because these children had other diagnoses than ASD (n=338), an IQ below 70 (n=41), or they met one of the other exclusion criteria (n=10). The clinical DSM-IV-TR classification was obtained by a multi-disciplinary team on the basis of elaborate assessment of early development, semi-structured interviews carried out with parents or caretakers, psychiatric observation of the child in a one-to-one situation, psychological assessment, a parent questionnaire: the Children's Social Behaviour Questionnaire ([CSBQ]; Luteijn et al., 2000a), medical information and school information (Eussen et al., 2013; Greaves-Lord et al., 2013). Of the 114 children meeting the inclusion criteria, 8 (7.0 %) met DSM-IV TR criteria for Autistic Disorder; 10 patients (8.8 %) met criteria for Asperger Syndrome and 96 patients (84.2 %) received the diagnosis PDD-NOS. Furthermore, an extensive neuropsychological assessment was performed, including tests on CC and EF.

At follow-up, at the second assessment wave (T2), 87 (76.3%) of the 114 initially selected children agreed to participate in the follow-up study, implicating a drop-out rate between T1 and T2 of 23.7%. The 87 T2 participants did not differ from the 27 adolescents who did not participate at T2 with regard to gender, initial age, IQ, scores on the CSBQ, the parent questionnaire, and on ADOS total score at T1. At T2, diagnosis was obtained by combining ADOS total scores with data from the Autism Diagnostic Interview-revised (ADI-R; Lord, 1994). According to these rather strict criteria, 16 participants (18.4 %) had autism; 47 participants (54.0 %) had autism spectrum disorder and 24 participants (27.6 %) did not meet criteria for a diagnosis within the autism spectrum.

Ethics

At Time 1, parents/caretakers of the participating children signed informed consent forms prior to participation in the study. At Time 2 both parents and adolescents signed the informed consent forms. The Medical Ethics Committee of the Erasmus Medical Centre approved the study.

Procedure:

At T1, after finishing the diagnostic assessment and the ADOS, psychological assessment and testing were performed on two occasions, separated by a week, in a quiet room and always in the morning to minimize effects of fatigue and to maximize concentration. At the first occasion, the Wechsler's Intelligence Scale for Children (WISC-R) was administered. During the second visit, a test on central coherence, namely the CEFT was administered.

At T2, approximately seven years later, the ADOS was again administered to assess ASD symptom severity at T2.

Materials:

Children's Embedded Figures Test (CEFT)

The CEFT (Witkin et al., 1971) is a perceptual task, which has been widely used to assess visual-spatial cognitive style. Participants are required to locate a previously seen, hidden figure (namely the shape of 1. a tent or 2. a house) within a larger complex and abstract design. In the first practising part, that is preceding the test, children are allowed to look at a specimen of the tent or the house shape. In eleven of the figures (set A), the simple condition, the outline of a tent (triangle) is embedded. In the next fourteen figures (set B), the complex condition, the outline of a house (pentagon) is embedded. Children are instructed to try and find the embedded shapes as quickly as possible. Whether the child is able to detect the embedded shape is noted for each trial (i.e. accuracy score). The time needed to correctly spot the shape of the tent (set A) in the simple condition or the house (set B) in the complex condition, is the reaction time (RT) which was recorded using a stop watch.

Children with ASD in general perform well on the CEFT because they are not captured by the global image, which allows them to focus on the individual elements and find the hidden targets quickly and accurately (Jolliffe & Baron-Cohen, 1997; Edgin & Pennington, 2005; Pellicano et al., 2005; Pellicano et al., 2006; De Jonge et al., 2006). As such, fast reactions (i.e. short RT's) and high accuracy on the CEFT reflect a more detail-focused cognitive style. Because the superior performance of children with ASD mostly shows in the complex condition (Schlooz et al., 2006) and because ceiling effects may play a role in the simple condition (Schlooz et al., 2006), a ratio of scores between the two conditions reflects performance across conditions. Thus, both for accuracy and RT scores in the complex (house) versus the simple (tent) condition, the ratio's between the scores in the complex versus the simple condition were calculated, to provide indices reflecting performance in one condition relative to another. As for the RT scores, only the reaction times in the correct trials were used (as suggested by Happé et al., 2001 and De Jonge et al., 2006), since usually a relatively long RT is registered when a subject fails to detect the pattern, i.e. difficulties with accuracy have a large influence on the reaction times (De Jonge et al., 2006; White & Saldana, 2011). Thus, two separate ratio's were calculated: 1. the ratio of the accuracy in the complex (house) versus the simple (tent) condition (CEFT Acc. Ratio); and 2. the ratio of the reaction times in the complex versus the simple conditions (CEFT RT Ratio). Finally, an overall performance index was calculated, i.e. the accuracy in the complex condition divided by the RT in the complex condition

(CEFT Perf. Ratio). Scores on each of these three indices are higher in a child with superior disembedding performance, because accuracy and RT in the complex condition will be relatively good compared to the simple condition (which serves as an intra-individual control situation). The CEFT Perf. Ratio is higher in a child with superior disembedding capacities, because this child is capable of correctly identifying complex figures from a background in a shorter amount of time.

Outcome measure at T2: Autism Diagnostic Interview Schedule (ADOS):
The ADOS was used to assess the severity of RRBI at T1 and T2. The ADOS is considered to be a "gold standard" diagnostic tool and provides a standardized context for observation and scoring of ASD symptoms in the domains of Language and Communication, Reciprocal Social Impairments, and Stereotyped Behaviours and Restricted Interests. Lord and colleagues (2002, 2012) showed that the psychometric properties of the ADOS and the ADOS-2 are good with an excellent internal consistency. The ADOS comprises four age appropriate modules (Lord et al., 2002). At T1 the ADOS module 3 was used (Lord et al., 2002; Gotham et al., 2007; Gotham et al., 2009). At T2, ADOS module 4 was primarily used, although in nine children module 3 was used (Lord et al., 2012). The observation of the children was performed by trained and certified clinicians who were blind for all previous diagnostic information. ADOS items are scored on a 4-point scale from 0 (no evidence of abnormality related to autism) to 3 (definite evidence of abnormality related to autism). Some items include a score of 3 to indicate particularly severe abnormalities. However, in the ADOS scoring algorithm, scores of 3 are converted to 2 scores, thus in the scoring algorithm, scores of 0, 1 or 2 are used. We used the ADOS calibrated severity scores for RRBI for ADOS module 4 (Hus et al., 2013).

Putative covariates:

Age:
Age was taken into account as possible covariate, because a positive association between age and performance on the CEFT has been found (Jarrold et al., 2005; Bolte et al., 2007; Chen et al., 2009; White & Saldana, 2011).

IQ, measured with WISC-R at T1
Because measures of central coherence might be related to level of intelligence and to performance IQ (Chen et al., 2009; White & Saldana, 2011) and because there might be an association between RRBI symptom severity and intelligence, performance IQ (PIQ) and Verbal IQ (VIQ) at T1 were taken into consideration as putative covariates. The Dutch version of the Wechsler Intelligence Scale for Children-Revised (WISC-R)

was administered (WISC-R Projectgroep, 1986). The WISC-R is composed of several verbal subtests: Information, Similarities, Arithmetic, Vocabulary and Comprehension, and of several performance subtests: Digit Span, Picture Completion, Picture Arrangement, Block Design, Object Assembly, Coding and Mazes. Like the original version, the Dutch version has good reliability and validity (WISC-R Projectgroep, 1986).

Attention problems:
The level of attention problems was measured with the Child Behavior Checklist, Attention Problems subscale (CBCL, 4-18; Achenbach, 1991). Attention problems (i.e. distractibility) might influence performance on the CEFT, as it was found that hyper-focusing of attention (i.e. low attention problems) was associated with the decreased capacity for switching attention between the global and the local level (Iarocci et al., 2006).

Statistical analyses:

For descriptive purposes, means and standard deviations or frequencies were calculated regarding age, sex, PIQ, VIQ, ADOS RRBI calibrated severity scores (T1 and T2), regarding the CEFT measures on RT and accuracy in the complex and the simple condition and regarding the three ratio's CEFT Acc. Ratio (the accuracy ratio of the complex versus the simple condition), the CEFT RT Ratio (the RT ratio of the complex versus the simple condition) and the CEFT Perf. Ratio (accuracy in complex condition divided by time needed)

Analyses were conducted in two steps:

(1) Identification of relevant covariates: To examine which variables needed to be included as covariates in the main analyses, bivariate correlations between putative covariates (i.e. age, sex, VIQ, PIQ, attention problems) and the predictor variables (i.e. CEFT measures) were calculated using Pearson's correlations in the case of continuous variables or Spearman's correlations in the case of ordinal variables. Bivariate correlations between the putative covariates and the outcome variable (T2 ADOS CSS RRBI) were calculated in the same way. Covariates were retained in the subsequent analyses if a covariate correlated both with the predictor and with the outcome variable.

(2) Multiple regression analyses examining whether the three indices of detail-focused cognitive style, namely: 1) CEFT Acc. Ratio, 2) CEFT RT Ratio and 3) CEFT Perf. Ratio were predictive of ADOS RRBI calibrated severity scores (CSS) at T2, while taking into account relevant covariates (resulting from step 1) as well as baseline (i.e. T1) levels of ADOS RRBI CSS. In other words, we tested whether these three CEFT measures were predictive of T2 ADOS RRBI CSS over and above the effect of concur-

rent (i.e. baseline/T1) ADOS RRBI CSS. Three separate sets of regression analyses were performed for these three ratio's, because these indices were based on the same variables and thus were interrelated. The explained variance was calculated for these three ratio's in order to determine which measure constituted the most critical and influential factor. Forward regressions were performed to isolate the most powerful predictors of the T2 ADOS RRBI score among the CEFT measure, T1 ADOS RRBI CSS and potential covariates.

For all analyses, we used SPSS software (Version 20.0). All analyses were two-tailed, and the alpha was set at 0.05.

RESULTS:

Descriptives

Table 1 provides the descriptive information on the demographic characteristics of the sample, the putative covariates (i.e. sex, age, FSIQ, VIQ and PIQ), predictors (accuracy and RT in the simple and complex CEFT conditions and the CEFT Acc. Ratio, the CEFT RT Ratio and the CEFT Perf. Ratio), the covariate ADOS RRBI CCS T1 and the outcome measure ADOS RRBI CCS T2.

Identification of relevant covariates

As shown in Table 2, a significant correlation was found between age and the CEFT Acc. Ratio (r=.46; p=<.01), between age and CEFT Perf. Ratio (r=.50; p=<.01) and between age and ADOS RRBI CSS T1 (r=.24; p=.01) . Significant correlations were also found between FSIQ and CEFT Acc. Ratio (r=.27; p=.01) and between FSIQ and CEFT Perf. Ratio (r=.23; p=.03). High correlations were also found between PIQ and ADOS RRBI CSS T1 (r=.25; p=.02), between PIQ and CEFT Acc. Ratio (r=.36; p<.01) and between PIQ and CEFT Perform. Ratio (r=.39; p=<.01).

No other significant correlations were found. Because none of the putative covariates correlated significantly with the predictor variables (i.e. CEFT measures) as well with the outcome variable (ADOS RRBI CCS T2), none of these variables were included in the subsequent regression analysis.

Main analyses

In all analyses, the ADOS RRBI CSS T1 was included to determine whether our CEFT indices predicted outcome on the ADOS RRBI at T2 over and above the influence of the ADOS RRBI CSS T1 scores. No further covariates were entered in the models, since none of these variables correlated significantly with the predictor as well the outcome variables. Using the CEFT Acc. Ratio as predictor variable resulted in a

Table 1: Descriptives of the sample

	Mean (SD)	Range
Gender	89.6% boys	
Age at T1	9.23 (1.85)	6.54-13.02
FSIQ at T1	95.8 (14.4)	70-128
PIQ at T1	98.3 (15.4)	61-129
VIQ at T1	97.0 (14.1)	65-144
Attention problems CBCL raw scores	9.7 (3.7)	2-18
ADOS total, weighted scores T1	.55 (.28)	.00-1.44
ADOS RRBI CSS T1	4.56 (2.38)	1.0-9.0
ADOS total, weighted scores T2	.56 (.25)	.07-1.32
ADOS RRBI CSS T2	5.83 (1.86)	1.0-10.0
CEFT RT simple condition	8.0 (3.7)	1.7-18.0
CEFT RT complex condition	15.6 (7.8)	3.1-43.9
CEFT RT Ratio (complex/simple)	2.1 (1.1)	.64-8.34
CEFT accuracy simple condition	7.1 (2.3) [64.5%]	2-11
CEFT accuracy complex condition	5.4 (3.4) [38.6%]	0-13
CEFT Acc. Ratio (complex/simple)	.79 (.40)	0-1.75
CEFT Perf. Ratio (accuracy/RT)	.42 (.33)	0-1.50

Caption Table 1: FSIQ at T1: Full Scale IQ as measured by WISC-R. PIQ at T1: Performance IQ as measured at T1. VIQ at T1: Verbal IQ as measured at T1. Attention problems: raw scores on the attention problems scale of the CBCL; 9 items were scored as 0,1 or 2; resulting in a minimum score of 0 and a maximum score of 18. ADOS total, weighted scores at T1 and at T2: mean score per item on the ADOS for all domains. ADOS RRBI CSS at T1 and T2: Calibrated Severity Scores on the ADOS, domain of Repetitive and Restricted Behaviors and Interests. CEFT RT simple: mean score in seconds on the simple (tent) condition of the CEFT. CEFT RT complex: mean score in seconds on the complex (house) condition of the CEFT. CEFT RT Ratio: ratio between the time needed to complete the complex and the simple task. CEFT accuracy simple: mean number of correct answers in 11 trials of the simple (tent) CEFT condition. Percentage accuracy between brackets. CEFT accuracy complex: mean number of correct answers in 14 trials of the complex (house) condition. Percentage accuracy between brackets. CEFT Acc. Ratio: ratio of the accuracy in the complex and the simple condition. CEFT Perf. Ratio: accuracy in complex condition divided by RT in complex condition.

model with good characteristics ($F(2,76) = 6,9$; $R2=.15$; $p<.01$). The CEFT Acc. Ratio significantly predicted ADOS RRBI CSS T2 scores, explaining 13 % of the variance in the outcome measure ($p< .01$; $\beta = .35$; 95% CI= .67- 2.66, $\Delta R2=.13$; Table 3), representing a medium effect size. The CEFT RT Ratio yielded a non-significant model. Using the CEFT Perf. Ratio also yielded a model with good characteristics ($F(2,74) = 7,6$; $R2=.17$; $p<.01$; Table 3). The CEFT Perf. Ratio explained 15% of the variance in the outcome measure ($p< .01$; $\beta = .37$; 95% CI= .93-3.50; $\Delta R2=.15$; Table 3), representing a medium effect size. Thus higher performance in the complex condition of the CEFT, indicative of superior

Table 2: Bivariate correlations (r) and levels of significance (p) between the covariates (age, IQ, PIQ, VIQ, sex), predictor variables (CEFT time complex/simple; CEFT accuracy complex/simple) and outcome variables (ADOS T2 CSS RRBI;).

r, p	CEFT RT Ratio	CEFT Acc. Ratio	CEFT Perf. Ratio	Age	VIQ	PIQ	Att. Problems	FSIQ	ADOS RRBI CSS T1	ADOS RRBI CSS T2
CEFT RT Ratio	1									
CEFT Acc. Ratio	-,104	1								
	,353									
CEFT Perf. Ratio	-,185	,673**	1							
	,10	,000								
Age	-,134	,459**	,50**	1						
	,226	,000	,000							
VIQ	,118	,085	,002	-,009	1					
	,287	,438	,99	,932						
PIQ	,132	,360**	,39**	,131	,547**	1				
	,235	,001	,001	,196	,000			,		
Attention problems	-,10	-,20	-,135	-,12	,02	-,23*	1			
	,39	,08	,246	,30	,86	,04				
FSIQ	,142	,272*	,23*	,067	,880**	,876**	-,13	1		
	,200	,012	,03	,508	,000	,000	,25			
ADOS RRBI CSS T1	-,177	,006	,009	-,244*	-,077	-,246*	,08	-,179	1	
	,110	,960	,94	,013	,450	,014	,46	,077		
ADOS RRBI CSS T2	-,219	,368**	,38**	,049	-,125	,038	,08	-,041	,17	1
	,056	,001	,001	,643	,237	,722	,53	,701	,12	

Caption: CEFT RT Ratio= Reaction time on the CEFT complex condition relative to simple condition. CEFT Acc. Ratio= Accuracy on the CEFT complex condition relative to simple condition. CEFT Perf. Ratio= Accuracy on the CEFT, complex condition divided by time needed to complete the task. VIQ= Verbal IQ. PIQ=Performance IQ.Att. Problems=Attention Problems on CBCL

FSIQ=Full Scale IQ. ADOS RRBI CSS T1= Autism Diagnostic Observation Schedule, domain Restrictive and Repetitive Behaviors and Interests Calibrated Severity Scores at T1. ADOS RRB CSS T2= Autism Diagnostic Observation Schedule, domain Restrictive and Repetitive behaviors Calibrated Severity Scores at T2.

*significant at p<.05 level and ** significant at p<.01 level.

Table 3. Multiple regression analyses with ADOS RRBI CSS at T2 as outcome variable and ADOS RRBI CSS T1 as covariate

	Beta	t	p	F, df	95% CI Lower	95% CI Upper	R2
Set 1: Predictor CEFT RT Ratio (RT complex relative to simple)							
Model			.08	(2,74)=2.7			.07
CEFT RT Ratio	-.20	-1.53	.13		-.69	.09	.04
ADOS RRBI CSS T1	.14	1.19	.23		-.008	.30	
Set 2: Predictor CEFT Acc. Ratio (accuracy complex relative to simple)							
Model			<.01	(2,76)=6.9			.15
CEFT Acc. Ratio	.35	3.3	.01		.67	2.66	.13
ADOS RRBI CSS T1	.14	1.3	.20		-.06	.28	
Set 3: Predictor CEFT Perf. Ratio (accuracy complex divided by time needed)							
Model			<.01	(2,74)=7.6			.17
CEFT Perf. Ratio	.37	3.4	<.01		.93	3.5	.15
ADOS RRBI CSS T1	.15	1.4	.16		-.005	.29	

Caption: CEFT RT Ratio= Reaction time on the CEFT complex condition relative to simple condition. CEFT Acc. Ratio= Accuracy on the CEFT complex condition relative to simple condition. CEFT Perf. Ratio: Accuracy on the CEFT, complex condition divided by time needed to complete the task. ADOS RRBI CSS T1 or T2 = Calibrated Severity Scores on the Autism Diagnostic Observation Schedule, domain Restrictive and Repetitive Behaviors and Interests at T1 or at T2.

disembedding performance and high accuracy in the complex CEFT condition relative to the simple condition both predicted higher ADOS RRBI CSS scores seven years later.

DISCUSSION:

The aim of the current study was to explore whether a detail-focused cognitive style (i.e. a superior disembedding performance) in childhood predicted higher RRBI symptom severity in adolescence in individuals with ASD. We found that a superior disembedding performance -as assessed in childhood using the CEFT- predicted higher scores on the ADOS RRBI CSS seven years later, while controlling for childhood levels of RRBI. The overall performance in the complex condition accounted for fifteen percent of the variance in the T2 ADOS RRBI CSS, which represents a medium effect size. This finding is relevant considering the cognitive styles that underlie ASD (i.e.'endophenotypes'), as well as for clinical practice (i.e. the potential prognostic value of cognitive tests).

WCC as an underlying cognitive style

The theoretical concept of Weak CC contains two independent dimensions, namely a reduced tendency to integrate information (diminished global processing) and an increased tendency to process specific features (augmented local processing) (Happé & Booth, 2008). Our finding pertains to the augmented tendency for local processing, namely superior disembedding performance on specific tests. Aspects of global processing are not addressed in the current study. A more refined version of the CC theory states that shifting attention between the local and the global level is hampered in ASD and that individuals with ASD by preference focus on local aspects of a situation. We did not directly test this latter theory, but in our analyses we considered whether the level of attention problems influenced the main effects we found, which was not the case.

An intriguing discussion is whether weak CC or more specifically a detail-focused cognitive style in ASD qualifies as an endophenotype for this condition. Our finding that a detail -focused cognitive style predicts future symptom severity may demonstrate its potential as an endophenotype. Further arguments in favor are that weak CC has been repeatedly demonstrated in individuals with ASD (O'Riordan et al., 2001; Edgin & Pennington, 2005; Jarrold et al., 2005; Pellicano et al., 2005; Pellicano et al., 2006; De Jonge et al., 2006); and in their non-affected relatives (Bolte et al., 2007). However, previous findings that weak CC is not specific for ASD, but has also been found in schizophrenia, Williams syndrome and right hemisphere dysfunction (Happé & Frith, 2006) constitute an argument against weak CC as an exclusive endophenotype for ASD. Furthermore, the effect sizes of the difference found between individuals with ASD and neurotypicals are usually small (White & Saldana, 2011). The question whether weak CC is an exclusive endophenotype for ASD cannot be settled by the current study, because we did not compare the predictive value of childhood CEFT for future symptom severity between ASD and other disorders like psychosis.

The underlying brain mechanisms of a detail-focused cognitive style are not yet fully understood. In the field of visual perception, using texture discrimination tasks and Event Related Potentials (ERP's), it has been demonstrated that the balance of feedforward processing (from primary visual cortex to integrative fields in the infero-temporal cortex) and feed-back processing (control loops back from secondary visual fields to primary fields) may be disturbed in ASD. By presenting visual stimuli, which disentangle feedforward and feedback processing, it has been demonstrated, that in ASD visual feed-back processing is relatively strong in relation to feed forward processing (Dakin & Frith, 2005; Vandenbroucke, 2008; Vandenbroucke, et al., 2009; Simmons et al., 2009 for an overview). ERP research, especially research on Mismatch Negativity (MMN: negative component of ERP as a reaction to

an odd auditory stimulus within a sequence of highly predictable auditory stimuli) has revealed, that participants with ASD are very sensitive in noticing low-level local changes (showing in enhanced and earlier MMN sensory responses), but have difficulties with picking-up changes in the high-level, global fronto-parietal predictive system (Van de Cruys et al., 2014). In several functional Magnetic Resonance Imaging (fMRI) studies, in which participants performed the CEFT, an increased visual cortical activation and a decreased prefrontal activation was found in participants with ASD as compared to TD individuals (Lee et al., 2007). This increased visual cortical activation in the CEFT is in line with increased bottom-up visual processing in ASD as hypothetised by the aberrant precision theory of Lawson et al. (2014). It has also been postulated that the detail-focused cognitive style mirrors a reduced long distance connectivity in brain circuits in relation to an overdeveloped local circuitry (Minshew & Williams, 2007). This enhanced local circuitry in individuals with ASD has not yet been empirically demonstrated. Two studies investigated fMRI indices of functional connectivity in school aged children with ASD, with one study finding evidence for long distance under connectivity (Mostofsky et al., 2009), but the other study not finding such support (Lee et al., 2009). To summarize: data from visual perception, ERP and fMRI studies provide evidence for enhanced local processing or detail oriented cognitive style in ASD, which line up with the current findings.

Clinical significance of disembedding performance

Our finding that a superior disembedding performance is associated with restricted and repetitive behaviors is in accordance with the cross-sectional findings of Chen et al. (2009). We add to their findings by using a longitudinal approach: a superior disembedding performance is not only related with concurrent RRBI, but also predicts later RRBI symptom severity. Given the controversies about the usefulness of visuo-spatial tasks in clinical practice (White & Saldana, 2011) and the necessity to use these tasks in a standardized and subtle way (De Jonge et al., 2006), we recommend careful use of the CEFT and to be prudent in the interpretation of the test results.

Methodological considerations and directions for future research

The longitudinal design with a 7-year follow-up using the ADOS in a relatively large sample is a strength of the current study. Yet, several methodological pitfalls of research on the CEFT have been previously discussed: scores on the CEFT are related to the age of participants and to their PIQ; and studies with positive results often have small sample sizes (White & Saldana, 2011). Along with this, the effect-size of the differences between TD children and children with ASD on the CEFT tests are usually small (White & Saldana, 2011). In the current study we avoided these

pitfalls by considering the effects of age and PIQ. Also, we investigated a relatively large sample of 87 individuals, and we were able to reveal an effect with a moderate effect size.

We found a positive association between age and performance on the CEFT, which is in accordance with the findings of other authors (Jarrold et al., 2005; Bolte et al., 2007; Chen et al., 2009). This association mirrors the ongoing cognitive development. We also found a positive association between CEFT accuracy and IQ measures (FSIQ and PIQ) at T1, which is in accordance with Chen et al. (2009).

An elegant aspect of the central coherence theory is that it explains the weaknesses of individuals with ASD (i.e. the reduced capacity to integrate information), but also their strengths (the ability to focus on details). In the current study, we found that superior disembedding performance was related with a higher RRBI symptom severity at follow up, but also with a higher concurrent PIQ. Thus, although the human tendency to focus initially on the global aspects before allocating attention to local or detailed features has proven to be an advantage during evolution (Navon, 1977), the detail-focused orientation of people with ASD may also offer advantages in our modern world with increasing application of technology, as individuals with ASD rely on concrete sensory input and display a high perceptual precision. However, these perceptual advantages are bought at the price of a tendency towards sensory overload, which manifests itself as repetitive and ritualistic behaviors, insisting on sameness, and high levels of anxiety and stress in complex situations. (Lawson, 2014; Van de Cruys, 2014). Therefore, we encourage future research not only to focus on the relation of detail-focused cognitive style with the weaknesses of individuals with ASD, but also with the strengths of people with ASD (Happé & Frith, 2006, Pellicano, 2010), for instance in computer related tasks.

Finally, we want to emphasize that all participants were referred to a university outpatient clinic for child and adolescent psychiatry, specialized in diagnosing cognitively able children with ASD. The current study thus only included this subgroup of individuals with ASD; therefore conclusions and implications should be confined to this particular sub-population of children with ASD.

This study endorses the use of visuo-spatial tasks on disembedding performance as a tool to predict future severity of restricted and repetitive behaviors. It would be useful to acquire more detailed information on the developmental course of ASD and the prognostic significance of visuo-spatial tests on disembedding performance by assessing different visuo-spatial measures of CC (CEFT, Rey's complex figure, Navon tasks) repeatedly throughout development in individuals with ASD.

CONCLUSIONS:

A detail oriented cognitive style in childhood, operationalized as superior disembedding performance on a visuo-spatial test, predicted RRBI symptom severity in adolescence in 87 children with ASD over and above RRBI symptom severity in childhood. Therefore a detail oriented cognitive style partially determines future symptom severity in ASD between childhood and adolescence. This underscores the usefulness of visuo-spatial tasks in the assessment of ASD and it strengthens the arguments for using a detail oriented cognitive style as an endophenotype for ASD.

Chapter 7

GENERAL DISCUSSION

Mart L.J.M. Eussen

INTRODUCTION

The aim of this thesis was to examine the phenotypical heterogeneity of ASD (Part 1: Chapter 2 and 3), using a cross-sectional design; and to examine the predictive value of three putative endophenotypes for future symptom severity in ASD (Part 2: Chapter 4, 5 and 6), using a longitudinal design.

In the current chapter, the main results (as summarized in table 7.1) are discussed in the light of the existing literature. Then, methodological considerations concerning the studies in the current thesis are discussed, and clinical implications and recommendations for future research are given.

PART 1: PHENOTYPICAL VARIATION IN CORE ASD AND CO-OCCURRING PSYCHIATRIC SYMPTOMS

Main findings

The first cross-sectional study (chapter 2) aimed at studying phenotypical variation of individuals with ASD without a theoretical a priori bias by using latent class analysis on ADOS data of 234 six to twelve year old children. Three classes of children were distinguished: one class with high levels of symptoms in all three ASD symptom domains, a second class with moderate levels of symptoms in all three ASD symptom domains, and a third class with low levels of symptoms in all three ASD symptom domains. This kind of distribution, namely three classes which differ only in levels of severity, favours a dimensional model of ASD. A categorical model would reveal different profiles of symptoms among classes, for instance one class with high symptom levels on social interaction and low symptom levels on RRBI or vice versa. Children with low and moderate levels of ASD symptoms showed significantly higher levels of co-occurring internalizing and externalizing problems than children with high levels of ASD symptoms. Differences were particularly found regarding anxiety and conduct problems; children with moderate ASD symptoms especially showed problems in regulating their emotions and behaviors.

As for co-occurring psychiatric symptoms, in chapter 3 it was further investigated how anxiety was related to ASD symptom severity, to quality of social relations and to intelligence. In a multivariate model, overall ASD symptom severity was inversely correlated with anxiety. Better quality of social relations was associated with lower anxiety levels and no association with IQ was observed.

High anxiety levels were correlated with lower ASD symptom severity, which is in line with the findings of other authors (i.e. Szatmari, Bartolucci, Bremner et al., 1989; Gadow, Devincent, Pomeroy et al., 2005; Pearson, Loveland, Lachar et al.,

Table. 7.1 Main findings

Research Questions	Main findings
Part I:	
1 a. Do symptom profiles of children with ASD support a dimensional or a categorical view of ASD?	a. Using latent class analysis a three class model was found with low, medium or high symptom severity in each domain. This supports a dimensional model of ASD.
b. How are co-occurring psychiatric symptoms related to the severity of core ASD symptoms?	b. More co-occurring anxiety symptoms and more externalising problems were found in the group with mild symptom severity, indicating a reverse relationship between severity of core ASD symptoms and co-occurring psychiatric symptoms.
2 a. Which of three important determinants for anxiety contributes most to the manifestation of anxiety in ASD: quality of social relations, ASD symptom severity or intelligence ?	a. ASD symptom severity contributed with medium effect size to anxiety; quality of social relations with a small effect size and intelligence did not show a significant association with anxiety levels.
b. Do ASD symptom severity or intelligence moderate the relation between quality of social relations and anxiety in children with ASD ?	b. ASD symptom severity and intelligence did not moderate the relation between quality of social relations and anxiety in children with ASD.
Part II: outcome in adolescence of children with symptoms of ASD	
3. Does formal thought disorder in childhood predict high symptom severity of ASD in adolescence? Does formal thought disorder in childhood predict prodromal symptoms of psychosis in adolescence?	One type of formal thought disorder, i.e. illogical thinking predicted a higher ASD symptom severity seven years later. Formal thought disorder did not predict prodromal symptoms of psychosis in adolescence.
4. Does a slow or an inaccurate facial recognition or identification of facial emotions in childhood predict a higher symptom severity of ASD in adolescence?	A less accurate facial recognition predicted a higher ASD symptom severity in adolescence. Slow facial recognition or the accuracy or time measures on identification of facial emotions did not predict higher ASD symptom severity in adolescence.
5. Does a detail oriented cognitive style in childhood predict higher symptom severity in the repetitive and restrictive behaviours domain in adolescence ?	A detail oriented cognitive style, namely a superior disembedding performance, predicted higher symptom severity in the repetitive and restrictive behaviours domain in adolescence

2006; Mazurek & Kanne, 2010). A better quality of social relations was associated with less anxiety which is in line with findings in non-ASD samples (La Greca & Lopez, 1998; Ginsburg, La Greca, Silverman, 1998) and in samples of children with ASD (White & Roberson-Nay, 2009 b; Mazurek & Kanne, 2010).

In the study on core and co-occurring symptoms (n=234; chapter 2) we found an inverse relation between symptom severity and co-occurring symptoms, while in

a more recent, larger study (n=949 (Greaves-Lord, Eussen, Verhulst et al., 2013), we found a positive relationship between symptom severity and co-occurring symptoms. There are however important methodological differences between the studies that may explain this difference in results. In the study based on the smaller sample (chapter 2), a semi-structured observation schedule, the ADOS was used to assess ASD symptom severity while in the larger study (Greaves-Lord et al., 2013), a parent rapport, the Childhood Social Behaviour Questionnaire (CSBQ) was used to assess ASD symptom severity. The fact that ASD symptom severity was assessed by a clinician based on a 45 minute direct observation in one study and by parents based on their observations during the past six months in the second study, may partly explain the differences in the results. Different raters report on behaviours, observed across different settings; thus scores do show discrepancies (i.e. Laird & De Los Reyes, 2013). Moreover, it has been shown that the concurrent validity of ADOS and CSBQ was modest on the "understanding", "change", "tuned" and "orientation" scales of the CSBQ and reasonable on the "contact" and "stereotypy" scales (De Bildt, Mulder, Hoekstra et al., 2009). Thus, although these measures both assess the construct of ASD severity, they may not tap onto exactly the same underlying ASD features (i.e. content validity). For this reason in ASD diagnostic assessment it is recommended to use both type of measures and combine them in order to get a more reliable diagnostic picture (Kanne, Abbacchi, Constantino, 2009). Since our findings are contrasting when investigating the measures separately, this again emphasises the importance of the combination of information on ASD symptom severity from different sources.

The overall conclusion from the studies on phenotypical variation are threefold: the distribution of core symptoms, that we found, strongly favours a dimensional model of ASD; high scores on internalizing and externalizing problems, but especially on anxiety were found in individuals with less severe core ASD symptoms and more anxiety was associated with less ASD symptom severity and with a worse quality of social relations. Two explanations for the inverse relationship between symptom severity and anxiety have been brought forward. Perhaps, ASD children with milder impairments are placed in more challenging social situations, because their social abilities are overestimated by the environment, with an increased level of anxiety as a result (Pearson et al., 2006). A second explanation could be, that the awareness of own social deficits and the confrontation with social failure may contribute to anxiety in children with ASD and an average to high IQ (Bellini, 2004; Chamberlain, Kasari, Rotheram-Fuller, 2007). In severe cases of ASD poor emotional understanding and worse perspective-taking skills may act as a buffer against developing anxiety symptoms (Mazurek & Kanne, 2010). This mechanism has more provocatively been called "ignorant bliss" or "happy obliviousness" (Chamberlain et al., 2007).

PART 2: THE ASSOCIATION OF PUTATIVE ENDOPHENOTYPES IN CHILDHOOD WITH ASD SYMPTOM SEVERITY IN ADOLESCENCE.

Main findings

Three putative endophenotypes were tested for their association with future ASD symptom severity: 1) formal thought disorder, which is considered as a linguistic endophenotype by some investigators and as an social cognitive endophenotype by others (Docherty, McCleery, Divilbiss et al., 2013); 2) facial and emotion recognition, a social cognitive endophenotype and 3) a detail oriented cognitive style, a non-social endophenotype. The underlying idea was that the presence of these presumed endophenotypes may have an important influence on further development and future course. It is considered an ideal demonstration of causality, when an endophenotype measure at T1 predates the emergence of certain symptoms or pathological behavior at T2 (De Geus & Boomsma, 2001; Viding & Blakemore, 2007). Almost all previous studies on endophenotypes in ASD are based on cross-sectional data and there are almost no studies on longitudinal associations between presumed endophenotypes and the developmental course of ASD.

Formal thought disorder (FTD, chapter 4): The presence of illogical thinking predicted the severity of autistic symptoms seven years later while illogical thinking or loose associations did not predict prodromal symptoms of psychosis seven years later. Therefore FTD in ASD may not be an early sign of psychosis, but rather a manifestation of the social communication difficulties that by definition are part of ASD. The finding that illogical thinking in this study predicted severity of autistic symptoms at T2 seven years later with a medium effect size, even when taking the ADOS scores in childhood (T1) into account, underscores the importance of illogical thinking as a predictor for the future severity of ASD. The contribution of the present study is that these findings are replicated and extended using longitudinal data, thereby fulfilling the developmental criterion of an endophenotype.

One should note that perhaps the relation between FTD and impending psychosis could not be demonstrated in view of the young age of the participants in our sample. The average age at which individuals manifest a first episode psychosis is 19 years for males and 22 year for females; prodromal symptoms emerge around two years earlier (Armenteros & Davies, 2006). Therefore, the adolescents in our sample aged between 12.8 and 19 years at T2, may still be too young to display prodromal symptoms of psychosis and might go on to develop prodromal symptoms in the next five years.

FTD meets some of the criteria, which must be fulfilled to qualify as an endophenotype (Table 7.2). The association of FTD with ASD has been demonstrated (Solomon, Ozonoff, Carter et al., 2008) and it has been shown that FTD is a trait of

Table 7.2: Fulfillment of general criteria for endophenotypes by the three proposed endophenotypes

	Formal thought disorder (FTD)	Facial and Emotion Recognition (FR and IFE)	Detail oriented style; Weak Central Coherence
Heritability	+ for schizophrenia ? for ASD	+	+, mixed findings
Associated with specific genotype	?	Polymorphism Oxytocin Receptor- gene and IFE	?
Associated with ASD	+	+	+, mixed findings
Trait marker of ASD	+	+	+
Cosegregation with disorder	+ for schizophrenia ? for ASD	+	?
Runs in non-affected family members	+, for schizophrenia ? for ASD	+	+
Altered brain circuitry	+, for schizophrenia ? for ASD	+	+, mixed findings
Predicts future course	+ This thesis	+ This thesis	+ This thesis

ASD (Van der Gaag, Caplan, van Engeland et al., 2005). However, research on FTD has concentrated more on schizophrenia than on ASD. The heritability of FTD (Docherty & Gottesman, 2000), the co segregation in families (Docherty, Miller, Lewis, 1997) and the emergence of FTD in non-affected family members (Docherty, 2005) have been demonstrated in schizophrenia, but not in ASD. The clinical use of FTD as an endophenotype faces some serious drawbacks: assessing FTD is difficult and time-consuming and it is not clear whether FTD must be further deconstructed into more basic concepts like working memory, sustained attention and sequencing (Docherty, 2005). It is assumed nowadays that autism and psychosis share common pathophysiological mechanisms (Sporn, Addington, Gogtay et al., 2004) and the advantage of FTD is that it lays on a cross-road between ASD and psychosis. For that reason FTD might be helpful to uncover similarities and differences between these disorders. Therefore, despite the lack of studies on FTD in ASD and in ASD multiplex families, it remains an interesting endophenotype, which may constitute a linking pin between psychotic disorders and ASD.

Facial recognition (FR) and identification of facial emotions (IFE, chapter 5): We found that less accurate FR in childhood significantly predicted higher ASD symptom severity scores in adolescence. The association of FR accuracy with ASD severity seven years later remained significant after adjusting ASD symptom severity in childhood. Results did not provide support for our second hypothesis, that childhood IFE scores would be associated with later ASD symptom severity. The current findings

on FR indicate that atypical face processing is indeed present in individuals with ASD and may influence future ASD symptom severity. FR in infants and toddlers has been extensively studied, but there is a lack of knowledge concerning the further development of FR, IFE and social behavior between childhood and adolescence. The current prospective findings thus add to the previous cross-sectional literature regarding FR and IFE.

Our findings lend support to FR as an endophenotype for ASD, because an inaccurate FR predicts future symptom severity, thereby fulfilling the developmental criterion of an endophenotype. Results from a variety of other studies also support the use of FR as an endophenotype for ASD: less accurate FR capacities have been repeatedly demonstrated in individuals with ASD (Klin, Sparrow, De Bildt et al., 1999; Joseph & Tanaka, 2003; Wolf, Tanaka, Klaiman et al., 2008; Weigelt, Koldewyn, Kanwisher, 2012 and 2013); in their non-affected relatives (Bolte & Poustka, 2006) and atypical processing of FR stimuli in participants with ASD has been found in many studies using brain imaging or event related potentials (Schultz, Gauthier, Klin et al., 2000; Pierce, Muller, Ambrose et al., 2001; Dziobek, Bahnemann, Convit et al., 2010; for overview: Harms, Martin, Wallace, 2010). Altogether, FR, which is strongly theoretically anchored in the social motivation and the enactive mind theory, holds a strong argument for being a useful endophenotype of ASD, because the majority of criteria set for endophenotypes are met (Table 7.2.). Arguments against FR as an endophenotype include the mixed findings in the literature (Celani, Battacchi, Arcidiacono, 1999). Detail oriented cognitive style (Chapter 7): The overarching theoretical concept of Weak CC contains two independent dimensions, namely a reduced tendency to integrate information (diminished global processing) and an increased tendency to process specific features (augmented local processing or detail oriented cognitive style) (Happé & Booth, 2008). We found that a superior disembedding performance on visuo-spatial tests or -in other words- an augmented tendency for local processing predicted more RRBI symptoms seven years later. The children with ASD, who performed better and more accurate on the CEFT, had higher scores on the ADOS RRBI, while taking into account childhood levels of RRBI.

Our finding that a detail oriented cognitive style predicts future symptom severity supports its potential use as an endophenotype for ASD, because the developmental criterion of an endophenotype is fulfilled. Detail oriented cognitive style qualifies as an endophenotype for ASD, because it has been repeatedly demonstrated in individuals with ASD (O'Riordan, Plaisted, Driver et al., 2001; Edgin & Pennington, 2005; Jarrold, Gilchrist, Bender, 2005; Pellicano, Gibson, Maybery et al, 2005; Pellicano, Maybery, Durkin et al., 2006; De Jonge, Kemner, van Engeland, 2006) and in their non-affected relatives (Bolte, Holtmann, Poustka et al., 2007). An interesting aspect of this endophenotype is, that it emphasizes superior functioning of ASD children

in a certain domain instead of dysfunctional behavior. Arguments against detail oriented cognitive style as an endophenotype include its moderate sensitivity and moderate specificity, as it has also been found in schizophrenia, Williams syndrome and right hemisphere dysfunction (Happé & Frith, 2006). Weak CC might be better seen as an endophenotype for general disordered brain development rather than for ASD in particular. Research into Central Coherence or a detail oriented cognitive style as an endophenotype for ASD has yielded mixed findings in the past (Happé, Ronald, Plomin, 2006) and this theory lacks support form neurobiological research. However, a recent reformulation of this theory (Pellicano & Burr, 2012; Lawson, Rees, Friston, 2014) has refueled research in this field. These authors interpret the detail oriented style as an overdependence on bottom-up sensory information and the lack of central coherence is interpreted as insufficient confidence in a priori top-down beliefs (Lawson et al., 2014). The empirical evidence for this view is derived mainly from Event Related Potenials (ERP) research, which provides a neurophysiological basis for WCC.

To summarize, we found that FR accuracy and FTD (illogical thinking) predicted higher ASD total symptom severity seven years later and that a detail oriented cognitive style predicted higher symptom severity in the RRBI domain.

Methodological considerations

The specific methodological considerations to each study have been discussed in the previous chapters. In this section methodological considerations, pertaining to all studies will be discussed:

Firstly, in all papers we investigated associations with continuous measures of ASD severity, rather than a comparison among a categorical measure of ASD. Thus, we did not compare between different categories of children, for instance between AD, AS and PDD-NOS and we did not include a control group of typically developing (TD) children. However, in our opinion, advantages of this approach exceeded the disadvantages:

a. it has become increasingly clear that symptoms of ASD are dimensionally distributed and the categorical subclassifications of ASD have been subject of growing criticism. Therefore, investigating ASD using continuous rather than categorical measures, is probably more fruitful than comparing among children of the different presumed subcategories of ASD;

b. an abundance of studies already exists, comparing TD and ASD children or comparing the different diagnostic categories within the autism spectrum on all kinds of parameters. Studies however, which used quantitative measures of severity within the autism spectrum, like we did, are scarce.

Secondly, it seemed counter-intuitive, that a longitudinal association between a presumed endophenotype and the severity of the disorder after seven years persists even after correcting for the cross-sectional association between this endophenotype and the severity of the disorder at the same moment. To our opinion endophenotypical traits keep exerting their influence during development and therefore once subtle phenotypical differences between persons with or without a certain endophenotypical trait may augment in the course of time. For instance, lack of social attention early in life may result in disruptions in social cognition processes, such as less accurate FR. Less accurate facial recognition may have limited influence on autistic symptom severity in childhood, but due to increasing social demands during adolescence, it may exert a larger influence on symptom severity in adolescence. This mechanism can be conceptualised as an interactive process between the endophenotype, which generates a certain vulnerability and increasing demands from the environment. These kind of interactions between a certain vulnerability and level of environmental stress are described in the diathesis-stress model (Zubin & Spring, 1977). If the FR difficulties in ASD would be caused by a static perceptual dysfunction, lower order visual perception would be compromised. If FR difficulties in ASD would arise from a dynamic developmental process as described above than higher order face perception, attention and motivation would be compromised. Indeed ERP studies, which are characterized by an excellent temporal resolution, revealed that lower level visual processing in the occipital cortex, emerging 0-100 milliseconds after an event, is intact in ASD. The following stages of visual perception, emerging 100-400 milliseconds after an event, all seem to be compromised in ASD. Visual attentional processes (striato-prefrontal networks), facial discrimination (fusiform face area) and reward systems i.e. social motivation (orbito-frontal cortex and nucleus accumbens) all show some dysfunctions, supporting the view that different aspects of higher order face perception are affected in ASD (Jeste & Nelson, 2009).

A final methodological consideration concerns the role and the utility of endophenotypes in autism research. The hope and the promise was that endophenotypes would represent simpler clues to genetic underpinnings; would reduce heterogeneity; and would help to bridge the gap between genotype and phenotype (Gottesman & Gould, 2003)). At the genetic level a dazzling complexity rules. Many genes variants, each of a small effect create heterogeneous phenotypical manifestations of ASD and heterogeneous endophenotypical manifestations, as observed for instance in neuropsychological assessment (Reinvall, Voutilainen, Kujala et al., 2013). These genetic risk variants each have probabilistic effects and these gene variants are usually not associated with one psychiatric disorder, but with a range of psychiatric disorders (Rutter & Thapar, 2014). The genetic complexity involves many genes of small

effects; copy number variations, resulting in milder or more severe forms of ASD; and from Genome Wide Association Studies (GWAS) we know that Single Nucteotide Polymorfisms (SNP) in ASD are not only located in the coding regions (exons) of genes, but also in the noncoding or regulatory regions (introns) (Waterhouse, 2011; Rutter & Thapar, 2014). Therefore the chance of finding a one-to-one relationship between an certain endophenotype and a certain genotype in ASD is close to zero and to connect a given endophenotype to a genetic variant we have to understand the complete functional architecture of that gene. Paradoxically, as a result of this dazzling genetic complexity, endophenotypes have gained in importance for two reasons. Nowadays, research on endophenotypes strives after a more modest goal by trying to bridge the gap between the neuropsychological, the cognitive and the neurobiological level, for instance by combining data on neuropsychological and social cognitive tests with event related potentials (neurophysiological) or with fMRI (neuroanatomical). The neuropsychological and social cognitive endophenotypes in ASD are well suited to fulfill an important role in the recently proposed Research Domain Criteria (RDoC) (Cuthbert & Insel, 2013). These RDoC can be conceptualized as a future research paradigm for psychiatry, grounded on the idea that symptom and phenotype oriented research will offer no solutions for psychiatry (Cuthbert & Insel, 2013). According to these RDoC, psychiatric research should be directed first at finding associations between neuropsychological/ social cognitive endophenotypes and altered brain circuitry, which is one level closer to the genotype and in the next step these findings could be combined with data from genetic research. Furthermore, endophenotypes in ASD may hold promise for fruitful and innovative therapeutic interventions, for instance interventions based on ameliorating facial recognition.

Limitations

The specific limitations to each study have been discussed in the previous chapters. In this section, limitations that pertained to all studies will be discussed:

Firstly, we included a specific group of individuals with ASD symptoms in the current studies, i.e. individuals that were referred to one particular university outpatient department of child and adolescent psychiatry/psychology. This university outpatient department is specialised in diagnosing and treating cognitively able children with complicated and non-straightforward forms of ASD. Therefore, the described study sample may not be representative for the total ASD population and certainly children with ASD and an intellectual disability are underrepresented. Including more children with intellectual disability would perhaps have yielded different patterns of comorbidity, for instance more anxiety in children with ASD in the IQ range between 70 and 85 (Van Steensel, Bogels, Perrin, 2011). In the studies

on the predictive value of presumed endophenotypes, we excluded children with IQ's below 70, because these neuropsychological and social cognitive tests cannot be reliably measured in the lower IQ ranges. Including more children with severe and straightforward forms of ASD would probably have strengthened the findings of these longitudinal studies on presumed endophenotypes.

Secondly, in part two (chapters 4, 5, and 6) of this thesis, the outcome in adolescence of individuals with ASD symptoms in childhood was described. We only included two assessment waves, one in childhood and one in adolescence. Therefore, the developmental course of the ASD symptoms between childhood and adolescence could not be monitored with optimal accuracy, as we did not include intermediate assessment waves. For statistical reasons, tracking changes in ASD symptoms over more than two assessment waves may lead to more detailed prognostic estimates, as well as opportunities to study the course of this disorder more precisely (Szatmari, Bryson, Duku et al., 2009; Gotham, Bishop, Hus et al. 2013).

Clinical implications

The results of the first study fit well in a long line of studies, that challenge the validity of existing subtypes of ASD in DSM-IV-TR (i.e. Mandy, Charman, Gilmour et al., 2011; Mandy Charman, Skuse, 2012; Frazier, Youngstrom, Speer et al., 2012). A dimensional distribution fits into the proposal to merge the subtypes into one single domain of ASD (Witwer & Lecavalier, 2008; Lord, Risi, DiLavore et al., 2006).

We found an inverse relation between anxiety and ASD symptom severity; anxiety is most prominent in milder cases of ASD with symptom levels just above the diagnostic threshold of the DSM-IV-TR. Therefore, it is important in these milder ASD cases, to explicitly diagnose the comorbid anxiety disorder in order to facilitate treatment that focuses not only on the social and communication impairments, but also on the co-occurring anxiety.

Existing individual or group treatment programs against anxiety can be administered in a slightly adapted way in children with milder forms of ASD. Chalfant, Rapee, Caroll (2007) and van Steensel et al. (2011) showed that high functioning ASD children benefited from cognitive behavioural therapy for anxiety, which was adapted to the more concrete learning style of these children, focussing on exercises and practice instead of verbal interventions, and in which children were allowed to choose functional thoughts from a list of possible alternatives. The effects of cognitive behaviour anxiety therapy in children with ASD are supported by a small, but growing body of evidence (Chalfant et al.; 2007, Reaven, Blakeley-Smith, Nicols et al., 2009; van Steensel et al., 2011). In addition, we found that a better quality of social relations was related to less anxiety. Thus, social relations should be an important aspect in preventive or intervention programs aimed at reducing anxiety

in children with ASD. This is in line with the treatment philosophy behind the PEERS program (Laugeson & Frankel, 2010). We also found that ASD symptom severity and quality of social relations were largely independent. Therefore interventions can be directed at improving quality of social relations without intervening effects of ASD symptom severity, and influencing quality of social relations in a positive way may be a helpful approach for all children with ASD. In the PEERS program (Laugeson & Frankel, 2010) teenagers with ASD and their parents are trained systematically to make and to keep friends and to engage more in "get togethers" with other teens. A strong conviction in this empirically based social skills training is that making friends can be taught and that having friends enhances social development (Laugeson & Frankel, 2010).

Childhood FTD, namely illogical thinking, predicted more severe symptoms of ASD in adolescence, over and above the effect of ASD symptom severity in childhood. Because illogical thinking constitutes a significant and independent contribution to future ASD severity, diminishing illogical thinking could contribute to a more favourable course of ASD. In theory antipsychotics could be used to reduce formal thought disorder (RUPP, 2002; Arnold, Vitiello, McDougle et al., 2003; RUPP, 2005). However, there is a paucity of research data with respect to long term effects of these compounds (Troost, Lahuis, Steenhuis et al., 2005) and the knowledge about long term cognitive effects of antipsychotics is too scarce to justify prescription of medication for longer periods of time (Aman, Hollway, McDougle et al., 2008; Pandina, Zhu, Cornblatt, 2009). Our results concerning formal thought disorder seem to indicate, that the use of antipsychotics does not lead to a diminishment of symptom severity at follow-up. However, no conclusions can be drawn from this observation, because clearly we did not perform a medication effect study

Our findings indicate that children's face recognition abilities might be a useful assessment tool providing additional information regarding future prognosis. Thus, disturbed FR in childhood might indicate worsening ASD symptom severity over time.

It would be too early to draw conclusions on treatment issues in ASD. However, the Let's Face It! intervention (Wolf, et al., 2008) specifically targets improving face processing abilities, namely face recognition and identification of facial emotions in children with ASD by using a computer game platform, which is highly motivating for children. More recently, using FaceSay, a computer based social skills training program for children with ASD, it was shown that enhancing FR and IFE were crucial factors in the improvement of social skills of these children (Hopkins, Gower, Perez et al, 2011). Bearing in mind the results of this study, enhancing FR through these kinds of treatment programs could have a direct influence upon the future course

of ASD, since we demonstrate that better FR predicted lower ASD symptom severity scores in the long run.

In children with ASD, visuo-spatial tests on disembedding performance might be a useful tool, providing some additional prognostic information regarding future symptom severity in the domain of RRBI. Yet, given the controversies about the usefulness of these visuo-spatial tasks (White & Saldana, 2011) and the necessity to use these tasks in a standardized and subtle way (De Jonge et al., 2006), we do recommend careful use of the CEFT and to be prudent in the interpretation of the test results.

Recommendations for future research

Based on the methodological considerations that we discussed in the previous paragraph, several suggestions for future research are presented in the current section.

First, we encourage future studies to include participants from more than one centre, including academic as well as non-academic centres, which would lead to a more representative sample. In addition, including individuals with more stringent ASD classifications (i.e. AD or high symptom severity according to DSM 5) and an IQ below 70 would lead to a better representation of the total ASD spectrum and this would result in a better generalizability of findings.

Second, follow-up studies should try to include more than two assessment waves to be able to draw firmer conclusions concerning of the developmental course of ASD symptoms. Assessing ASD symptoms over three or more assessment waves may lead to more detailed prognostic estimates and the opportunity to study the developmental course of ASD more precisely (Gotham, et al., 2013; Szatmari, et al., 2009). In line with this the outcome of the current sample into adulthood would be worthwhile to observe. The Interagency Autism Coordinating Committee (IACC) encouraged researchers to conduct longitudinal studies. The results from longitudinal studies are necessary for the planning of adult services that can meet the specific needs of adults with ASD. These services will improve functioning and quality of life of adults with ASD (IACC), which is a major concern from the client's viewpoint (Pellicano, Dinsmore, Charman, 2014). The ultimate goal would be to have consecutive series of targeted interventions, each directed towards a specific problem in different critical stages of the individual life span.

More knowledge should be obtained about the development over the life span of facial and emotion recognition in typically developing children and in children with ASD of different ages (Harms et al., 2010). Furthermore it would be interesting to investigate longitudinally the predictive value of other visuo-spatial tests, which focus on detail oriented versus global cognitive style, i.e. the Rey-Osterich complex

figure test (Schlooz, Hulstijn, van den Broek et al. 2006; Kuschner, Bodner, Minshew, 2009). To bridge the gap between the neuropsychological and the neurobiological level, studies combining neuropsychological and social cognitive measures with fMRI or event related potentials (ERP) are needed (Campatelli, Frederico, Apicella et al., 2013). Of these two possible lines of research the combination of neuropsychological measures with fMRI has been performed in many studies (i.e Schultz et al., 2000; Pierce et al., 2001; Dziobek et al., 2010). On the other hand combining neuropsychological measures with visual ERP's has received less attention and could contribute to finding functional endophenotypes for ASD. Most promising measures for this line of research would be FR and IFE, combined with the middle and late visual ERP components (100 milliseconds to 400 milliseconds after event) (Jeste & Nelson, 2009) or early ERP signals (up to 200 milliseconds; N1 and P2) for studying the hypothesis of hypo-priors in ASD (relying too much on detailed, situation specific information and not relying on prior general knowledge of the world) (Pellicano & Burr, 2012; Lawson et al., 2014).

We hope that this thesis will contribute to a better understanding of the heterogeneity of ASD. A better understanding of this heterogeneity hopefully leads to more targeted and tailor-made interventions. Hopefully the findings described in the present thesis help to provide a point of departure for further investigations.

Chapter 8

References

Summary

Samenvatting

CV

PhD-portfolio

Publications

Dankwoord

REFERENCES

Abrahams BS & Geschwind DH (2008) Advances in autism genetics: on the threshold of a new neurobiology, Nature Reviews Genetics, 9(5), 341-355.

Achenbach TM & Rescorla LA (2001) Manual for the ASEBA School-Age Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Achenbach TM (1991) Manual for the Child Behavior Checklist/ 4-18 and 1991 profiles. Burlington: University of Vermont, Department of Psychiatry.

Aman MG, Hollway JA, McDougle CJ, Scahill L, Tierney E, McCracken JT, Arnold LE, Vitiello B, Ritz L, Gavaletz A, Cronin P, Swiezy N, Wheeler C, Koenig K, Ghuman JK & Posey DJ (2008) Cognitive effects of risperidone in children with autism and irritable behavior. Journal of Child and Adolescent Psychopharmacology, 18(3), 227-236.

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders (5th edition) Washington. DC: American Psychiatric Association.

American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders (4th edition TR). Washington DC: American Psychiatric Association.

Amone-P'Olak K, Ormel J, Oldehinkel AJ, Reijneveld SA, Verhulst FC & Burger H (2010) Socioeconomic position predicts special mental health service use independent of clinical severity: the TRAILS study. Journal of the American Academy of Child and Adolescent Psychiatry, 49 (7), 647-655.

Anderson GM, Horne WC, Chatterjee D, Cohen DJ (1990) The hyperserotonemia of autism, Annuals of the New York Academy of Sciences, 600, 331-340.

Andreasen NC (1979) Thought, language, and communication disorders. Archives of General Psychiatry, 36(12), 1315-1330.

Arango C (2011) Attenuated psychotic symptoms syndrome: how it may affect child and adolescent psychiatry. European Child and Adolescent Psychiatry, 20(2), 67-70.

Armenteros JL & Davies M (2006) Antipsychotics in early onset schizophrenia. Systematic review and meta-analysis. European Child and Adolescent Psychiatry, 15(3), 141-148.

Arnold LE, Vitiello B, McDougle C, Scahill L, Shah B, Gonzalez NM, Chuang S, Davies M, Holloway J, Aman MG, Cronin P, Koenig K, Kohn AE, McMahon DJ & Tierney E (2003) Parent-defined target symptoms respond to risperidone in RUPP autism study: customer approach to clinical trials. Journal of the American Academy of Child and Adolescent Psychiatry, 42 (12), 1443-1450.

Baltaxe CA & D' Angiola N (1992) Cohesion in the discourse interaction of autistic, specifically language-impaired, and normal children. Journal of Autism and Developmental Disorders, 22(1), 1-21.

Baron-Cohen S, Ring HA, Wheelwright S, Bullmore ET, Brammer MJ, Simons A & Williams SC (1999) Social intelligence in the normal and autistic brain: An fMRI study. European Journal of Neuroscience, 11 (6), 1891-1898.

Bearden CE, Wu KN, Caplan R & Cannon TD (2011) Thought disorder and Communication Deviance as Predictors of Outcome in Youth at Clinical High Risk for Psychosis. Journal of the American Academy of Child and Adolescent Psychiatry, 50 (7), 669-680.

Begeer S, Koot H, Rieffe C, Meerum Terwogt M & Stegge H (2008) Emotional competence in children with autism: Diagnostic criteria and empirical evidence. Developmental Review, 28, 342-369.

Bellini S (2004) Social skills deficits and anxiety in high-functioning adolescents with autism spectrum disorders. Focus on Autism and Other Developmental Disabilities, 19 (2), 78-86.

Bender L (1947) Psychopathic behaviour disorders in children In: Lindner RM en Seliger RV, editors. Handbook of correctional psychology, Oxford Philosophical Library. 360-377.

Billstedt E, Gillberg IC & Gillberg C (2007) Autism in adults: symptom patterns and early childhood predictors. Use of the DISCO in a community sample followed from childhood. Journal of Child Psychology and Psychiatry and Allied Disciplines, 48(11), 1102-1110.

Billstedt E, Gillberg IC & Gillberg C (2005) Autism after adolescence: population-based 13- to 22-year follow-up study of 120 individuals with autism diagnosed in childhood. Journal of Autism and Developmental Disorders, 35(3), 351-360.

Bishop DV (1998) Development of the Children's Communication Checklist (CCC): A method for assessing qualitative aspects of communicative impairment in children. Journal of Child Psychology and Psychiatry and Allied Disciplines, 39(6):879-91.

Blair RJR (2003) Facial expressions, their communicatory functions and neuro-cognitive substrates. Philosophical transactions of the Royal Society of London. Series B, Biological Sciences, 358 (1431), 561-572.

Bleuler E (1950) Dementia Praecox or the Group of Schizophrenia's. ed. New York, International University Press.

Bolte S, Holtmann M, Poustka F, Scheurich A & Schmidt L (2007) Gestalt perception and local-global processing in high-functioning autism. Journal of Autism and Developmental Disorders, 37 (8), 1493-1504.

Bolte S & Poustka F (2006) The broader cognitive phenotype of autism in parents: how specific is the tendency for local processing and executive dysfunction? Journal of Child Psychology and Psychiatry, 47 (6), 639-645.

Boraston Z, Blakemore SJ, Chilvers R & Skuse D (2007) Impaired sadness recognition is linked to social interaction deficit in autism. Neuropsychologia, 45 (7), 1501-1510.

Bradley EA, Ames CS, Bolton PF (2011) Psychiatric conditions and behavioural problems in adolescents with intellectual disabilities: correlates with autism. Canadian Journal of Psychiatry / La Revue Canadienne de Psychiatrie, 56(2), 102-109.

Campatelli G, Federico RR, Apicella F, Sicca F & Muratori F (2013) Face processing in children with ASD: Literature review. Research in Autism Spectrum Disorders, 7(3), 444-454.

Cannon TD, Cadenhead K, Cornblatt B, Woods SW, Addington J, Walker E, Seidman LJ, Perkins D, Tsuang M, McGlashan T & Heinssen R (2008) Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. Archives of General Psychiatry, 65(1), 28-37.

Caplan R, Guthrie D, Komo S, Siddarth P, Chayasirisobhon S, Kornblum H, Sankar R, Hansen R, Mitchell W & Shields WD (2002) Social communication in children with epilepsy. Journal of Child Psychology and Psychiatry and Allied Disciplines, 43 (2), 245-253.

Caplan R, Guthrie D, Tang B, Neuchterlein KH & Asarnow RF (2001) Thought disorder in attention-deficit hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry, 40(8), 965-972.

Caplan R, Guthrie D, Tang B, Komo S & Asarnow RF (2000) Thought disorder in childhood schizophrenia: Replication and update of concept. Journal of Child Psychology and Psychiatry and Allied Disciplines, 39(6), 771-778.

Caplan R (1994) Thought disorder in childhood. Journal of the American Academy of Child and Adolescent Psychiatry, 33 (5), 605-615.

Caplan R, Guthrie D, Fish B, Tanguay PE & David-Lando G (1989) The Kiddie Formal Thought Disorder Rating Scale: Clinical Assessment, Reliability, and Validity. Journal of the American Academy of Child and Adolescent Psychiatry, 28(3), 408-416.

Castelli F (2005) Understanding emotions from standardized facial expressions in autism and normal development. Autism, 9 (4), 428-449.

Celani G, Battacchi MW & Arcidiacono L (1999) The understanding of the emotional meaning of facial expressions in people with autism. Journal of Autism and Developmental Disorders, 29(1), 57-66.

Chalfant AM, Rapee R, Caroll L (2007) Treating anxiety disorders in children with high functioning autism spectrum disorders: a controlled trial. Journal of Autism and Developmental Disorders 37(10), 1842-1857.

Chamberlain B, Kasari C, Rotheram-Fuller E (2007) Involvement or isolation? The social networks of children with autism in regular classrooms. Journal of Autism and Developmental Disorders, 37 (2), 230-242.

Chen YH, Rodgers J & McConachie H (2009) Restricted and repetitive behaviours, sensory processing and cognitive style in children with autism spectrum disorders. Journal of Autism and Developmental Disorders, 39(4), 635-642.

Chevallier C, Kohls G, Troiani V, Brodkin ES & Schultz RT (2012) The social motivation theory of autism. Trends in Cognitive Science, 16 (4), 231-239.

Cohen J (1988) Statistical power analysis for the behavioral sciences. Hillsdale, New Jersey: Lawrence Erlbaum Associates.

Constantino JN, Gruber CP, Davis S, Hayes S, Pasanante N & Przybeck T (2004) The factor structure of autistic traits. Journal of Child Psychology and Psychiatry and Allied Disciplines, 45(4), 719-726.

Constantino JN, Przybeck T, Friezen D & Todd RD (2000) Reciprocal social behavior in children with and without pervasive developmental disorders. Journal of Developmental and Behavioral Pediatrics, 21(1), 2-11.

Courchesne E, Pierce K, Schumann CM, Redcay E, Buckwalter JA, Kennedy DP & Morgan J (2007) Mapping early brain development in autism. Neuron, 56(2), 399-413.

Cuthbert BN & Insel TR (2013) Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BioMedCentral, 11, 126, 1-8.

Dakin S & Frith U (2005) Vagaries of visual perception in autism. Neuron, 48(3), 497-507.

Dawson G, Webb SJ & McPartland J (2005a) Understanding the nature of face processing impairment in autism: insights from behavioral and electrophysiological studies. Developmental Neuropsychology, 27(3), 403-424.

Dawson G, Webb SJ, Wijsman E, Schellenberg G, Estes A, Munson J & Faja S (2005b) Neurocognitive and electrophysiological evidence of altered face processing in parents of children with autism: Implications for a model of abnormal development of social brain circuitry in autism. Development and psychopathology, 17(3), 679-697.

Dawson G, Carver L, Meltzhoff AN, Panagiotides H, McPartland J & Webb SJ (2002) Neural correlates of face and object recognition in young children with autism spectrum disorder, developmental delay and typical development. Child development, 73 (3), 700-717.

Dayton CM & Macready GB (1988) Concomitant variable latent class models. Journal of the American Statistical Association, 83 (401), 173-178.

De Bildt AA, Greaves-Lord K & de Jonge M (2013) ADOS-2. Autisme diagnostisch observatieschema. Handleiding. Dutch Translation of Autism Diagnostic Observation Schedule-2 Manual. Hogrefe, Amsterdam.

De Bildt A, Mulder EJ, Hoekstra PJ, Van Lang ND, Minderaa RB & Hartman CA (2009) Validity of the Children's Social Behavior Questionnaire (CSBQ) in children with intellectual disability: comparing the CSBQ with ADI-R, ADOS, and clinical DSM-IV-TR classification. Journal of Autism and Developmental Disorders, 39(10), 1464-1470.

De Bildt A, Blijd-Hoogewys EMA, Dijkstra SP, Huizinga P, Ketelaars CEJ, Kraijer DW (2007) Pervasieve ontwikkelingsstoornissen. In F Verheij, FC Verhulst & RF Ferdinand (eds). Kinder- en jeugdpsychiatrie; behandeling en begeleiding (31-81). Assen: Van Gorcum.

De Bruin EI, De Nijs PF, Verheij F, Hartman CA & Ferdinand RF (2007a) Multiple complex developmental disorder delineated from PDD-NOS. Journal of Autism and Developmental Disorders, 37 (6), 1181-1191.

De Bruin EI, Ferdinand RF, Meester S, De Nijs PF & Verheij F (2007b) High rates of psychiatric comorbidity in PDD-NOS. Journal of Autism and Developmental Disorders, 37(5), 877-886.

De Geus EJC & Boomsma DI (2001) A genetic neuroscience approach to human cognition. European Psychologist, 6(4), 241-253.

De Jonge MV, Kemner C & van Engeland H (2006) Superior disembedding performance of high-functioning individuals with autism spectrum disorders and their parents: The need for subtle measures. Journal of Autism and Developmental Disorders, 36(5), 677-683.

De Sonneville LM (1999) Amsterdam Neuropsychological Tasks: A computer aided assessment program. In: den Brinker BLPM, Beek PJ, Brand AN, Maarse SJ, Mulder JM (Eds.) Cognitive ergonomics, clinical assessment and computer assisted learning: Computers in psychology, Vol. 6, 187-203. Lisse, Swets en Zeitlinger.

Demjaha A, Valmaggia L, Stahl D, Byrne M & McGuire P (2012) Disorganization/ cognitive and negative symptom dimensions in the at-risk mental state predict subsequent transition to psychosis. Schizophrenia Bulletin, 38 (2), 351-359.

Docherty NM, McCleery A, Divilbiss M, Schumann EB, Moe A & Shakeel MK (2013) Effects of social cognitive impairment on speech disorder in schizophrenia. Schizophrenia Bulletin, 39 (3), 608-616.

Docherty NM (2012) On identifying the processes underlying schizophrenic speech disorder. Schizophrenia Bulletin, 38 (6), 1327-1335.

Docherty NM (2005) Cognitive impairments and disordered speech in schizophrenia: thought disorder, disorganization, and communication failure perspectives. Journal of Abnormal Psychology, 114(2), 269-278.

Docherty NM & Gottesman II (2000) A twin study of communication disturbances in schizophrenia. Journal of Nervous and Mental Disease, 188(7), 395-401.

Docherty NM, Miller TN & Lewis MA (1997) Communication disturbances in the natural speech of schizophrenic patients and non-schizophrenic parents of patients. Acta Psychiatrica Scandinavica, 95(6), 500-507.

Dziobek I, Bahnemann M, Convit A & Heekeren HR (2010) The role of the fusiform-amygdala system in the pathophysiology of autism. Archives of General Psychiatry, 67(4), 397-405.

Eagle RF, Romanczyk RG & Lenzensweger MF (2010). Classification of children with autism spectrum disorders: a finite mixture modelling approach to heterogeneity. Research in Autism Spectrum disorders, 4(4), 772-781.

Edgin JO & Pennington BF (2005) Spatial cognition in autism spectrum disorders: Superior, impaired, or just intact? Journal of Autism and Developmental Disorders, 35(6), 729-745.

Eussen MLJM, Van Gool AR, Verheij F, De Nijs PF, Verhulst FC & Greaves-Lord K (2013) The association of quality of social relations, symptom severity and intelligence with anxiety in children with autism spectrum disorders. Autism 17(6), 723-735.

Evans DW, Elliott M & Packard MG (2001) Visual organization and perceptual closure are related to compulsive-like behavior in typically developing children. Merrill-Palmer Quarterly, 47(3), 323-335.

Ewing L, Pellicano E & Rhodes G (2013) Reevaluating the selectivity of face-processing difficulties in children and adolescents with autism. Journal of Experimental Child Psychology, 115(2), 342-355.

Faja S, Aylward E, Bernie R, Dawson G (2008) Becoming a face expert: a computerized face-training program for high-functioning individuals with autism spectrum disorders. Developmental Neuropsychology, 33 (1), 1-24.

Fein D, Stevens M, Dunn M., Waterhouse L, Allen D, Rapin I & Feinstein C (1999) Subtypes of Pervasive developmental Disorder, Clinical Characteristics. Child Neuropsychology, 5(1):1-23.

First MB (2005) Clinical utility: a prerequisite for the adoption of a dimensional approach in DSM. Journal of Abnormal Psychology, 114(4), 560-564.

Fombonne E (2009) Epidemiology of pervasive developmental disorders. Pediatric Research, 65(6), 591-598.

Frazier TW, Youngstrom EA, Speer L, Embacher R, Law P, Constantino J, Findling RL, Hardan AY & Eng C (2012) Validation of proposed DSM-5 criteria for autism spectrum disorder. Journal of the American Academy of Child and Adolescent Psychiatry, 51(1), 28-40.

Frith U (1989) Autism: explaining the enigma. Blackwell, Oxford UK.

Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Valmaggia L, Barale F, Caverzasi E & McGuire P (2012) Predicting psychosis. Meta-analysis of transition outcomes in individuals at high clinical risk. Archives of General Psychiatry, 69(3), 220-229.

Gadow KD (2012) Schizophrenia spectrum and attention-deficit/hyperactivity disorder symptoms in autism spectrum disorder and controls. Journal of the American Academy of Child and Adolescent Psychiatry, 51(10), 1076-1084.

Gadow KD, Devincent CJ, Pomeroy J & Azizian A (2005) Comparison of DSM-IV symptoms in elementary school-age children with PDD versus clinic and community samples, Autism 9 (4), 392-415.

Georgiades S, Szatmari P, Zwaigenbaum L, Duku E, Bryson S, Roberts W, Goldberg J & Mahoney W (2007) Structure of the autism symptom phenotype: A proposed multidimensional model. Journal of the American Academy of Child and Adolescent Psychiatry, 46(2),188-196.

Ghaziuddin M (2002) Asperger Syndrome: Associated psychiatric and medical conditions. Focus on Autism and Other Developmental Disabilities, 17(3), 138-144.

Ginsburg GS, La Greca AM & Silverman WK (1998) Social anxiety in children with anxiety disorders: Relation with social and emotional functioning. Journal of Abnormal Child Psychology, 26(3), 175-185.

Gotham K, Bishop SL, Hus V, Huerta M, Lund S, Buja A, Krieger A & Lord C (2013) Exploring the relationship between anxiety and insistence on sameness in autism spectrum disorders. Official Journal of the International Society for Autism Research, 6(1), 33-41.

Gotham K, Pickles A, Lord C (2009) Standardizing ADOS scores for a measure of severity in autism spectrum disorders. Journal of Autism and Developmental Disorders, 39(5), 693-705.

Gotham K, Risi S, Dawson G, Tager-Flusberg H, Joseph R, Carter A, Hepburn S, McMahon W, Rodier P, Hyman SL, Sigman M, Rogers S, Landa R, Spence MA, Osann K, Flodman P, Volkmar F, Hollander E, Buxbaum J, Pickles A & Lord C (2008) A replication of the Autism Diagnostic Observation Schedule (ADOS) revised algorithm. Journal of the American Academy of Child and Adolescent Psychiatry, 47 (6), 642-651.

Gotham K, Risi, S, Pickles A & Lord C (2007) The Autism Diagnostic Observation Schedule: Revised algorithms for improved diagnostic validity. Journal of Autism and Developmental Disorders, 37(4), 613-627.

Gottesman II & Gould TD (2003) The endophenotype concept in psychiatry: etymology and strategic intentions. American Journal of Psychiatry, 160(4), 636-645.

Greaves-Lord K, Eussen MLJM, Verhulst FC, Minderaa RB, Mandy W, Hudziak JJ, Steenhuis MP, de Nijs P & Hartman CA (2013) Empirically based phenotypic profiles of children with pervasive developmental disorders: Interpretation in the light of the DSM-5. Journal of Autism and Developmental Disorders, 43(8), 1784-1797.

Greimel E, Schulte-Ruther M, Kamp-Becker I, Remschmidt H, Herpertz-Dahlmann B, Konrad K (2014) Impairment in face processing in autism spectrum disorder; a developmental perspective. Journal of Neural Transmission, 121(9), 1171-81.

Grether JK, Rosen NJ, Smith KS & Croen LA (2009) Investigation of shifts in autism reporting in the California Department of Developmental Services. Journal of Autism and Developmental Disorders, 39, 1412-1419.

Grinter EJ, Van Beek PL, Maybery MT & Badcock DR (2009) Brief report: visuospatial analysis and self-rated autistic-like traits. Journal of Autism and Developmental Disorders, 39(4), 670-677.

Hallett V, Ronald A, Rijsdijk F, Happé F (2010) Association of autistic-like and internalizing traits during childhood: A longitudinal twin study. The American Journal of Psychiatry, 167 (7), 809-817.

Happé F & Booth R (2008) The power of the positive: Revisiting weak central coherence in autism spectrum disorders. The Quarterly Journal of Experimental Psychology, 61 (1), 50-63.

Happé F & Ronald A (2008) The 'fractionable autism triad': a review of evidence from behavioural, genetic, cognitive and neural research. Neuropsychological Review 18(4), 287-304.

Happé F & Frith U (2006) The weak coherence account: Detail-focused cognitive style in autism spectrum disorders. Journal of Autism and Developmental Disorders, 36(1), 5-25.

Happé F, Ronald A & Plomin R (2006) Time to give up on a single explanation for autism. Nature Neuroscience, 9 (10), 1218-1220.

Happé F, Briskman J & Frith U (2001) Exploring the cognitive phenotype of autism: weak "central coherence" in parents and siblings of children with autism: I. experimental tests. Journal of Child Psychology and Psychiatry and Allied Disciplines, 42 (3), 299-307.

Harms MB, Martin A & Wallace GL (2010) Facial emotion recognition in autism spectrum disorders: a review of behavioral and neuroimaging studies. Neuropsychology Review, 20(3), 290-322.

Hartman CA, Luteijn E, Serra M. & Minderaa R (2006) Refinement of the Children's Social Behavior Questionnaire (CSBQ): an instrument that describes the diverse problems seen in milder forms of PDD. Journal of Autism and Developmental Disorders, 36(3), 325-342.

Herba CM, de Bruin E, Althaus M, Verheij F & Ferdinand RF (2008) Face and emotion recognition in MCDD versus PDD-NOS. Journal of Autism and Developmental Disorders, 38(4), 706–718.

Herba C & Phillips M (2004) Annotation: Development of facial expression recognition from childhood to adolescence: behavioural and neurological perspectives. Journal of Child Psychology and Psychiatry and Allied Disciplines, 45(7), 1185-1198.

Hobson PR, Chidambi G, Lee A & Meyer J (2006) Self-awareness in developmental perspective. Monographs of the Society for Research in Child Development, 71(2), 1-28.

Hopkins IM, Gower MW, Perez TA, Smith DS, Amthor FR, Wimsatt FC & Biasini FJ (2011) Avatar assistant: Improving social skills in students with an ASD through a computer based intervention. Journal of Autism and Developmental Disorders, 41(4), 1543-1555.

Howlin P, Goode S, Hutton J & Rutter M (2004) Adult outcome for children with autism. Journal of Child Psychology and Psychiatry and Allied Disciplines, 45(2), 212-229.

Humphreys K, Minshew N, Leonard GL, Behrmann M (2007) A fine-grained analysis of facial expression processing in high-functioning adults with autism. Neuropsychologia, 45(4), 685-695.

Hus V, Bishop S, Gotham K, Huerta M & Lord C (2013) Commentary: advancing measurement of ASD severity and social competence: a reply to Constantino and Frazier. Journal of Child Psychology and Psychiatry and Allied Disciplines, 54 (6), 698-700.

Hus V, Pickles A, Cook EH Jr, Risi S & Lord C (2007) Using the autism diagnostic interview - revised to increase phenotypic homogeneneity in genetic studies of autism. Journal of Biological Psychiatry, 61(4), 438-448.

Iacoboni M (2006) Failure to deactivate in autism: The co-constitution of self and other. Trends in Cognitive Sciences, 10 (10), 431-433.

Iarocci G, Burack JA, Shore DI, Mottron L & Enns JT (2006) Global-local visual processing in high functioning children with autism: structural vs. implicit task biases. Journal of Autism and Developmental Disorders, 36 (1), 117-129.

Insel TR (2014) The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. American Journal of Psychiatry, 171(4), 395-397.

Insel TR, Cuthbert BN, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C & Wang P (2010) Research Domain Criteria (RDoC): toward a new classification framework for research on mental disorders. American Journal of Psychiatry, 167(7), 748-751.

Jarrold C, Gilchrist ID & Bender A (2005) Embedded figures detection in autism and typical development: preliminary evidence of a double dissociation in relationships with visual search. Developmental Science, 8(4), 344-351.

Jeste SS & Geschwind DH (2014) Disentangling the heterogeneity of autism spectrum disorder through genetic findings. Nature Reviews Neurology. 10(2), 74-81.

Jeste SS & Nelson CA (2009) Event related potentials in the understanding of autism spectrum disorders: an analytical review. Journal of Autism and Developmental Disorders, 39(3), 495-510.

Jolliffe T & Baron-Cohen S (1997) Are people with autism and Asperger syndrome faster than normal on the Embedded Figures Test? Journal of Child Psychology and Psychiatry and Allied Disciplines, 38(5), 527-534.

Jones W & Klin A (2013) Attention to eyes is present but in decline in 2-6-month-old infants later diagnosed with autism. Nature 504 (7480), 427-431.

Jones CR, Pickles A, Falcaro M, Marsden AJS, Happé F, Scott SK, Sauter D, Tregay L, Phillips RJ, Baird G, Simonoff E & Charman T (2011) A multimodal approach to emotion recognition ability in autism spectrum disorders. Journal of Child Psychology and Psychiatry and Allied Disciplines, 52 (3), 275-285

Jones W, Carr K & Klin A (2008) Absence of preferential looking to the eyes of approaching adults predicts level of disability in 2-year old toddlers with autism spectrum disorder. Archives of General Psychiatry, 65(8), 946-954.

Joseph RM & Tanaka J (2003) Holistic and part-based face recognition in children with autism. Journal of Child Psychology and Psychiatry and Allied Disciplines, 44 (4), 529-542.

Kaiser MD, Hudac CM, Shultz S, Lee SM, Cheung C, Berken AM, Deen B, Pitskel NB, Sugrue DR, Voos AC, Saulnier CA, Ventola P, Wolf JM, Klin A, Vander Wyk BC & Pelphrey KA (2010) Neural signatures of autism. Proceedings of the National Academy of Sciences of the United States of America, 107(49), 21223-21228.

Kaland N, Mortensen EL & Smith L (2007) Disembedding performance in children and adolescents with Asperger syndrome of high-functioning autism. Autism, 11(1), 81-92.

Kamp-Becker I, Smidt J, Ghahreman M, Heinzel-Gutenbrunner M, Becker K & Remschmidt H (2010) Categorical and dimensional structure of autism spectrum disorders: the nosologic validity of Asperger Syndrome. Journal of the Autism and Developmental Disorders, 40 (8), 921-929.

Kanne SM, Abbacchi AM & Constantino JN (2009) Multi-informant ratings of psychiatric symptom severity in children with autism spectrum disorders: the importance of environmental context. Journal of Autism and Developmental Disorders, 39(6), 856-864.

Kanner L (1943). Autistic disturbances of affective contact. Nervous Child, 2, 217-250.

Kass RE & Wasserman L (1995) A reference Bayesian test for nested hypotheses and its relationship to the Schwarz criterion. Journal of the American Statistical Association, 90(431), 928-934.

King BH & Lord C (2011) Is schizophrenia on the autism spectrum? Brain Research; 1380, 34-41.

Klin A, Jones W, Schultz RT & Volkmar FR (2005) The enactive mind-from actions to cognition: Lessons from autism. In: Volkmar FR, Paul R, Klin A, Cohen DJ (Eds.) Handbook of Autism and Pervasive Developmental Disorders. Volume 1, 682-703. Hoboken, NJ, John Wiley &Sons.

Klin A, Sparrow SS, de Bildt A, Cicchetti DV, Cohen DJ & Volkmar FR (1999) A normed study of face recognition in autism and related disorders. Journal of Autism and Developmental Disorders, 29(6), 499-508.

Klosterkotter J, Hellmich M, Steinmeyer EM & Schultze-Lutter F (2001) Diagnosing schizophrenia in the initial prodromal phase. Archives of General Psychiatry, 58(2), 158-164.

Krebs JF, Biswas A, Pascalis O, Kamp-Becker I, Remschmidt H & Schwartzer G (2011) Face processing in children with autism spectrum disorder: independent or interactive processing of facial identity and facial expression. Journal of Autism and Developmental Disorders, 41(6), 796-804.

Krol NPCM, De Bruyn EEJ Coolen JC & Aarle van EJM (2006) From CBCL to DSM: A comparison of two methods to screen for DSM-IV diagnoses using CBCL data. Journal of Clinical Child and Adolescent Psychology, 35(1), 127-135 .

Kuschner ES, Bodner KE & Minshew NJ (2009) Local vs. Global approaches to reproducing the Rey Osterrieth Complex Figure by children, adolescents, and adults with high-functioning autism. Autism Research, 2(6), 348-358.

La Greca AM & Lopez N (1998) Social anxiety among adolescents: linkages with peer relations and friendships. Journal of Abnormal Child Psychology, 26(2), 83-94.

Laird RD & De Los Reyes A (2013) Testing informant discrepancies as predictors of early adolescent psychopathology: why difference scores cannot tell you what you want to know and how polynomial regression may. Journal of Abnormal Child Psychology, 41(1), 1-14.

Laugeson EA & Frankel F (2010) Social skills for teenagers with developmental and Autism Spectrum Disorders: The PEERS Treatment Manual, New York, Routledge.

Lawson RP, Rees G & Friston KJ (2014) An aberrant precision account of autism. Frontiers in Human Neuroscience, 14(8), 302.

Lee PS, Yerys BE, Della Rosa A, Foss-Feig J, Barnes KA, James ID, Van Meter J, Vaidya CJ, Gaillard WD & Kenworthy LE. (2009) Functional connectivity of the inferior frontal cortex changes with age in children with autism spectrum disorders. A fcMRI study of response inhibition. Cerebral Cortex, 19(8), 1787-1794.

Lee PS, Foss-Feig J, Henderson JG, Kenworthy LE, Gilotty L, Gaillard WD & Vaidya CJ (2007) Atypical neural substrates of Embedded Figures Task performance in children with Autism Specturm Disorder. Neuroimage 38(1), 184-193.

Leyfer OT, Folstein SE, Bacalman S, Davis NO, Dinh E, Morgan J, Tager-Flusberg H & Lainhart JE (2006) Comorbid psychiatric disorders in children with autism: interview development and rates of disorders. Journal of Autism and Developmental Disorders, 36(7), 849-861.

Lindner JL & Rosen LA (2006) Decoding of emotion through facial expression, prosody and verbal content in children and adolescents with Asperger's syndrome. Journal of Autism and Developmental Disorders, 36 (6), 769-777.

Loewy RL, Bearden CE, Johnson JK, Raine A & Cannon TD (2005). The prodromal questionnaire (PQ): preliminary validation of a self-report screening measure for prodromal and psychotic syndromes. Schizophrenia Research, 79(1), 117-125.

Lord C, Rutter M, DiLavore PC, Risi S, Gotham K & Bishop SL (2012a) Autism diagnostic observation schedule-2 manual. Los Angeles, CA, Western Psychological Services.

Lord C, Petkova E, Hus V, Gan W, Lu F, Martin DM, Ousley O, Guy L, Bernier R, Gerdts J, Algermissen M, Whitaker A, Sutcliffe JS, Warren Z, Klin A, Saulnier C, Hanson E, Hundley R, Piggot J, Fombonne E, Steiman M, Miles J, Kanne SM, Goin-Kochel RP, Peters SU, Cook EH, Guter S, Tjernagel J, Green Snyder LA, Bishop S, Esler A, Gotham K, Luyster R, Miller F, Olson J, Richler J & Risi S (2012b) A multisite study of the clinical diagnosis of different autism spectrum disorders. Archives of General Psychiatry, 69 (3), 306-313.

Lord C, Risi S, DiLavore PS, Shulman C, Thurm A & Pickles A (2006) Autism from 2 to 9 years of age. Archives of General Psychiatry, 63(6), 694-701.

Lord C, Rutter M, DiLavore PC & Risi S (2002) Autism diagnostic observation schedule Manual. Los Angeles, CA, Western Psychological Services.

Lord C, Rutter M, DiLavore PC & Risi S (1999) Autism Diagnostic Observation Schedule-WPS (ADOS-WPS). Los Angeles, CA, Western Psychological Services.

Lord C, Rutter M, Le Couteur A (1994) Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. Journal of Autism and Developmental Disorders, 24 (5), 659-685.

Luteijn E, Luteijn F, Jackson S, Volkmar F & Minderaa R (2000a). The Children's Social Behavior Questionnaire for milder variants of PDD problems: Evaluation of the psychometric characteristics. Journal of Autism and Developmental Disorders, 30 (4), 317-330.

Luteijn EF, Serra M, Jackson S, Steenhuis MP, Althaus M, Volkmar F & Minderaa R (2000b). How unspecified are disorders of children with a Pervasive Developmental Disorder Not otherwise Specified? A study of social problems in children with PDDNOS and or ADHD. European Child and Adolescent Psychiatry, 9(3), 168-179.

Maenner MJ, Rice CE, Arneson CL, Cunniff C, Schieve LA, Carpenter LA, Van Naarden Braun K, Kirby RS, Bakian AV & Durkin MS (2014) Potential impact of DSM-5 criteria on autism spectrum disorder prevalence estimates. JAMA Psychiatry, 71(3), 292-300.

Mandy W, Charman T & Skuse DH (2012) Testing the construct validity of proposed criteria for DSM-5 autism spectrum disorder. Journal of the American Academy of Child and Adolescent Psychiatry, 51(1), 41-50.

Mandy W, Charman T, Gilmour J. & Skuse D (2011) Toward specifying Pervasive Developmental Disorder-Not Otherwise Specified. Autism Research, 4(2), 121-131.

Mazurek MO & Kanne SM (2010) Friendship and internalizing symptoms among children and adolescents with ASD. Journal of Autism and Developmental Disorders, 40(12), 1512-1520.

McGovern CW& Sigman M (2005) Continuity and change from early childhood to adolescence in autism. Journal of Child Psychology and Psychiatry and Allied Disciplines, 46(4), 401-408.

Minshew NJ & Williams DL (2007) The new neurobiology of autism: Cortex, connectivity and neuronal organisation. Archives of Neurology, 64 (7), 945-950.

Mitchell P & Ropar D (2004) Visuo-spatial abilities in autism: A review. Infant and Child Development, 13(3), 185-198.

Mostofsky SH, Powell SK, Simonds DJ, Goldberg MC, Cafoo B & Pekar JJ (2009) Decreased connectivity and cerebellar activity in autism during motor task performance. Brain, 132(9), 2413-2425.

Mottron L, Burack JA, Iarocci G, Belleville S & Enns JT (2003) Locally oriented perception with intact global processing among adolescents with high-functioning autism: evidence from multiple paradigms. Journal of Child Psychology and Psychiatry and Allied Disciplines, 44(6), 904-913.

Mottron L, Belleville S & Ménard E (1999) Local bias in autistic subjects as evidenced by graphic tasks: perceptual hierarchisation or working memory deficit? Journal of Child Psychology and Psychiatry and Allied Disciplines, 40(5), 743-755.

Muthén LK & Muthén BO (2007) Mplus. Statistical Analyses with Latent Variables. User's Guide, 4th edition. Los Angeles, CA: Muthén & Muthén.

Navon D (1977) Forest before trees: The precedence of global features in visual perception. Cognitive Psychology, 9, 353-383.

Nylund KL, Asparouhov T & Muthén BO (2007) Deciding on the number of classes in latent class analyses and growth mixture modeling: A Monte Carlo Simulation Study. Structural Equation Modeling 14 (4), 535-569.

O'Riordan M, Plaisted KC, Driver J & Baron-Cohen S (2001) Superior visual search in autism. Journal of Experimental Psychology: Human Perception and Performance, 27(3), 719-730.

Ozonoff S, Pennington B & Solomon M (2006) Neuropsychological perspectives on developmental psychopathology. In: Cichetti D, Cohen D, editors. Developmental Psychopathology, Volume 2: developmental neuroscience (2nd edition). Hoboken, NJ: John Wiley & Sons Inc: 332-380.

Pandina GJ, Zhu Y & Cornblatt B (2009) Cognitive function with long-term risperidone in children and adolescents with disruptive behaviour disorder. Journal of Child and Adolescent Psychopharmacology, 19(6), 749-756.

Pearson DA, Loveland KA, Lachar D, Lane DM, Reddoch SL, Manosur R & Cleveland LA (2006) A comparison of behavioral and emotional functioning in children and adolescents with Autistic Disorder and PPD NOS. Child Neuropsychology, 12(4-5), 321-333.

Pellicano E, Dinsmore A & Charman T (2014) What should autism research focus upon? Community views and priorities from the United Kingdom. Autism, 18 (7), 756-770.

Pellicano E & Burr D (2012) When the world becomes 'too real': a Bayesian explanation of autistic perception. Trends in Cognitive Sciences, 16(10), 504-510.

Pellicano E (2010) Individual differences in executive function and central coherence predict developmental changes in theory of mind in autism. Developmental Psychology, 46 (2), 530-544.

Pellicano E, Maybery M, Durkin K & Maley A (2006) Multiple cognitive capabilities/deficits in children with an autism spectrum disorder: "weak" central coherence and its relationship to theory of mind and executive control. Development and Psychopathology, 18(1), 77-98.

Pellicano E, Gibson L, Maybery M, Durkin K & Badcock DR (2005) Abnormal global processing along the dorsal visual pathway in autism: a possible mechanism for weak visuospatial coherence? Neuropsychologia, 43(7), 1044-1053.

Pelphrey KA, Sasson NJ, Reznick JS, Paul G, Goldman BD & Piven J (2002) Visual scanning of faces in autism. Journal of Autism and Developmental Disorders, 32 (4), 249-261.

Persico & Sacco (2014) Endophenotypes in autism spectrum disorder. In: Patel (Ed.) Comprehensive Guide to Autism, Springer Science and Business Media, New York.

Pierce K, Muller R-A, Ambrose J, Allen G, Courchesne E (2001) Face processing occurs outside the fusiform face area in autism: evidence from functional MRI. Brain, 124(10), 2059-2073.

Poulton R, Caspi A, Moffitt TE, Cannon M, Murray R & Harrington H (2000) Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. Archives of General Psychiatry, 57(11), 1053-1058.

Rapaport J, Chavez A, Greenstein D, Addington A & Gogtay N (2009) Autism spectrum disorders and childhood onset schizophrenia: clinical and biological contributions to a relation revisited. Journal of the American Academy of Child and Adolescent Psychiatry, 48(1), 10-18.

Reaven J, Blakeley-Smith A, Nichols S, Dasari M, Flanigan E & Hepburn S (2009) Cognitive-behavioral group treatment for anxiety symptoms in children with high-functioning autism spectrum disorders: A pilot study. Focus on Autism and Other Developmental Disabilities, 24(1), 27-37.

Reinvall O, Voutilainen A, Kujala T & Korkman M (2013) Neurocognitive functioning in adolescents with autism spectrum disorder. Journal of Autism and Developmental Disorders, 43(6), 1367-1379.

Research Units on Pediatric Psychopharmacology-Autism Network (2005). Risperidone Treatment of Autistic Disorder: Longer-Term Benefits and Blinded Discontinuation After 6 Months. American Journal of Psychiatry, 162, 1361-1369.

Research Units on Pediatric Psychopharmacology-Autism Network (2002) Risperidone in children with autism and serious behavioral problems. The New England Journal of Medicine , 347, 314-321.

Rieffe C, Oosterveld P, Terwogt MM, Mootz S, van Leeuwen E & Stockmann L (2011) Emotion regulation and internalizing symptoms in children with autism spectrum disorders. Autism, 15(6), 655-670.

Ronald A, Happé F, Bolton P, Butcher LM, Price TS, Weelwright S, Baron-Cohen S, & Plomin R (2006) Genetic heterogeneity between the three components of the autism spectrum: a twin study. Journal of the American Academy of Child and Adolescent Psychiatry, 45(6), 691-699.

Ronald A, Happé F & Plomin R (2005) The genetic relationship between individual differences in social and nonsocial behaviours characteristic of autism. Developmental Science, 8(5), 444-458.

Ropar D & Mitchell P (2001) Susceptibility to illusions and performance on visuospatial tasks in individuals with autism. Journal of Child Psychology and Psychiatry and Allied Disciplines, 42(4), 539-549.

Rump KM, Giovanelli, Minshew NJ, JL & Strauss M.S (2009) The development of emotion recognition in individuals with autism. Child Development, 80(5), 1434-1447.

Rutter M & Thapar A (2014) Genetics of autism spectrum disorders. In: Handbook of autism and pervasive developmental disorders, 4th edition. In: Volkmar FR, Rogers SL, Paul R, Pelphrey KA (Eds.). Wiley, Hoboken, New Jersey.

Rutter M (2005) Incidence of autism spectrum disorders: changes over time and their meaning. Acta Pediatrica, 94(1), 2-15.

Rutter M (1972) Childhood schizophrenia reconsidered. Journal of Autism and Childhood Schizophrenia, 2 (4), 315-337.

Schlooz WA, Hulstijn W, Broek PJ van den, Pijll AC van der, Gabreëls F, Gaag RJ van der & Rotteveel JJ (2006) Fragmented visuospatial processing in children with pervasive developmental disorder. Journal of Autism and Developmental Disorders, 36(8), 1025-1037.

Schultz RT, Gauthier I, Klin A, Fulbrigth RK, Anderson AW, Volkmar FR, Skudlarski P, Lacadie C, Cohen DJ & Gore JC (2000) Abnormal ventral temporal cortical activity during face discrimination among individuals with autism and Asperger syndrome. Archives of General Psychiatry, 57 (4), 331-340.

Serra M, Althaus M, de Sonneville LM, Stant AD, Jackson AE & Minderaa RB (2003) Face recognition in children with a pervasive developmental disorder not otherwise specified. Journal of Autism and Developmental Disorders, 33(3), 303-317.

Shaffer D, Fisher P, Lucas CP, Dulcan MK & Schwab-Stone ME (2000) NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. Journal of the American Academy of Child and Adolescent Psychiatry, 39(1), 28-38.

Simmons DR, Robertson AE, McKay LS, Toal E, McAleer P & Pollick FE (2009) Vision in autism spectrum disorders, Vision Research, 49(22): 2705-2739.

Simonoff E, Pickles A, Charman T, Chandler S, Loucas T & Baird G (2008) Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity and associated factors in a population-derived sample. Journal of the American Academy of Child and Adolescent Psychiatry, 47(8), 921-929.

Skuse DH (2012) DSM-5's conceptualization of autistic disorders. Journal of the American Academy of Child and Adolescent Psychiatry, 51(4), 344-346.

Snow AV & Lecavalier L (2011) Comparing Autism, PDD-NOS, and other developmental disabilities on parent-reported behavior problems: little evidence for ASD subtype validity. Journal of Autism and Developmental Disorders, 41(3), 302-310.

Solomon M, Ozonoff S, Carter C & Caplan R (2008) Formal thought disorder and the autism spectrum: relationship with symptoms, executive control, and anxiety. Journal of Autism and Developmental Disorders; 38(8), 1474-1484.

Sporn AL, Addington AM, Gogtay N, Ordonez AE, Gornick M, Clasen L, Greenstein D, Tossell JW, Gochman P, Lenane M, Sharp WS, Straub RE & Rapoport JL (2004) Pervasive developmental disorder and childhood-onset schizophrenia: comorbid disorder or a phenotypic variant of a very early onset illness? Biological Psychiatry, 55 (10), 989-994.

Stevens MC, Fein DA, Dunn M, Allen D, Waterhouse LH, Feinstein C & Rapin I (2000) Subgroups of children with autism by cluster analysis: a longitudinal examination. Journal of the American Academy of Child and Adolescent Psychiatry, 39 (3), 346-352.

Sukhodolsky DG, Scahill L, Gadow KD, Arnold LE, Aman MG, McDougle CJ, McCracken JT, Tierney E, White WS, Lecavalier L & Vitiello B (2008) Parent-rated anxiety symptoms in children with pervasive developmental disorders: frequency and association with core autistic symptoms and cognitive functioning. Journal of Abnormal Child Psychology, 36(1), 117-128.

Szatmari P, Bryson S, Duku E, Vaccarella L, Zwaigenbaum L, Bennett T & Boyle MH (2009) Similar developmental trajectories in autism and Asperger syndrome: from early childhood to adolescence. Journal of Child Psychology and Psychiatry and Allied Disciplines, 50 (12), 1459-1467.

Szatmari P, Merette C, Bryson SE, Thivierge J, Roy MA, Cayer M & Maziade M (2002) Quantifying dimensions in autism: a factor-analytic study. Journal of the American Academy of Child and Adolescent Psychiatry 41(4), 467-474.

Szatmari P, Bartolucci G, Bremner R, Bond S & Rich S (1989) A follow-up study of high-functioning autistic children. Journal of Autism and Developmental Disorders, 19(2), 213-225.

Tantam D (2000) Psychological disorder in adolescents and adults with Asperger syndrome. Autism, 4, 47-62.

Toth K & King BH (2008) Asperger's syndrome: diagnosis and treatment. American Journal of Psychiatry, 165(8), 958-963.

Troost PW, Lahuis BE, Steenhuis MP, Ketelaars CE, Buitelaar JK, van Engeland H, Scahill L, Minderaa RB & Hoekstra PJ (2005) Long-term effects of risperidone in children with autism spectrum disorders: a placebo discontinuation study. Journal of the American Academy of Child and Adolescent Psychiatry, 44 (11), 1137-1144.

Uljarevic M & Hamilton A (2013) Recognition of emotions in autism: a formal meta-analysis. Journal of Autism and Developmental Disorders, 43(7), 1517-1526.

Vandenbroucke MWG, Scholte HS, Van Engeland H, Lamme VAF. & Kemner C (2008) A neural substrate for atypical low-level visual processing in autism spectrum disorder. Brain, 131(Pt 4), 1013-1024.

Vandenbroucke MWG, Scholte HS, Van Engeland H, Lamme VAF. & Kemner C (2009) A new approach to the study of detail perception in autism spectrum disorder (ASD): Investigating visual feedforward, horizontal and feedback processing. Vision Research, 49(9), 1006-1016.

Van de Cruys S, Evers K, Van der Hallen R, Van Eylen L, Boets B, de Wit L & Wagemans J (2014) Precise minds in uncertain worlds: predictive coding in autism. Psychological Review, 121 (4), 649-675.

Van der Gaag RJ, Caplan R, van Engeland H, Loman F & Buitelaar JK (2005) A controlled study of formal thought disorder in children with autism and multiple complex developmental disorders. Journal of Child and Adolescent Psychopharmacology, 15(3), 465-76.

Van der Gaag RJ, Buitelaar J, Van den Ban E, Bezemer M, Njio L & Van Engeland H. (1995) A controlled multivariate chart review of multiple complex developmental disorder. Journal of the American Academy of Child and Adolescent Psychiatry, 34(8), 1096-1106.

Van Engeland H & Van der Gaag RJ (1994) MCDD in childhood: A precursor of schizophrenic spectrum disorder. Schizophrenia Research, 11 (2), 197-207.

Van Lang ND, Boomsma A, Sytema S, de Bildt AA, Kraijer DW, Ketelaars C & Minderaa RB (2006) Structural equation analysis of a hypothetised symptom model in the autism spectrum. Journal of Child Psychology and Psychiatry and Allied Disciplines, 47(1), 37-44.

Van Os J, Hanssen M, Bijl RV & Vollebergh W (2001) Prevalence of psychotic disorder and community level of psychotic symptoms: an urban-rural comparison. Archives of General Psychiatry, 58(7), 663-668.

Van Steensel FJ, Bogels SM, Perrin S (2011) Anxiety disorders in children and adolescents with autistic spectrum disorders: a meta-analysis. Clinical Child and Family Psychological Review, 14(3), 302-317.

Verhulst FC & Ende van der J. (2013) Handleiding ASEBA. Vragenlijsten voor leeftijden 6 tot en met 18 jaar. Rotterdam: ASEBA Nederland.

Verhulst FC, Ende van der J & Koot HM (1996) Manual for the Child Behavior Checklist (in Dutch). Rotterdam, the Netherlands: Department of Child and Adolescent Psychiatry, ErasmusMC/ Sophia Children's Hospital.

Viding E, Blakemore SJ (2007) Endophenotype approach to developmental psychopathology: implications for autism research. Behavior Genetics, 37(1), 51-60.

Volden J & Lord C (1991) Neologisms and idiosyncratic language in autistic speakers. Journal of Autism and Developmental Disorders, 21(2), 109-130.

Volkmar FR, State M, Klin A (2009) Autism and autism spectrum disorders: diagnostic issues for the coming decade. Journal of Child Psychology and Psychiatry and Allied Disciplines, 50(1-2), 108-115.

Volkmar FR & Cohen DJ (1991) Comorbid association of autism and schizophrenia. American Journal of Psychiatry, 148(12), 1705-1707.

Walker DR, Thompson A, Zwaigenbaum L, Goldberg J, Bryson SE, Mahoney WJ, Strawbridge CP & Szatmari P (2004) Specifying PDD-NOS: A comparison of PDD-NOS, Asperger syndrome, and autism. Journal of the American Academy of Child and Adolescent Psychiatry, 43(2), 172-180.

Waterhouse L (2011) Autism Endpohenotypes are not unified by Gene Variants or Chromosome Number Variants. In: D.A. Fein (Ed.) The neuropsychology of autism, 482-499. Oxford University Press, Oxford, New York.

Waterhouse L, Morris R, Allen D, Dunn M, Fein D, Feinstein C, Rapin I & Win L (1996) Diagnosis and Classification in Autism. Journal of Autism and Developmental Disorders, 26(1), 59-86.

Wechsler D (1974) Wechsler Intelligence Scale for Children-Revised Manual (WISC-R). New York: The Psychological Corporation,

Weigelt S, Koldewyn K & Kanwisher N (2013) Face recognition deficits in autism spectrum disorders are both domain specific and process specific. PLoS ONE 8 (9); e74541.

Weigelt S, Koldewyn K & Kanwisher N (2012) Face identity recognition in autism spectrum disorders: A review of behavioral studies. Neuroscience and Biobehavioral Reviews, 36(3), 1060-1084.

Weisbroth DM, Gadow KD, Devincent CJ & Pomeroy J (2005) The presentation of anxiety in children with pervasive developmental disorders. Journal of Child and Adolescent Psychopharmacology, 15(3), 477-496.

White SW, Oswald D, Ollendick T & Scahill L (2009a) Anxiety in children and adolescents with autism spectrum disorders. Clinical Psychology Review, 29(3), 216-229.

White SW & Roberson-Nay R (2009b) Anxiety, social deficits, and loneliness in youth with autism spectrum disorders. Journal of Autism and Developmental Disorders, 39(7), 1006-1013.

White SJ & Saldana D (2011) Performance of children with autism on the Embedded Figures Test: a closer look at a popular task. Journal of Autism and Developmental Disorders, 4(11), 1565-1572.

WISC-R Projectgroep: Van Haasen PP, De Bruyn EEJ, Pijl YJ, Poortinga YH, Spelberg HC, Van der Steene G, Coetsier P, Spoelders-Claes R & Stinissen J (1986) WISC-R. Wechsler Intelligence Scale for Children-Revised, Dutch version. Lisse: Swets & Zeitlinger.

Witkin HA, Oltman PK, Raskin E & Karp S (1971) A manual for the embedded figures test. Palo Alto, CA, Consulting Psychologists Press.

Witwer AN & Lecavalier L (2010) Validity of comorbid psychiatric disorders in youngsters with autism spectrum disorders. Journal of Developmental and Physical Disabilities, 22, 367-380.

Witwer AN & Lecavalier L (2008) Examining the validity of autism spectrum disorder subtypes. Journal of Autism and Developmental Disorders, 38(9), 1611-1624.

Wolf JM, Tanaka JW, Klaiman C, Cockburn J, Herlihy L, Brown C, South M, McPartland J, Kaiser MD, Philips R & Schultz RT (2008) Specific impairment of face processing abilities in children with autism spectrum disorder using the Let's Face It! skills battery. Autism Research, 1(6), 329-340.

Wolff S & McGuire RJ (1995). Schizoid personality in girls: a follow-up study-what are the links with Asperger's syndrome? Journal of Child Psychology and Psychiatry and Allied Disciplines, 36(5), 793-817.

Wolff S (1991) 'Schizoid' personality in childhood and adult life. I: The vagaries of diagnostic labelling. III: The childhood picture. British Journal of Psychiatry. 159:615-620, 634-635.

Wright B, Clarke N, Jordan J, Young AW, Clarke P, Miles J, Nation K, Clarke L & Williams C (2008) Emotion recognition in faces and the use of visual context in young people with high-functioning autism spectrum disorders. Autism, 12 (6), 607-626.

Yoshida Y & Uchiyama T (2004) The clinical necessity of assessing attention deficit hyperactivity disorder symptoms in children with high-functioning pervasive developmental disorder. European Child and Adolescent Psychiatry, 13(5), 307-314.

Yung AR & McGorry PD (2007) Prediction of psychosis: setting the stage. British Journal of Psychiatry - Supplementum, 51, s1-8.

Yung AR, Yuen HP McGorry PD, Phillips LJ, Kelly D, Dell'Olio M, Francey SM, Cosgrave EM, Killackey E, Stanford C, Godfrey K & Buckby J (2005) Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. Australian and New Zealand Journal of Psychiatry, 39 (11-12), 964-971.

Yung AR, Phillips LJ, Yuen HP & McGorry PD (2004) Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. Schizophrenia Research, 67 (2-3), 131-142.

Yung AR, Phillips LJ, Yuen HP, Francey SM, McFarlane CA, Hallgren M & McGorry PD (2003) Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. Schizophrenia Research, 60 (1), 21-32.

Ziermans TB, Schothorst PF, Sprong M & van Engeland H (2011) Transition and remission in adolescents at ultra high-risk for psychosis. Schizophrenia Research, 126 (1-3), 58-64.

Zubin J & Spring B (1977) Vulnerability – a new view of schizophrenia. Journal of Abnormal Psychology, 86(2), 103-126.

LIST OF ABBREVIATIONS:

ADI-R	Autism Diagnostic Interview-Revised
ADOS	Autism Diagnostic Observation Schedule
ANCOVA	Analysis of Covariance
ANT	Amsterdam Neuropsychological Tasks
ASD	Autism Spectrum Disorders
BIC	Bayesian Information Criterion
BS	Baseline Speed
CAARMS	Composite Assessment of At Risk Mental States
CBCL	Child Behavior Check List
CC	Central Coherence
CEFT	Childhood Embedded Figures Test
CCC	Children's Communication Checklist
CI	Communication Impairments
CNV	Copy Number Variations
CSBQ	Childhood Social Behaviour Questionnaire
CSS	Calibrated Severity Scores
DISC-P	Diagnostic Interview Schedule for Children-Parent version
DSM	Diagnostic and Statistical Manual of Mental Disorders
ERP	Evoked Response Potential
fMRI	functional Magnetic Resonance Imaging
FTD	Formal Thought Disorder
FR	Facial Recognition
FSIQ	Full Scale IQ
IFE	Identification of Facial Emotions
IQ	Intelligence Quotient
KFTDS	Kiddie-Formal Thought Disorder rating Scale
LCA	Latent Class Analysis
LPA	Latent Profile Analysis
MCDD	Multiple Complex Developmental Disorder
PDD NOS	Pervasive Developmental Disorder Not Otherwise Specified
PIQ	Performance IQ
PQ	Prodromal Questionnaire
PR	Pattern Recognition
RRBI	Repetitive and Restrictive Behaviors and Interests
RT	Reaction Time
SCI	Social Communication & social Interaction (DSM 5)
SI	Social Impairments (SI)

SNP	Single Nucleotide Polymorfisms
UHR	Ultra High-Risk for developing psychosis
TD	Typically Developing
VIQ	Verbal IQ
WISC-R	Wechsler's Intelligence Scale for Children-Revised

SUMMARY

The aim of the current thesis was to contribute to the clarification of the heterogeneity within Autism Spectrum Disorder (ASD). The current studies were performed, using cross-sectional as well as longitudinal data. In the first part of this thesis, cross-sectional data were used, and we aimed at gaining more insight in the phenotypical variance of core and co-occurring symptoms of ASD (Chapters 2, 3). Core symptoms of ASD include social interaction problems, communication problems and repetitive and restrictive behaviors and interests (RRBI). Co-occurring psychiatric symptoms include all additional internalizing (depressive-, anxious-) problems and externalizing (behavioral-, attention-, oppositional-) problems. In the second part of this thesis (Chapters 4, 5, 6), longitudinal data were used and we explored whether three presumed endophenotypes as assessed in childhood (age 6-12) predicted a greater ASD symptom severity seven years later in adolescence (age 12-19).

In Chapter 1 general background information concerning the heterogeneity of ASD with respect to core and co-occurring psychiatric symptoms was provided. We defined endophenotypes as internal, not directly observable characteristics, which can be detected by biochemical tests, brain imaging or neuropsychological tests. The concept of endophenotypes was introduced in psychiatry in order to bridge the gap between the highly heterogenic genotype and the highly heterogenic phenotype in disorders like ASD. Three presumed endophenotypes were tested for their association with future ASD symptom severity in this thesis, namely: formal thought disorder, a linguistic and a social cognitive endophenotype; facial and emotion recognition, a social cognitive endophenotype and a detail oriented cognitive style, a non-social endophenotype. Also the main research questions were presented. The research questions concerning the first part of the thesis were as follows:

Do symptom profiles on core ASD symptoms support a categorical view with different underlying diagnostic categories or do they reflect a dimensional distribution of ASD symptoms?

How are co-occurring symptoms associated with severity of core ASD symptoms?

What is the influence of quality of social relations, ASD symptom severity and IQ on the manifestation of co-occurring anxiety in ASD?

The research questions concerning the second part of the thesis were:

Does Formal Thought Disorder (FTD) in school aged children with ASD predict a higher symptom severity of ASD in adolescence over and above the ASD symptom severity in childhood ? Or does FTD predict prodromal symptoms of psychosis in adolescence?

Does poor performance on indices of social cognition, namely Facial Recognition (FR) and Identification of Facial Emotions (IFE) in childhood predict higher symptom severity of ASD in adolescence over and above the ASD symptom severity in childhood?

Does a detail-focused cognitive style in childhood, operationalized as superior disembedding performance on a visuo-spatial test, predict higher symptom severity of RRBI symptoms in adolescence over and above the RRBI symptom severity in childhood?

In Chapter 2 we investigated in children with varying degrees of autistic symptoms whether classes could be discerned with different ASD symptom profiles. Furthermore, relations between core autistic traits and co-occurring internalizing and externalizing problems were assessed. Firstly, we detected profiles within the core symptom domains of ASD, as assessed with the Autism Diagnostic Observation Schedule (ADOS) in 234 clinically referred 6-13 year old children with varying degrees of autistic traits. Subsequently, we examined whether groups with different ASD symptom profiles differed regarding co-occurring internalizing and externalizing problems. Latent profile analyses revealed three classes that showed low, moderate versus high scores on all ADOS domains. Children with moderate ASD symptom profiles -often classified as PDD-NOS- showed relatively high levels of co-occurring internalizing and externalizing problems. Therefore, clinical attention is warranted for co-occurring problems in individuals with relatively low levels of ASD symptoms.

In Chapter 3 the influence of quality of social relations, ASD symptom severity and IQ on the manifestation of co-occurring anxiety in ASD was studied. The current study replicated and extended earlier findings by combining these three determinants of anxiety in ASD in one study. The sample consisted of 134 school aged children with ASD, of whom 58 (43%) had a comorbid anxiety disorder according to the Diagnostic Interview Schedule for Children-Parent version (DISC-P). In this sample, we tested associations between these determinants and anxiety using univariate and multivariate analyses to clarify the unique contribution of all determinants. Since we hypothesized that the association between limited quality of social relations and anxiety would be amplified by low symptom severity and/or high intelligence, we additionally tested for moderating effects. We found that higher anxiety levels were associated with a lower symptom severity ($\Delta R2 = 9.4$ %) and with a limited quality of social relations ($\Delta R2 = 4.6$ %). The variance in the dependent variable (anxiety levels) was mainly explained by lower ASD symptom severity. In this mainly high-functioning sample, intelligence was not related to

anxiety levels. No moderation effects were found. These findings support the idea that being aware of one's own social deficits -as is usually the case in individuals with low ASD symptom severity- augments levels of anxiety. Since limited quality of social relations are associated with higher anxiety levels in children with ASD, therapeutic interventions aimed at reducing anxiety in ASD should pay attention to improving social relations. Presumably children with a lower symptom severity could benefit most from such interventions, because these children are more self-conscious and they experience higher anxiety levels.

In Chapter 4 it was studied, whether childhood Formal Thought Disorder (FTD) predicted a higher ASD symptom severity in adolescence over and above ASD symptom levels in childhood. Furthermore we studied, whether childhood FTD predicted prodromal symptoms of psychosis in adolescence. FTD is a disruption in the flow of thought, which is inferred from disorganization of spoken language and which can be measured systematically using the KFTDS. The sample for this seven-year follow-up study consisted of 91 individuals with ASD, initially aged 5-12 years and 12-19 years at follow-up. Symptom severity was assessed using the ADOS in childhood (T1: ages 5-12 years) and again seven years later during adolescence (T2: ages 12-19 years). FTD in childhood, namely illogical thinking, predicted ASD symptom severity in adolescence over and above ASD symptom severity in childhood ($\Delta R2 = 13$ %). In this sample of children with ASD, FTD in childhood did not predict prodromal symptoms of psychosis in adolescence. We concluded that illogical thinking predicts severity of ASD symptoms in adolescence, but FTD does not predict prodromal symptoms of psychosis. These findings indicate that FTD in ASD is probably not an early sign of psychosis, but rather a manifestation of pragmatic language abnormalities in ASD. This finding further supports the importance of FTD in individuals with ASD for predicting future symptom severity and it underscores its potential value as an endophenotype. One precaution has to be stated, concerning the finding that FTD did not predict prodromal state of psychosis: Perhaps the relation between FTD and impending psychosis could not be demonstrated given the relatively early age of the participants in our sample. The average age at which individuals manifest a first episode psychosis is 19 year for men and 22 year for women; prodromal symptoms emerge around two years earlier. Therefore, the adolescents in our sample who were aged between 12.8 and 19 years at T2, may still be too young to display prodromal symptoms of psychosis and might go on to developing prodromal symptoms in the years to come.

In Chapter 5 we studied whether Facial Recognition (FR) and Identification of Facial Emotions (IFE) in childhood predict higher ASD symptom severity in adolescence

over and above ASD symptom severity in childhood. The sample for this seven year follow-up study consisted of 87 children with ASD, aged 6-12 years. FR and IFE were assessed during childhood (T1: age 6-12) using the Amsterdam Neuropsychological Tasks (ANT). ASD symptom severity was assessed using the ADOS in childhood and again seven years later during adolescence (T2: age 12-19).

More accurate FR significantly predicted lower adolescent ASD symptom severity scores ($\Delta R2 = 9\%$) even when controlling for childhood ASD symptom severity. IFE was not a significant predictor of ASD symptom severity in adolescence. We concluded that in children with ASD, the accuracy of FR in childhood is a relevant predictor of ASD symptom severity in adolescence. If FR is altered in childhood, this may indicate worse ASD symptom severity in adolescence. From a theoretical standpoint, these results underscore that alterations in FR are a core deficit in ASD, which partly determines future symptom severity and underscores the potential value as an endophenotype.

In Chapter 6 we studied whether a detail-oriented cognitive style, operationalized as having a superior disembedding performance on a visuo-spatial test in childhood, predicted a higher symptom severity of RRBI in adolescence over and above the RRBI symptom severity in childhood. The sample for this seven year follow-up study consisted of 87 children with ASD, aged 6-12 years. The detail-oriented cognitive style in childhood was assessed with the Childhood Embedded Figures Test (CEFT). ASD symptom severity (i.e. RRBI) was assessed using the ADOS in childhood (T1: ages 6-12 years) and again seven years later during adolescence (T2: ages 12-19).The overall performance in the CEFT test (accuracy in the complex condition divided by the time needed) significantly predicted a higher severity of RRBI symptoms in adolescence ($\Delta R2= 15\%$). This finding further supports the importance of a detail-oriented cognitive style in individuals with ASD for predicting future severity of RRBI symptoms and it underscores its potential value as an endophenotype.

In the last chapter of this thesis, Chapter 7, the main results and conclusions of this thesis were presented. Taken together, we found that the distribution of ASD core symptoms favored a dimensional model of ASD rather than a categorical model; that overall ASD symptom severity was inversely correlated with internalizing problems and especially anxiety; and that higher levels of anxiety were associated with milder ASD symptoms and with a worse quality of social relations. FTD and inaccurate FR in childhood predicted a higher ASD symptom severity in adolescence over and above ASD symptom severity in childhood and a superior disembedding performance or –in other words- an augmented tendency for local processing predicted a higher symptom severity of RRBI in adolescence over and above the RRBI symptom severity in childhood.

We discussed whether the three presumed endophenotypes fulfilled the general criteria for endophenotypes and especially the developmental criterion, which implies that endophenotypes have the potential to influence future course or symptom severity of a disorder. The three presumed endophenotypes met this developmental criteria for endophenotypes, because it was shown in this thesis that each of them had the potential to influence future symptom severity. Finally, the possible role of endophenotypes in future ASD research was highlighted; we argued that combining data from endophenotypical research, originating from different biological levels with genetic findings holds promise for future ASD research.

The current cross-sectional and longitudinal studies into the heterogeneity of ASD contribute a small step in the process of grasping the complex symptomatology and the complex social cognitive and neuropsychological underpinnings of ASD. We hope to provide the readers with some insights that will ultimately lead to bigger steps in the detection of evidence based endophenotypes, which ideally give rise to more reliable diagnostic procedures and to effective treatments for individuals with ASD.

SAMENVATTING

Het doel van dit proefschrift was om de grote variatie in symptomen en beloop van de autismespectrumstoornis (ASS) te verhelderen. Hierbij maakten we deels gebruik van gegevens, die op één meetmoment verzameld werden (cross-sectioneel) en deels van gegevens, die op twee verschillende momenten bij dezelfde deelnemers verzameld werden (longitudinaal). Met het eerste, cross-sectionele deel van dit proefschrift werd beoogd om meer inzicht te verkrijgen in de variatie in de kernsymptomen en de bijkomende (of comorbide) psychiatrische symptomen van ASS (Hoofdstukken 2 en 3). De kernsymptomen van ASS omvatten problemen in de sociale interactie, de communicatie en het derde cluster van kernsymptomen heeft betrekking op repetitieve, restrictieve gedragingen en interesses (RRBI). De comorbide psychiatrische symptomen omvatten alle bijkomende internaliserende (depressieve- of angst-) problemen en de externaliserende (gedrags-, aandachts-, oppositionele-) problemen. Het totaal van deze uiterlijk waarneembare kenmerken van een individu of van een aandoening wordt het fenotype genoemd. Het totaal van de erfelijke eigenschappen van een individu wordt genotype genoemd. Om de kloof tussen het variabele genotype en het eveneens variabele fenotype bij psychiatrische aandoeningen te overbruggen, werden de endophenotypen geïntroduceerd. Dit zijn inwendige, niet direct waarneembare kenmerken, die opgespoord worden met behulp van biochemische tests, beeldvormende technieken of neuropsychologische tests. Idealiter hangt een endophenotype van een aandoening samen met de genetische aanleg aan de ene kant en met de waarneembare symptomen aan de andere kant. In het tweede, longitudinale deel van dit proefschrift (hoofdstukken 4, 5, 6) werd van drie vermoedelijke endophenotypen één voor één onderzocht of hun aanwezigheid in de kinderleeftijd (leeftijd 6-12 jaar) ernstigere symptomen van ASS voorspelden in de adolescentie (leeftijd 12-19 jaar).

In hoofdstuk 1 werd nader toelichting gegeven over de heterogeniteit van ASS en daarbij kwam de variatie in kernsymptomen en de variatie in comorbide psychiatrische symptomen aan bod. Endophenotypen werden gedefinieerd en de criteria waaraan ze moeten voldoen, werden opgesomd. De drie specifieke endophenotypen die in dit proefschrift aan bod kwamen, werden uitgebreid toegelicht, namelijk formele denkstoornissen, een linguïstisch en sociaal-cognitief endophenotype; gezichts- en emotieherkenning, een sociaal cognitief endophenotype en een detailgeoriënteerde cognitieve stijl, een niet-sociaal endophenotype. De belangrijkste onderzoeksvragen werden gepresenteerd, namelijk voor het eerste deel van dit proefschrift:

Passen symptoomprofielen van ASS kernsymptomen bij een categorale opvatting met verschillende onderliggende diagnostische categorieën of zijn de ASS kernsymptomen dimensioneel verdeeld?

Hoe zijn de ernst van de ASS kernsymptomen en de ernst van comorbide psychiatrische symptomen geassocieerd?

Wat is de invloed van de kwaliteit van sociale relaties, de ernst van de ASS symptomen en het IQ op de manifestatie van comorbide angst symptomen bij ASS?

In het tweede deel van het proefschrift waren de onderzoeksvragen:

Voorspellen formele denkstoornissen (Formal Thought Disorder; FTD) bij basisschool kinderen met ASS ernstigere ASS symptomen in de adolescentie, ook na correctie voor de ernst van ASS symptomen op de kinderleeftijd? Of voorspelt FTD het optreden van prodromale verschijnselen van psychose in de adolescentie?

Voorspellen slechtere resultaten op sociaal cognitieve tests voor gezichtsherkenning (Facial Recognition; FR) en emotieherkenning (Identification of Facial Emotions; IFE) bij basisschool kinderen met ASS ernstigere ASS symptomen in de adolescentie, ook na correctie voor de ernst van ASS symptomen op de kinderleeftijd?

Voorspelt een detail georiënteerde cognitieve stijl ernstigere RRBI symptomen in de adolescentie ook na correctie voor de ernst van RRBI symptomen op de kinderleeftijd?

In Hoofdstuk 2 onderzochten we in een groep kinderen met uiteenlopende ernst van autistische symptomen of er bepaalde klassen onderscheiden konden worden elk met kenmerkende symptoomprofielen. Hierbij werd gebruik gemaakt van latente klasse analyse, een statistische techniek, waarmee groepen ingedeeld worden op basis van allerhande kenmerken zonder dat er gebruik gemaakt wordt van a priori hypothesen. De profielen binnen de kernsymptomen van ASS werden bepaald op basis van de scores op het Autism Diagnostic Observation Schedule (ADOS) bij 234 klinisch verwezen kinderen van 6-13 jaar. Vervolgens onderzochten we of groepen met verschillende ASS symptoomprofielen verschilden met betrekking tot de comorbide internaliserende en externaliserende problemen. De latente klasse analyse onthulde drie klassen die zich achtereenvolgens kenmerkten door lage, matige en hoge scores op alle ADOS symptoom domeinen, hetgeen strookt met een dimensionele opvatting van ASS. Kinderen met een matige ernst van ASS symptomen - doorgaans geclassificeerd als PDD NOS - hadden relatief hoge niveaus van internaliserende en externaliserende problemen. Hulpverleners dienen zich bewust te zijn, dat comorbide psychiatrische problemen juist bij kinderen met relatief mildere autistische symptomen ernstigere niveaus kunnen aannemen.

In Hoofdstuk 3 werd de invloed van de kwaliteit van sociale relaties, de ernst van ASS symptomen en het IQ op de ernst van comorbide angst symptomen bij kinderen met ASS bestudeerd. Met onze studie wilden we eerdere bevindingen

repliceren en deze uitbreiden door bovenstaande drie determinanten van angst bij ASS in één studie en in één statistisch model te integreren. De steekproef voor deze studie bestond uit 134 basisschool kinderen met ASS, van wie er 58 (43%) een comorbide angststoornis volgens de Diagnostic Interview Schedule for Children-Parent version (DISC-P) hadden. In de onderzoeksgroep werden associaties tussen deze determinanten eerst univariaat en vervolgens multivariaat getoetst om de unieke bijdrage van elke determinant te bepalen. Omdat we veronderstelden dat de drie determinerende factoren elkaar zouden versterken, werden ook zogenaamde moderatie effecten getoetst. We vonden dat hogere angstniveaus geassocieerd waren met een lagere ernst van ASS symptomen (ΔR2 [verklaarde variantie] = 9.4 %) en met een beperktere kwaliteit van sociale relaties (ΔR2 [verklaarde variantie] = 4.6 %). In deze, voornamelijk hoger-functionerende groep van kinderen met ASS was IQ niet gerelateerd aan angstniveaus. We vonden geen moderatie effecten. De kinderen met een lage ernst van ASS symptomen ervaren waarschijnlijk meer angst in het dagelijks leven doordat ze zich meer bewust zijn van hun eigen sociale tekortkomingen. Omdat een beperkte kwaliteit van sociale relaties geassocieerd is met hogere angstniveaus, dienen therapeutische interventies tegen angst bij ASS mede gericht te zijn op het verbeteren van sociale relaties.

In Hoofdstuk 4 onderzochten we of formele denkstoornissen (Formal Thought Disorder; FTD) op de kinderleeftijd een hogere ernst van ASS symptomen voorspelde in de adolescentie, ook na correctie voor de ernst van ASS symptomen op de kinderleeftijd. Voorts bestudeerden we of FTD op de kinderleeftijd prodromale symptomen van psychose voorspelde in de adolescentie. FTD is een onderbreking van de normale gedachtestroom, die afgeleid wordt uit de desorganisatie van de gesproken taal en die systematisch vastgesteld kan worden. De onderzoeksgroep voor deze zeven jaar omvattende longitudinale studie bestond uit 91 kinderen met ASS, die bij het eerste meetmoment 5-12 jaar oud waren en bij het tweede meetmoment 12-19 jaar. FTD werd gemeten op de kinderleeftijd met behulp van de Kiddie Formal Thought Disorder Scale (KFTDS). De ernst van ASS symptomen op de kinderleeftijd en in de adolescentie werd vastgesteld met behulp van de ADOS. Een bepaald type FTD op de kinderleeftijd, namelijk onlogisch denken, voorspelde de ernst van ASS symptomen in de adolescentie, ook na correctie voor de ernst van ASS symptomen op de kinderleeftijd (ΔR2 [verklaarde variantie] = 13 %). FTD op de kinderleeftijd voorspelde niet het optreden van prodromale symptomen van psychose in de adolescentie. Deze bevindingen lijken erop te wijzen dat FTD bij kinderen met ASS geen vroeg teken van latent aanwezige psychose is, maar veeleer een uiting van een verstoorde taalexpressie en taalpragmatiek. Deze bevindingen onderstrepen het belang van FTD voor het voorspellen van de toekomstige ernst van ASS symptomen en ze onderstrepen het potentiële belang van FTD als endopheno-

type. Bij de bevinding dat FTD niet de prodromen van psychose voorspelde, dient aangetekend te worden dat de deelnemers in dit onderzoek relatief jong waren. De gemiddelde leeftijd waarop een eerste psychose zich manifesteert ligt rond de 19 jaar bij mannen en rond de 22 jaar bij vrouwen en prodromale symptomen doen zich doorgaans circa 2 jaar vroeger voor. De adolescenten in onze onderzoeksgroep varieerden in leeftijd van 12.8 tot 19 jaar, dus een deel van deze adolescenten was te jong om al prodromale verschijnselen van psychose te vertonen. Mogelijk zal een deel van deze adolescenten alsnog in de komende 5 jaar prodromen van psychose ontwikkelen.

In Hoofdstuk 5 onderzochten we of gezichtsherkenning (Facial Recognition; FR) en emotieherkenning (Identification of Facial Emotions; IFE) op de kinderleeftijd een hogere ernst van ASS symptomen in de adolescentie voorspelt, ook na correctie voor de ernst van ASS symptomen op de kinderleeftijd. De onderzoeksgroep van deze longitudinale studie bestond uit 87 kinderen met ASS, in leeftijd variërend van 6-12 jaar. FR en IFE werden gemeten op de kinderleeftijd (meetmoment 1: leeftijd 6-12 jaar) met behulp van de Amsterdam Neuropsychological Tasks (ANT). De ernst van symptomen werd zowel op de kinderleeftijd als in de adolescentie gemeten met behulp van de ADOS. Een nauwkeurige FR op de kinderleeftijd voorspelde een lagere ernst van ASS symptomen in de adolescentie ($\Delta R2$ [verklaarde variantie] = 9%), ook na correctie voor de ernst van ASS symptomen op de kinderleeftijd. IFE op de kinderleeftijd was niet voorspellend voor de ernst van ASS symptomen in de adolescentie. In deze studie bepalen FR problemen voor een deel de toekomstige ernst van ASS symptomen en de waarde van FR als potentieel endophenotype voor ASS wordt daarmee onderstreept.

In Hoofdstuk 6 bestudeerden we of een detail gerichte cognitieve stijl op de kinderleeftijd een hogere ernst van RRBI symptomen in de adolescentie voorspelde, ook na correctie voor de ernst van RRBI symptomen op de kinderleeftijd. De onderzoeksgroep voor deze longitudinale studie bestond uit 87 kinderen met ASS van 6-12 jaar. De mate van gerichtheid op details werd vastgesteld met de Childhood Embedded Figures Test (CEFT). Bij deze visuospatiële test dienen kinderen eenvoudige of lastige vormen te herkennen binnen ingewikkelde achtergrondpatronen. Hoge gerichtheid op details vertaalt zich in een beter vermogen om deze vormen snel en accuraat te herkennen. De ernst van ASS symptomen op de kinderleeftijd (T1: leeftijd 6-12 jaar) en in de adolescentie (T2: leeftijd 12-19 jaar) werd vastgesteld met behulp van de ADOS. Prestaties op de CEFT test (het vermogen om lastige vormen snel en accuraat te herkennen) op de kinderleeftijd voorspelde een hogere ernst van RRBI symptomen in de adolescentie ($\Delta R2$ [verklaarde variantie] = 15%), ook na correctie voor de ernst van ASS symptomen op de kinderleeftijd. Deze bevindingen onderstrepen het belang van een detail georiënteerde stijl bij kinderen met ASS

als voorspeller voor de toekomstige ernst van RRBI symptomen en als potentieel endophenotype voor ASS.

In het laatste hoofdstuk van dit proefschrift, hoofdstuk 7, werden de voornaamste resultaten en conclusies gepresenteerd en nader geïnterpreteerd. We bediscussieerden of de drie veronderstelde endophenotypen voldeden aan de algemene criteria voor endophenotypen en of ze voldeden aan het ontwikkelingsgerelateerde criterium, dat endophenotypen het toekomstige beloop of de toekomstige ernst van een aandoening kunnen beïnvloeden. De drie veronderstelde endophenotypen voldoen aan dit criterium, omdat we in drie studies hebben aangetoond dat deze endophenotypen de toekomstige ernst van ASS symptomen en het beloop beïnvloeden. Tot slot werd de mogelijke rol van endophenotypen in toekomstige ASS research geschetst. Het combineren van empirische data over endophenotypen van verschillende biologische niveaus met genetische research zal wellicht in de toekomst belangrijke resultaten opleveren.

Deze cross-sectionele en longitudinale studies naar de heterogeniteit van ASS dragen in bescheiden mate bij aan het begrijpen van de complexe symptomen en de complexe onderliggende sociaal-cognitieve en neuropsychologische oorzaken van ASS. We hopen dat op termijn de resultaten van deze studie, in combinatie met de resultaten van vele andere studies, zullen resulteren in empirisch stevig gefundeerde endophenotypen, die op hun beurt zullen bijdragen aan betrouwbare diagnostische procedures en effectieve behandelingen voor mensen met ASS.

CURRICULUM VITAE

Mart Eussen werd geboren op 1 april 1954 in Geleen. Hij behaalde zijn Gymnasium-β diploma aan het Sint Michiellyceum in Geleen. Van 1972 tot 1980 studeerde hij geneeskunde aan de Katholieke Universiteit Nijmegen. Hij onderbrak deze studie om over land naar India te reizen, voordat de Iraanse revolutie en de Russische inval in Afghanistan dit onmogelijk maakten. Hij vervulde de vervangende militaire dienst in het Groot Graffel (GGNet) te Warnsveld met als supervisor Jan Hofstra. De specialisatie tot psychiater doorliep hij in het Psycho-Medisch Streekcentrum Vijverdal te Maastricht met als opleiders Prof.Dr. Mark Richartz en Prof. Dr. Marius Romme. Tegelijkertijd volgde hij aan het RINO Maastricht de opleiding tot psychotherapeut met als specialisatie gezinstherapie bij Mieke Crolla-Baggen. De opleiding tot kinder- en jeugdpsychiater volgde hij aansluitend te Rotterdam, opleider Prof. Dr. Frank Verhulst en te Utrecht, opleider Prof. Dr. Herman van Engeland. Na zijn opleiding ging hij werken bij De Grote Rivieren, thans Yulius te Dordrecht. Samen met een aantal inspirerende collega's zette hij daar het kinder- en jeugdpsychiatrisch centrum de Kreek op.

Sinds 1996 is hij opleider aandachtsgebied kinder- en jeugdpsychiatrie bij Yulius. Tussen 1996 en 2015 heeft hij in totaal circa 45 (kinder- en jeugd)psychiaters opgeleid.

Van 1996 tot heden heeft Mart diverse leidinggevende taken binnen Yulius vervuld.

Van 2009 tot 2015 was hij lid van de visitatiecommissie psychiatrie en momenteel is hij voorzitter van het landelijk overleg opleiders in de kinder- en jeugdpsychiatrie. Sinds 2014 is hij lid van de Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam (TWOR).

Zijn bijzondere interesse gaat uit naar: acute kinder- en jeugdpsychiatrie, psychotische stoornissen en de voorstadia daarvan, ontwikkelingsstoornissen en psychiatrie bij verstandelijk beperkten. Over deze interessegebieden heeft hij diverse artikelen en hoofdstukken geschreven en veel voordrachten gehouden.

Vanaf 2008 werkte Mart aan zijn promotieonderzoek binnen de afdeling kinder- en jeugdpsychiatrie/psychologie van het Erasmus MC-Sophia (hoofd: Prof. Dr. Frank Verhulst). In deze periode werd de onderzoekslijn Autisme (hoofdonderzoeker Dr. Kirstin Greaves-Lord) vorm gegeven in een samenwerkingsverband tussen bovengenoemde afdeling en Yulius. De gegevens voor dit proefschrift zijn grotendeels ontleend aan de GAME studie (towards Genotypes in Autism, Measuring Endophenotypes), een vervolgstudie naar kinderen met een autismespectrumstoornis. In deze vervolgstudie werd uitgebreide vervolgdiagnostiek uitgevoerd bij

adolescenten, die zeven jaar eerder als kinderen ook uitgebreid onderzocht waren. De resultaten van dit promotieonderzoek staan in dit proefschrift beschreven.

Mart Eussen is getrouwd met Vera Lansink en heeft twee kinderen, David en Anne-Sophie.

PHD PORTFOLIO

OVERZICHT VAN PHD TRAINING, PUBLICATIES,

VOORDRACHTEN EN ONDERWIJSACTIVITEITEN

Naam:	Mart L.J.M. Eussen
Promotieperiode:	maart 2008 - eind 2014
Erasmus MC afdeling:	Kinder- en Jeugdpsychiatrie
Promotor:	Prof. Dr. F. C. Verhulst
Copromotor:	Dr. K. Greaves Lord

PhD training in Researchvaardigheden:

- Cursus Good Clinical Practice Maasstad Ziekenhuis Rotterdam en Basiscursus Regelgeving en Organisatie Klinisch Onderzoek, gevolgd door examen bij Examenbureau Medisch Wetenschappelijk Onderzoek, maart/april 2015, 14 uur.
- Erasmus Winter Program NIHES Netherlands Institute for Health Sciences. Regression Analysis for Clinicians by Brian Verdoux, 23-01-2012 until 28-01-2012, 40 hours.
- Erasmus Summer Program NIHES Netherlands Institute for Health Sciences Introduction to Data analysis by Adelin Albert, 09-08-2010 until 13-08-2010. 25 lesuren.
- Corsendonck cursus. Onderzoeksmethoden, 2001, 40 lesuren.

PUBLICATIES:

Internationaal:

M.L.J.M. Eussen, A. Louwerse, C.M. Herba, A.R. Van Gool, F. Verheij, F.C. Verhulst, K. Greaves-Lord (2015) Childhood facial recognition predicts adolescent symptom severity in autism spectrum disorders. Autism Research. DOI: 10.1002/aur.1443

M.L.J.M. Eussen, E.I. de Bruin, A.R. Van Gool, A. Louwerse, J. van der Ende, F. Verheij, F.C. Verhulst, K. Greaves-Lord (2014) Formal thought disorder in autism spectrum disorder predicts future symptom severity, but not psychosis prodrome. European Child and Adolescent Psychiatry. 24(2):163-72, 2015 Feb.

M.L.J.M Eussen , A.R. Van Gool, F. Verheij, P. de Nijs. FC. Verhulst, K. Greaves-Lord (2013) The association of quality of social relations, symptom severity and intelligence with anxiety in children with autism spectrum disorders. Autism 17 (6): 723-735.

L. de Boer-Schellekens, M. Keetels, M.L.J.M. Eussen, J. Vroomen (2013). No evidence for impaired multisensory integration of low-level audiovisual stimuli in adolescents and young adults with autism spectrum disorders. Neuropsychologia. 51: 3004–3013.

L. de Boer-Schellekens, M.L.J.M. Eussen, J. Vroomen (2013) Diminished sensitivity of audiovisual temporal order in autism spectrum disorder. Front Integrative Neuroscience;7:8.

K. Greaves-Lord, M.J.L.M. Eussen, F.C. Verhulst, R.B. Minderaa, W. Mandy, J.J. Hudziak, M.P. Steenhuis, P.F. de Nijs, C.A. Hartman (2013). Empirically based phenotypic profiles of children with pervasive developmental disorders: interpretation in the light of the DSM-5. Journal of Autism & Developmental Disorders; 43(8):1784-1797.

Submitted for publication: A. Louwerse, M.L.J.M. Eussen, P.F.A. de Nijs, A.R. Van Gool, F. Verheij, F.C. Verhulst, K. Greaves-Lord. Autism spectrum disorders from childhood to adolescence: diagnostic stability and predictors of diagnostic improvement.

F.C. Verhulst, M.L.J.M. Eussen, G-F.M.G. Berden, J. Sanders-Woudstra, J.v.d. Ende (1993) Pathways of problem behaviors from childhood to adolescence. Journal of the American Academy of Child and Adolescent Psychiatry, 32: 388-396

A. Arntz, B. v Beijsterveldt, R. Hoekstra, A. Hofman, M. Eussen, S. Sallaerts (1992) The Interrater reliability of a Dutch version of teh structured Clinical Interview for DSM 3 r Personality Disorders. Acta Psychiatrica Scandinavica, 85: 394-400.

Nationaal:

M.L.J.M. Eussen. Hoofdstuk Schizofreniespectrum en andere psychotische stoornissen. In: Kinder- en jeugdpsychiatrie. Redactie: F. Verheij, F.C. Verhulst, F. Verheij, M. Danckaerts. Van Gorkum, Assen 2014: 499-521.

K. Greaves-Lord, M.L.J.M. Eussen, C. Hartman. Symptoomprofielen van kinderen met een pervasieve ontwikkelingstoornis: Interpretatie in het kader van de DSM-5. Wetenschappelijk Tijdschrift Autisme 2013; 12(3): 50-53 .

K. Greaves-Lord, M.L.J.M. Eussen, J. Duvekot, A. Louwerse, L.W. ten Hoopen, P.F. de Nijs. Dimensionele en categoriale diagnostiek als solide basis voor zorg en onderzoek. Wetenschappelijk Tijdschrift Autisme 2012; 11(2): 68-71.

A. Louwerse, M.L.J.M. Eussen, K. Greaves-Lord. Het beloop van autismespectrumstoornissen, een sneak preview van 4 casussen uit een vervolgonderzoek. Wetenschappelijk Tijdschrift Autisme 2012: 119-128, jaargang 11, no. 4.

K. Greaves-Lord., M.L.J.M. Eussen, J. Duvekot, A. Louwerse, L.W. ten Hoopen, P.F. de Nijs (2012) Dimensionele en categoriale diagnostiek als solide basis voor zorg en onderzoek. Wetenschappelijk Tijdschrift Autisme 2012; 11(2): 68-71.

M.L.J.M. Eussen "Veranderen door het aanleren van nieuw gedrag (met pervasieve ontwikkelingsstoornissen als voorbeeld)", hoofdstuk 35 in Verheij. F (Red.): Integratieve kinder- en jeugdpsychotherapie. Van Gorkum, Assen, 2011, 2005: 515-528.

M.L.J.M. Eussen "Veranderen door het aanleren van nieuwe cognities (met aandachtstekort/hyperactiviteitstoornissen als voorbeeld)", hoofdstuk 36 in Verheij. F (Red.): Integratieve kinder- en jeugdpsychotherapie. Van Gorkum, Assen, 2011, 2005: 528-545.

M.H. de Jong, M.L.J.M. Eussen, A.R. Van Gool (2010). Antipsychotica en stimulantia: een zinvolle combinatie? Tijdschrift voor Psychiatrie 2010; 1: 51-57.

M.L.J.M. Eussen, G. Faber (2009). Antipsychotica bij kinderen en jeugdigen met eerste psychose. Psyfar 2009; vol. 4 nr. 2: 15-20.

R.T. Pauw, H.G. Dieleman, E.M. de Vogel, M.L.J.M. Eussen (2008) Retrospectief, observationeel onderzoek naar switchen en stoppen van ADHD-medicatie. PW Wetenschappelijk Platform; 2008; 2 (8): 183-187.

M.L.J.M. Eussen (2007) "Zelfverwondend gedrag bij jongeren met een verstandelijke beperking". Kind en Adolescent, Praktijk, september 2007; 6, no.3: 112-119.

M.L.J.M. Eussen, T. Franzen (2007) "Automutilatie bij jongeren". Kind en Adolescent, Praktijk, februari 2007; 6, no. 1: 24-32.

M.L.J.M. Eussen (2007) "Psychotische stoornissen en schizofrenie" in: Verheij F, Verhulst F.C en Ferdinand R.F (red.) Kinder- en jeugdpsychiatrie. Behandeling en begeleiding. Van Gorkum, Assen: 346-371.

M.L.J.M. Eussen (2003) " Psychotische stoornissen". In: Kinder,- en Jeugdpsychiatrie, Psychopathologie onder redactie van F.C. Verhulst, F. Verheij en R.F. Ferdinand (Red.), hoofdstuk 10. Van Gorkum, Assen: 396-412.

M.L.J.M. Eussen (2001) Klinisch psychiatrische zorgprogramma's in: J. Hermanns, C. Nijnatten, M. Smit, F. Verheij, M. Reuling (Red.) Handboek Jeugdzorg: methodieken, zorgprogramma's en doelgroepen. B. 8-1 tot 8-20. Bohn Stafleu, van Loghum, Houten/Diegem.

M.L.J.M. Eussen (2001) Schizofrenie en andere psychosen, hoofdstuk 5. In: F.C. Verhulst en F. Verheij (Red.); Adolescentenpsychiatrie. Van Gorkum, Assen: 119-130.

M.L.J.M. Eussen en J. Duyx (2000) Schizofrenie, hoofdstuk 14. In F.C. Verhulst en F. Verheij (red.) Kinder- en jeugdpsychiatrie. Onderzoek en diagnostiek. Van Gorkum.

M.L.J.M. Eussen (2000) Kinderen en Jeugdigen met depressieve klachten zijn op korte termijn geholpen met cognitieve gedragstherapie. In: Maandblad Geestelijke Volksgezondheid, no. 4: 360-363.

M.L.J.M. Eussen (1999) Vroege opsporing en onderkenning van psychotische stoornissen, hoofdstuk 14. In: F. Verheij, M. Monasso, M. Eussen en J. van Nuland (red.): Zorgbreedte van de kinder- en jeugdpsychiatrie. Van Gorkum, Assen: 119-130.

D.N. Oudshoorn, H.C.M. Brans, J.H.M. Duyx, M.L.J.M. Eussen (1998) , Kinder en adolescentenpsychiatrie, een praktisch leerboek. Bohn, Stafleu, van Loghum, Houten. Redactievoering bij de tweede druk.

M.L.J.M. Eussen (1996) Manisch-depressieve psychosen, hoofdstuk 16. In: F. Verheij (red.) Kinder- en Jeugdpsychiatrie. Behandeling en begeleiding, deel 3. Van Gorkum, Assen: 236-245.

M.L.J.M. Eussen (1992). Dissociatieve stoornissen bij kinderen en jeugdigen. Tijdschrift voor Orthopedagogiek, Kinderpsychologie en Kinderpsychiatrie (17), no.1:19-31.

VOORDRACHTEN:

"Psychopharmacologic agents in the treatment of Autism Spectrum Disorder: Consequences of long term use." International Congress on Autism and related developmental disorders, Campinas (Brazilie), 23-24-25 april 2015.

"Versterkte detailwaarneming op de kinderleeftijd voorspelt ernst van repetitief gedrag in de adolescentie: een zeven jaars follow-up studie van kinderen met autismespectrumstoornis." Voorjaarscongres Nederlandse Vereniging voor Psychiatrie. Maastricht, 1 april 2015.

"Psychiatrische stoornissen en met name autismespectrumstoornissen bij licht verstandelijk beperkten." Post-Academisch Onderwijs Geneeskunde voor kinderartsen en arts verstandelijk gehandicapten. Rotterdam, 5 juni 2014.

"Predictoren en correlaten van antipsychotica en stimulantia gebruik bij kinderen met autismespectrumstoornissen: een zeven jaars follow-up studie." Voorjaarscongres Nederlandse Vereniging voor Psychiatrie. Maastricht, 12 april 2014.

"Neuropsychologische diagnostiek bij autismespectrumstoornissen." Yulius Congres: De rol van cognitie bij psychiatrische stoornissen: theorie en praktijk. Ridderkerk, 19 november 2013.

"Does Formal Thought Disorder in Autism Spectrum Disorder predict Prodromal Symptoms of Psychosis?" Poster bij IMFAR congres San Sebastian, mei 2013.

"Predictieve waarde van neuropsychologische testen voor het functioneren 7 jaar later: een follow-up studie." Voorjaarscongres Nederlandse Vereniging voor Psychiatrie, (NVvP) Maastricht, 11 april 2013.

"Levensloop psychiatrie." Hofreferaat Yulius, 29 januari 2013.

"Psychologische interventies en met name cognitieve gedragstherapie bij (prodromen van) eerste psychose. Workshop bij Psychologen Conferentie GGZ Noord-Holland Noord, 4 oktober 2012.

"Does Formal Thought Disorder in Autism Spectrum Disorder predict Prodromal Symptoms of Psychosis?" Poster bij IMFAR congres Toronto, mei 2012.

"Behandeling van stemmen en wanen met cognitieve gedragstherapie in de vroege fase van een psychose". Workshop op het jubileumcongres van de Vereniging voor Kinder-en Jeugd Psychotherapie, 20 april 2012.

"Associatie van ernst van symptomen, kwaliteit van sociale relaties en intelligentie met angst bijkinderen met autismespectrumstoornissen". Voorjaarscongres Nederlandse Vereniging voor Psychiatrie, (NVvP) Maastricht, 4 april 2012.

"Opsporing en behandeling in de vroege fase van een eerste psychose." Nascholing voor vakgroep medici van Yulius. Rotterdam, 29-11-2011.

"Voorlopige data van een 7 jaars follow-up studie van 142 kinderen met autismespectrumstoornis" Congres: De kracht van autisme. Barendrecht, 15 en 16 november 2011.

"Neuro-biologie van autismespectrumstoornissen, toegespitst op mensen met autisme en verstandelijke bepreking." Regionale bijscholing Artsen Verstandelijk Gehandicapten, Sliedrecht, 19 september 2011.

Betekenis van neuro-psychologisch onderzoek bij de diagnostiek van autismespectrumstoornissen bij kinderen. Voorjaarscongres Nederlandse Vereniging voor Psychiatrie, Amsterdam, 31 maart 2011.

"Naar een evidence based, integratief behandelprogramma ADHD. Synopsis van de bijscholingsdag." Verdiepingscursus ADHD van het Landelijk Platform ADHD, Zeist, 15 februari 2011.

"Cognitieve Stijlkenmerken als endophenotypen bij autismespectrumstoornissen: implicaties voor diagnostiek en behandeling." Congres: Autisme en Behandeling. Het belang van de context. Rotterdam, 30 november 2010.

"Actuele kwesties met betrekking tot de diagnostiek van autismespectrumstoornissen, vooruitlopend op de DSM V." Hofreferaat Yulius, 21 september 2010.

"De relatie tussen de ernst van autismespectrumstoornissen en bijkomende psychopathologie." Voorjaarscongres Nederlandse Vereniging voor Psychiatrie, Maastricht, 15 april 2010.

"Specificering van het Autisme Spectrum Phenotype: Ordening binnen de diversiteit." Wetenschapsmarkt Yulius, 29 maart 2010.

"Neurobiologie van Autismespectrumstoornissen." Nascholing psychiaters Regio Rijnmond. Delta Psychiatrisch Ziekenhuis. 16 maart 2010.

"Psychologische interventies en beslismomenten in het zorgprogramma ADHD." Leerhuis Albert Schweitzer Ziekenhuis, 4 maart 2010.

"Neurobiology of autism spectrum disorders." tijdens de 'Brazilian Conference on Education and Care in Children and Adolescents' te Sao Paulo, Brazilië op 5 en 6 februari 2010.

M.L.J.M. Eussen, 'Treatment of Early Psychosis' tijdens de 'Brazilian Conference on Education and Care in Children and Adolescents' te Sao Paulo, Brazilië op 5 en 6 februari 2010.

"Subtypering binnen de autismespectrumstoornissen: ordening in de diversiteit?" in het kader van presentatie onderzoekslijn: Voorjaarscongres Vereniging voor Psychiatrie, 3 april 2009 te Groningen.

Behandeling van psychotische jongeren. Evidence based behandelen en kwaliteit. Congres : Van zorglijn naar speelruimte, 2 daags congres over behandelingen in de kinder-en jeugdpsychiatrie (tevens organisatie van dit congres). Maart 2009.

"Acute beelden in de kinder- en jeugdpsychiatrie." Congres "Hoofdzaken", over de rol van het brein bij kinderneurologische en kinderpsychiatrische aandoeningen. Vakgroep Kindergeneeskunde. Eramsus MC Rotterdam. Oktober 2008.

"Suïcide en suïcidepogingen bij kinderen en adolescenten." Middagsymposium over suïcide en suïcidepreventie. Georganiseerd door Stichting Na- en Bijscholing Psychiaters Brabant. Etten-Leur. September 2008.

"De behandeling van eerste psychosen in een zorglijn." RMPI congres: Vertrouwen en wantrouwen. Barendrecht. Mei 2008.

"Suïcide en automutilatie bij jongeren." Boerhaave cursus: Agressie in de kinder-en jeugdpsychiatrie. Leiden. November 2007.

"Psycho-therapeutische interventies bij eerste psychose. Een overzicht van keuze-criteria en effect." Symposium Zuid-West: Nieuwe ontwikkelingen in de behandeling van eerste psychosen. Dordrecht. Februari 2007.

"Automutilatie" in het kader van het blok "Emergencies in de kinder- en jeugdpsychiatrie". Boerhaave-cursus, nascholing voor (kinder-en jeugd)psychiaters te Leiden. Oktober 2006.

"Beddenreductie en de verhouding bedden en stoelen in de kinderpsychiatrie." Congres: Bedloze psychiatrie: over substitutie en beddenreductie in de psychiatrie. Congresreeks sociale psychiatrie. April 2006.

"Psychosen bij adolescenten" in het kader van het blok: "De adolescent" in de kinderartsenweek, bijscholingscursus voor kinderartsen. Erasmus MC te Rotterdam. Januari 2006.

"Interventies binnen de integratieve psychotherapie voor kinderen en jeugdigen" in het kader van het symposium "Integratieve Psychotherapie" te Rotterdam. Oktober 2005.

"Cannabis en geestelijke gezondheid". Referaat met G. Faber in het kader van nascholing van psychiaters in regio Rijnmond te Rotterdam. Mei 2005.

"Prodromen en vroege tekenen van psychose". Workshop bij het voorjaarscongres van de NVvP. April 2005.

"De toepassing van Assertive Community Treatment bij eerste psychose" . Symposium door het Netwerk Vroege Psychose bij het voorjaarscongres van de NVvP. Taak: voorzitter en organisator. Bijdragen van: J. de Kroon (Trimbos), P.J. Roks (GGZ-

Eindhoven), M. Hilwig (Universiteit Maastricht), I. Bandhoe (Rivierduinen). April 2005.

"Comorbiditeit van autisme en psychotische stoornissen." Congres: autisme en comorbiteit. Ederhorst, Ede. November 2004.

"Vroege opsporing en behandeling van eerste psychosen. Is behandeling in prodromale fase mogelijk en nuttig?" Tweede IJsselmeersymposium. September 2004.

"Nieuwe ontwikkelingen in onderzoek t.a.v. eerste psychose/prodromale fase." Netwerk vroege psychose, Amersfoort. September 2004.

"First psychotic episode: the clinical manifestation." Boerhaave curcus: The first psychotic episode, Leiden. Juni 2004.

"Psychopathologie in de adolescentie: psychotische stoornissen en schizofrenie." In het kader van kinderartsenweek: nascholing voor kinderartsen. Rotterdam. Januari 2004.

"Behandeling en neuropsychologische aspecten van eerste psychosen en prodromale fase van eerste psychosen" Tweede Veluwemeer symposium, Harderwijk. September 2003.

"De rol van de jeugdpsychiatrische kliniek bij de behandeling van psychotische stoornissen" Congres klinische jeugdpsychiatrie: "Speelveld tussen de lijnen, een machtig spel". Rotterdam. September 2003

"Vroegtijdige opsporing en onderkenning van psychotische stoornissen bij jongeren." Voorjaarscongres van de NVvP te Amsterdam. April 2003

"Ontwikkelingstheorieën van psychosen", bij het symposium "The state of the art bij de opvang van patiënten met een eerste psychose". Voorjaarscongres NVvP. April 2001. Rotterdam.

"Cognitieve aspecten van het gebruik van antipsychotica bij jongeren". Voordracht voor kinderpsychiaters regio Zuid-Holland, Juni 2001.

"Vroegtijdige opsporing van psychotische stoornissen en differentiaal diagnostiek" in het kader van het symposium: Psychotische stoornissen bij kinderen en adolescenten. Voorjaarscongres NVvP. Maart 2000 te Maastricht.

Pedagogische maatregelen in de kinder- en jeugdpsychiatrie: op het grensvlak van dwang en drang. Workshop bij Congres Samenwerken in de Jeugdzorg, 25 oktober 1999 te Ede.

"Vroege opsporing en onderkenning van psychotische stoornissen"bij het congres: Kwartetten, kinderspel. Januari 1998 Rotterdam.

"Early Intervention and treatment of schizophrenia from a child and adolescent psychiatrial point of view", tijdens congres: First Psychotic Episode of Schizophrenia, 28 en 29 november 1996 te Amsterdam.

ONDERWIJS (15.4 ECTS):

A-opleiding psychiatrie van het consortium Zuid-West Nederland:

- Blok Kinder- en Jeugdpsychiatrie 2008-2010, 16 uur per jaar, 1.6 ECTS
- Blok gezins- en systeemtherapie 2009-2012, 12 uur per jaar, 1.80 ECTS

Opleidingsconsortium Zuid-Holland kinder-en jeugdpsychiatrie:

- Blok Adolescentie en Psychotische stoornissen, 2008-2015, 16 uur per jaar, 4.75 ECTS
- Blok Crises en Crisismanagement, 2008-2015, 8 uur per jaar, 1.6 ECTS
- Blok middelenmisbruik, 201202015, 8 uur per jaar, 1.6 ECTS
- Cognitive gedragstherapie bij angst en depressie, 2008-2015, 4 uur per jaar, 0.75 ECTS .

PDO GGZ, psycho-pathologie- en psychotherapie-onderwijs voor GZ-psychologen en klinisch psychologen in opleiding:

- Psychotische stoornissen, 2008-2012, 8 uur per jaar, 1.6 ECTS
- Ontwikkeling adolescentie, 2008-2010, 4 uur per jaar, 0.6 ECTS
- Middelenmisbruik, 2008-2015, 8 uur per jaar, 1.6 ECTS

Supervisie: (12 ECTS): AIOS Kinder- en jeugdpsychiatrie, Dordrecht. Yulius, 60 uur per jaar.

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De ambitie om te promoveren koesterde ik al heel lang. Toch kwam de promotie lang niet van de grond door mijn drukke taken op het gebied van patiëntenzorg en beleid. Bij de start van dit promotie-traject in 2008 smeedde Jean-Luc Klompenhouwer vage plannen om tot tastbare werkelijkheid; Frank Verhulst schetste de contouren van de dissertatie en Kirstin Greaves-Lord en ik vertaalden deze contouren in concrete wetenschappelijke vraagstellingen. Ik wil bij voorbaat iedereen bedanken, die hieronder niet expliciet genoemd wordt en wel betrokken is geweest bij het onderzoek.

Mijn dank gaat in de eerste plaats uit naar de proefpersonen en hun ouders voor hun bereidheid mee te doen aan het eerste onderzoek (Chaos in mijn hoofd) en aan de vervolgstudie (GAME) zeven jaar later. In totaal werden op twee tijdstippen met een tussenpoos van zeven jaar per deelnemer zo'n 14 tot 18 uur aan testmateriaal verzameld. Zowel jullie openheid om te vertellen hoe het jullie op diverse levensgebieden verging, als de bereidheid om zoveel tijd te investeren in een onderzoek, waarderen we enorm. Deelname aan zo'n langlopende vervolgstudie vergt een bijzondere inspanning en volharding van de deelnemers, maar juist deze langlopende studies worden weinig uitgevoerd en kunnen belangrijke kennis opleveren. Esther de Bruin en Anneke Louwerse wil ik bedanken voor de nauwkeurige, gedegen en volhardende wijze waarop jullie op T1 en T2 de data verzameld hebben. Anneke, onze promotietrajecten liepen grotendeels parallel, ik heb je steeds bewonderd om je scherpzinnigheid, bijvoorbeeld bij de toepassing van SPSS en om je rustige onverstoorbaarheid, die me tijdens onze congresreis naar Brazilië in 2015 weer trof.

Dank aan mijn promotor Frank Verhulst. Beste Frank, we kennen elkaar zo'n 25 jaar en ik heb je achtereenvolgens meegemaakt als opleider toen ik AIOS was, als collega opleider en nu dus als promovendus. In al die hoedanigheden vond ik het een voorrecht om met je samen te werken. Charmant en innemend als collega en scherpzinnig als wetenschapper en promotor.

Co-promotor Kirstin Greaves-Lord, de samenwerking met jou heb ik steeds als inspirerend en boeiend ervaren, vooral ook door jouw grote engagement met het onderzoek en met je collega's. Je bent verbaal bijzonder sterk: je schaaft aan een artikel totdat elk woord op de juiste plek staat en tot er een maximale innerlijke samenhang bereikt is. Daarbij switch je uitstekend van grote lijnen naar details en omgekeerd. Toen we in 2008 begonnen was jij een enthousiaste, communicatief ingestelde jonge onderzoekster en ik een ervaren clinicus met weinig onderzoekservaring. Aan het eind van het promotie-traject vormden we een goed geolied team en ik hoop dat we deze samenwerking in andere vormen kunnen voortzetten.

Co-Co-promotor Arthur van Gool wil ik bedanken voor zijn scherpe en snelle reacties op de artikelen en voor zijn relativerende humor ("Publiceren is een jurysport"). Wanneer jouw commentaren vooraf gegaan werden door opmerkingen als: "Ik heb het vast niet begrepen" of "In mijn oneindige onwetendheid" kostte het me doorgaans een week hard werken om de geconstateerde wetenschappelijke rafelranden om te vormen tot een goed onderbouwd wetenschappelijk betoog.Jan van der Ende, de no nonsense statisticus bedank ik voor zijn waardevolle aanvullingen en suggesties.

Dank aan de leescommissie: Ik was zeer vereerd Tonya White, dat jij de voorzitter van de leescommissie wilde zijn. In onze contacten binnen Erasmusmc ben ik onder de indruk geraakt van je brede wetenschappelijke kennis. Prof. Dr. Fop Verheij, icoon van de Nederlandse kinder-en jeugdpsychiatrie: "Betrouwbaar als de bank van Engeland" en sinds de kredietcrisis: "Betrouwbaarder dan de bank van Engeland."

Prof. Dr. Ina van Berckelaer-Onnes, ook al ben je met emeritaat, ik hoop dat we nog vaak mogen genieten van jouw wijze en menselijke benadering van mensen met autisme. Prof. Dr. Rutger Jan van der Gaag en Prof. Dr. Caroline Rieffe, ik beschouw het als een eer en een genoegen dat jullie je snel bereid toonden om zitting te nemen in de corona. Prof. Dr. Jean Vroomen, we kennen elkaar al vele jaren en jouw aanwezigheid bij deze promotieplechtigheid waardeer ik zeer. Ik realiseer me, dat verweer voeren tegen jouw oppositie heel wat anders is dan vrijblijvend keuvelen over zintuiglijke integratie tijdens après-ski.

De donderdagen in Erasmusmc Sophia heb ik als een ontspannen vorm van geestelijke inspanning ervaren. De prettige, energieke en vrolijke sfeer onder de promovendi heeft daar veel aan bijgedragen. Ik wil jullie daarvoor allen bedanken (van GAME: Anneke Louwerse, van Ik-Puber: Linda Dekker, Jorieke Duvenkot en Kirstin Visser, en verder: Carolijn Dulfer, Hannan el Marroun,).

Andrea Ijff: zonder jou had deze promotie niet kunnen plaats vinden. Je hebt me op de jou eigen belangeloze manier grandioos geholpen bij het foutloos uitwerken en indienen van artikelen en bij de afhandeling van mijn andere taken. Tijdens de drukste momenten van mijn promotie voorkwam jouw organisatietalent, dat mijn agenda overliep.

Tineke Timmermans, bibliothecaresse van Yulius, hielp me altijd snel en efficiënt bij het opsporen van artikelen. Mijn dank voor deze steun, Tineke, en voor de manier waarop je de Yulius bibliotheek op hoog niveau gebracht hebt.

Een speciaal woord van dank voor mijn mede-opleiders bij Yulius (Gunnar Faber, Charlotte Oele, alweer Arthur van Gool en tot voor kort Paul Wisman), die ik als een hechte club geestverwanten beschouw. Gunnar gaf bij zijn promotie het promotie estafettestokje door aan mij. Mag ik nu doorgeven aan Charlotte? Dank aan de AIOS kinder-en jeugdpsychiatrie: mijn promotie was een voorbeeld van "Reculer pour

mieux sauter". Om wetenschappelijk een beter gekwalificeerde opleider te worden, was de tijd die ik aan de opleiding kon besteden gedurende de opleiding soms aan de krappe kant. Overigens ben ik er trots op dat binnen onze vakgroep kinderpsychiatrie acht bekwame kinderpsychiaters werken, die we zelf opgeleid hebben.

Dank aan alle collega's van Yulius, speciaal de oudgedienden en collega's van de Kreek (Tineke Franzen, Ad van der Sijde, Charlotte Oele, Trudy Groenenboom), maar ook de jongere generatie (Yashvir Sukul, Myrthe Koster) en het Barendrechtse smaldeel (Annerieke Luijendijk, Esther van der Vegt, Sanne Nonhebel). Ook binnen Yulius geniet ik het voorrecht om ingebed te zijn in een collegiale en hechte groep inspirerende mensen, die samen veel plezierige maar ook sommige nare gebeurtenissen gedeeld hebben. Hoe druk jullie het ook hadden; mij werd altijd zonder morren de vrije onderzoeksdag gegund en dat was van wezenlijk belang voor de voortgang van mijn onderzoek. Bedankt voor jullie collegialiteit.

De Raad van Bestuur van Yulius, Jan Menting en Jean-Luc Klompenhouwer wil ik danken. De daadkracht van tankcommandant Jean-Luc heeft deze promotie mogelijk gemaakt. Dank aan Ad Dijkhuizen, die in de zeven magere jaren het promotievuurtje smeulend hield. Dank aan de directie kinder-en jeugdpsychiatrie (Ronald Buijs, Ad van der Sijde en Maria van Rooijen) voor de geboden steun. Ik bewaar goede herinneringen aan congresreizen met Athanasios Maras; dank daarvoor. Dank aan de diverse managers, waar ik in de loop der jaren prettig mee heb samengewerkt (Bert van Baardwijk, Jan Jongbloed, Simon Kok, Shequita Kalloe). En aan de vakgroep kinder-en jeugdpsychiaters van Yulius, die fruitig en Bourgondisch geleid wordt door respectievelijk Youandi Dunker en Rudi Bruggemans.

Paranimfen: Ik voel me bevoorrecht met mijn paranimfen. Patrick Chatelion Counet, dierbare vriend, jij hebt de zeldzame eigenschap dat je excelleert in vrolijke humor en diepe ernst. En bij deze promotie ben je als hoogleraar paranimf. Wouter van der Does, ooit was je assistent bij mij en nu als collega en vriend waardeer ik je enorm om je loyale en bereidwillige grondhouding.

Mijn overleden ouders hebben een grote bijdrage aan deze promotie geleverd: ze hebben ons, hun drie zoons zeer liefdevol opgevoed en ze hebben ons gestimuleerd bij onze studies. Tante Mie (Crolla-Baggen), die precies één jaar geleden overleed, dank ik voor het feit dat ze mijn specifieke belangstelling voor de psychiatrie aangewakkerd heeft en omdat ze ons letterlijk en figuurlijk stimuleerde om over de grenzen te kijken. Mijn broers, Hay en Peter belichamen voor mij de voortzetting van deze familiewaarden in het hier en nu.

Onze vrienden en mijn schoonfamilie van beide kanten wil ik bedanken voor alle getoonde, oprechte interesse en het meeleven. Vaak informeerden jullie met enige reserve en ironie naar de voortgang van mijn promotie, omdat het inmiddels zo lang duurde dat jullie dachten een pijnlijk onderwerp aan te roeren.

Lieve David en Anne-Sophie, ik heb geprobeerd om jullie niet de dupe te laten worden van mijn ambitie om te promoveren en mijn drukke baan. Jullie aanwezigheid is voor mij steeds een bron van ontspanning en geluk geweest, omdat jullie zulke lieve en vrolijke kinderen zijn. David, jij bent een originele denker en een goede keukentafel komediant. Anne-Sophie, jij hebt een onafhankelijke geest en we luisteren met veel plezier naar je levendige verhalen.
Lieve Vera, jij hebt me steeds aangemoedigd in mijn wens om te promoveren en tijdens het promotie-traject heb je steeds aan mijn zijde gestaan. Als ik tegenslagen moest incasseren, kon ik bij jou terecht. Je hebt me geweldig gesteund; ik ben je daarvoor erg dankbaar. Zonder jou had ik deze klus niet kunnen klaren. Lieve Vera, ik hoop dat onze gezamenlijke toekomst even mooi en gelukkig zal zijn als ons gezamenlijk verleden.

"It's hard to make predictions - especially about the future."

Robert Storm Petersen (hoofdstukken 4,5,en 6)

"Hij was bijna niet in staat tot algemene platonische ideeen. Het kostte hem niet alleen moeite te begrijpen dat de soortaanduiding hond zoveel ongelijke eenlingen van verschillende grootte en verschillende vorm omvat; het hinderde hem dat de hond van veertien over drie (van de zijkant gezien) dezelfde naam had als de hond van kwart over drie (van voren gezien)....

Hij was niet erg in staat om te denken, want denken is verschillen vergeten, abstraheren en generaliseren. In de volgepropte wereld van Funes waren alleen maar details, die van moment op moment veranderden."

Jorge Luis Borges, de Zahir: "Het onverbiddelijke geheugen van Funes" (hoofdstuk 6).