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## Growing up with autism spectrum disorders: outcome in adolescence and adulthood

Barneveld, P.S.

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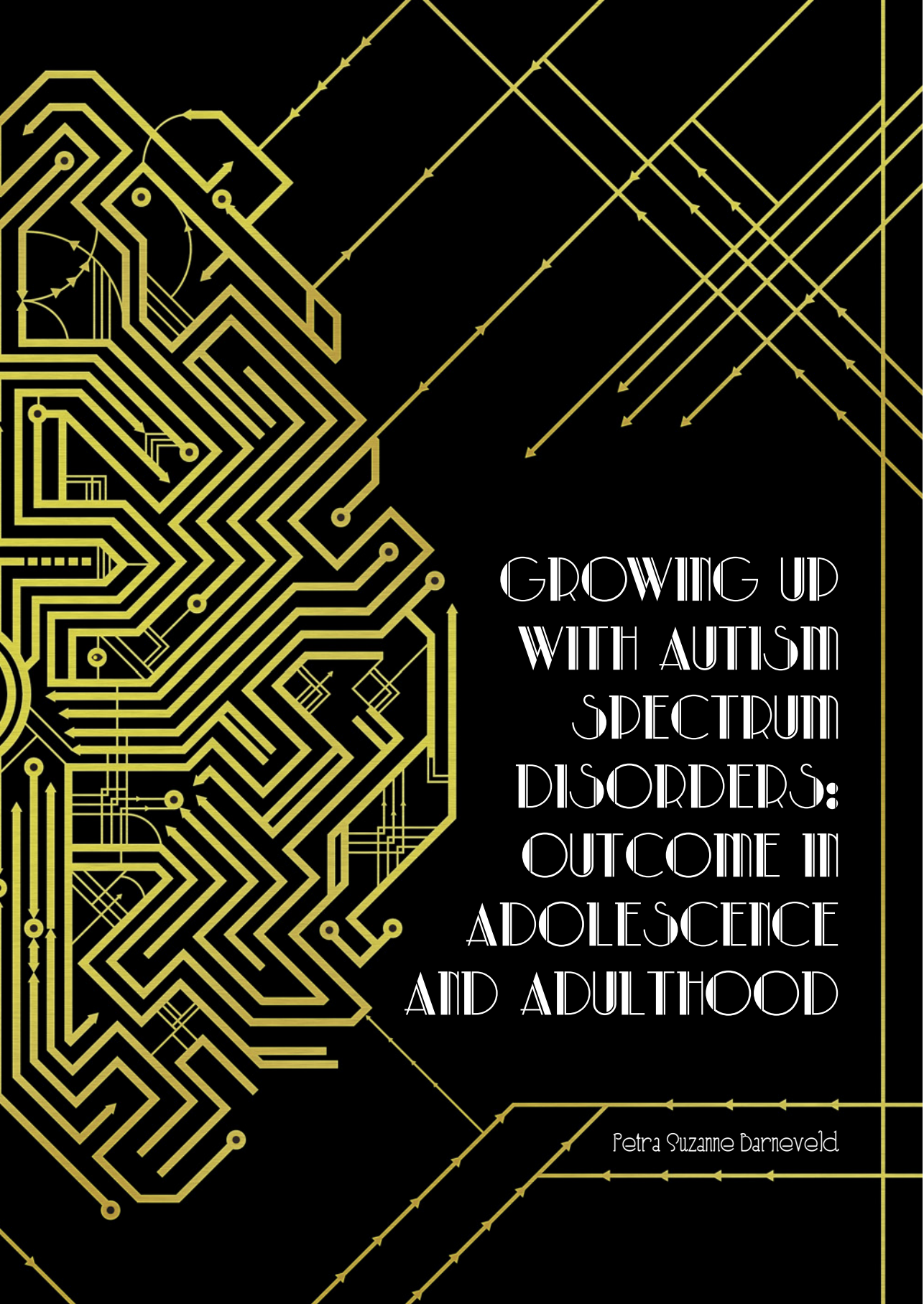


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**Author:** Barneveld, Petra Suzanne

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GROWING UP  
WITH AUTISM  
SPECTRUM  
DISORDERS:  
OUTCOME IN  
ADOLESCENCE  
AND ADULTHOOD

Petra Suzanne Darnveld.

Growing up with autism spectrum disorders: outcome in adolescence and adulthood

# **Growing up with autism spectrum disorders: outcome in adolescence and adulthood**

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Growing up with autism spectrum disorders: outcome in adolescence and adulthood

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Faculty of Social and Behavioural Sciences  
Department of Clinical Child and Adolescent Studies

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# CHAPTER 1

## General introduction

### Introduction

(ASD) are severe neurodevelopmental disorders characterised by deviant and delayed development of reciprocal social interaction, dysfunctional communication, as well as by restricted interests and stereotyped behaviour (American Psychiatric Association (APA), 2000). Children with ASD have difficulties adapting their behaviour to the social environment and to the behaviour of others. Social situations are often complex because a lot of information has to be processed at the same time, they are dynamic because of the interactive nature and there is a limited amount of time to interpret social signals and to respond in an adequate manner. Social behaviour depends on the child's abilities that are essential to process social relevant information in various dynamic environments and to react appropriately and effectively. Deficits in social information processing affects social adaptive functioning and the possibilities to have mutual relationships (Swaab, 2013; Van Rijn, 2011). The impairments in reciprocal social interactions in children with ASD are troublesome and sustained. Often the child's awareness of others is markedly impaired, they have difficulties attributing mental states, such as intentions, beliefs and desires to others and to themselves. They usually have difficulties to develop peer relationships appropriate to their developmental levels. Some children with ASD may have little or no interest in establishing friendships and others may have an interest in friendships but lack understanding of the conversations during social interaction (APA, 2000). Social or emotional reciprocity is often deficient and children with ASD may have marked impairments in the use and recognition of nonverbal behaviours (e.g., eye-to-eye gaze, facial expression, body postures and gestures), that are important for regulation of social interaction and communication. They may lack spontaneous seeking

to share experiences or interests with others. Disturbances in the social use of language is often evidenced by an inability to integrate words with gestures or problems in understanding humor or nonliteral aspects of speech. Finally, children with ASD often show restricted, repetitive, and stereotyped patterns of behaviour, interests, and activities. Deviations in daily routines may result in anxiety or panic (APA, 2000). ASD are lifelong conditions and it is therefore relevant to examine how children and adolescents develop and which factors contribute in an advantageous or an unfavourable way to development in ASD. Following, we will present an overview of studies examining these issues. In particular we will address present state of knowledge and raise questions that remain to be unanswered.

### **Social outcome: Quality of Life in ASD**

The problems with adaptation to the social environment in people with ASD have a serious impact on their functioning in daily life. These deficiencies increasingly hamper daily life functioning as demands for social relationships and independent living become larger and more prominent when growing older (Beauchamp & Anderson, 2010). Reviews of functioning in adulthood indicate that the prognosis of ASD is generally poor, notwithstanding considerable heterogeneity in social outcomes. A minority of individuals with ASD live independently, few individuals have social and intimate relationships, and education and employment levels are generally low, even when intelligence is within the normal range (reviews: Gillberg, 1991; Howlin, 2000; Seltzer et al., 2004; Sigman et al., 2006). The majority of follow-up studies examining the outcome of childhood ASD, have compared the quality of life (QoL) of individuals with ASD to typically developing individuals (e.g., Stokes et al., 2007), or made comparisons between different subtypes of ASD (e.g., Cederlund, et al., 2003). Whereas social development in ASD is challenged, only a few studies have studied whether the outcome of individuals with ASD is less favourable than that of individuals with other child psychiatric disorders. A cross-sectional study of Lee, Harrington, Louie, and Newschaffer (2008) examined whether or not child psychiatric disorders have a different impact on QoL. They reported that children with autism were more likely to miss school, more often repeated a grade and were less likely to participate in organized

activities than children with Attention Deficit Hyperactivity Disorders (ADHD) or typically developing children in the age range of 3 to 17 years. In addition, Bastiaansen, Koot, Ferdinand, and Verhulst (2004) examined QoL indicators in 6-to-18-year-old children referred for psychiatric problems to an outpatient child psychiatric clinic. Objective QoL indicators were examined, comprising living conditions, employment or school functioning, and social relationships. They reported that children with ASD had fewer friends and received more special education than children with ADHD or disruptive behaviour disorders, children with mood or anxiety disorders, and children with other disorders. Besides objective outcome criteria, they also studied subjective QoL, involving the perspective of the child, parents and clinician of the child's physical, emotional, social, and school functioning. Across multiple raters, the subjective QoL appeared to be poorest in those areas of life that are most affected by the symptoms specific to the diagnosis; social functioning in children with ASD, school and social functioning in children with ADHD or disruptive behaviour disorders, and emotional functioning in children with anxiety and mood disorders. Finally, Green, Gilchrist, Burton, and Cox (2000) reported that 11-to-19-year-old high-functioning adolescents with Asperger syndrome showed severe impairments in social functioning as compared to adolescents with Conduct disorders. They showed a profound lack of the ability for independent living and they showed difficulties in social relationships, despite good cognitive ability and absence of significant early language delay. These findings suggest that the QoL of children and adolescents with ASD is more disadvantageous than for those with other childhood disorders. To date, there are no known follow-up studies that have investigated outcome in adulthood on objective and subjective QoL of children with ASD, as compared to adult patients with other psychiatric disorders. Such a follow-up study would be worthwhile, since consequences of social impairments for social functioning may become more prominent when demands for personal independence increase with age. It can therefore be expected that impairments in social adaptation in adulthood are more profound in individuals with ASD than in individuals with other frequently diagnosed child psychiatric disorders.



## Cognitive dysfunction in relation to age in ASD

Problems with adaptive functioning in people with ASD can be explained by deficiencies in the way that they perceive and process information from their environment. Intelligence reflects the capacity to acquire and apply knowledge and deal effectively with the information from the environment (Wechsler, 1974). The long-established view was that up to 75% of individuals with ASD had an intellectual disability (ID) or mental retardation, defined by an IQ < 70. The prevalence of ID among children with core autism is supposed to be higher than among children with other types of ASD (Asperger's disorders, Pervasive Developmental Disorders Not Otherwise specified (PDD-NOS) (Goin-Kochel, Peters, Treadwell-Deering, 2008). For instance, Chakrabarti & Fombonne (2001) reported that a substantial portion of preschool children with core autism met criteria for ID (69%), whereas only 7% of children with PDD-NOS or Asperger's disorders met criteria for ID. Furthermore, another widespread view is that Verbal IQ (VIQ) is commonly lower than Performance IQ (PIQ), since patients with ASD are characterised by marked verbal problems (American Psychiatric Association, 2000). Some studies indeed found that PIQ was significantly higher than VIQ in patients with ASD (e.g., Lincoln, 1988), but some studies demonstrated that VIQ did not differ from PIQ in ASD (De Bruin et al., 2006; Verter, 1992; Siegel, 1996; Manjiviona & Prior, 1999), and in other studies, discrepancies with VIQ significantly higher than PIQ occurred nearly as often (Joseph 2002; Charman, 2011). These conflicting results might be explained by the influence of overall cognitive ability or by differences in age of assessment. Studies of the effect of overall ability on the VIQ-PIQ discrepancy indeed showed that this difference tends to be smaller when global intelligence levels are higher (Rumsey, 1992). Furthermore, Mayes and Calhoun (2003a) concluded in their cross-sectional study that discrepancies between VIQ and PIQ tend to be smaller in school-aged (6 to 15 years) children with autism when compared to preschool (3 to 5 years) children with autism. These discrepancies were observed in both lower IQ (total IQ < 80) and higher IQ (total IQ ≥ 80) groups, but the VIQ-PIQ difference was not significant yet at age 6 or 7 years in children with higher IQ's, whereas the VIQ-PIQ gap was closed at a later age (9 or 10 year-old) in children with lower IQ's. These results suggest that the impact of age should be considered when investigating intelligence profiles in ASD. This is in line with cognitive-developmental theories that

argue that the identification of deficits in cognitive domains related to psychopathology should be done in consideration of the pattern of hierarchical progression of cognitive abilities consistent with brain maturation processes of the central nervous system (Anderson, 2001).

The VIQ versus PIQ discrepancy might not be the most sensitive way to examine cognitive abilities in ASD, because factor analytic studies demonstrated that the variance in Wechsler subtest scores are best explained by a three-factor solution (review Kaufman, 1990). Lincoln and colleagues (1988) reviewed studies examining the three Wechsler factors in ASD: Verbal Comprehension (VC), Perceptual Organization (PO), and Freedom from Distractibility (FFD) and reported that the VC factor was depressed relative to the PO factor in individuals with autism. These findings suggest that persons with ASD have verbal comprehension deficits compared to their more effective visual-perception abilities. However, other studies found that the mean of FFD factor was significantly lower than the mean of the VC and PO factor in high functioning children with ASD, indicating concentration problems, distractibility and graphomotor difficulties (Calhoun & Mayes, 2005; De Bruin, 2006; Mayes & Calhoun, 2003b). Yet another way to investigate profiles of peaks and troughs in patients with ASD is analysing scores of performance at subtest level. Studies examining Wechsler subtest profiles suggest that patients with ASD perform better on tasks that require specific visuo-spatial functions and perform more poorly on tasks requiring language comprehension and social reasoning. This specific pattern of information processing is reflected in lower mean scores on the subtest Comprehension compared to the other verbal subtest scores, and higher mean scores on the subtest Block Design compared to the other performance subtests (Happé, 1995; Lincoln, et al., 1995; Mayes & Calhoun, 2003a; 2004; Siegel et al., 1996; Asarnow et al., 1987; Shah & Frith, 1993).

At present, studies of the effect of age on different abilities as expressed in intelligence profiles are nonexistent, with the exception of the study by Mayes & Calhoun (2003a). This is surprising since the comparison of cognitive impairments against age-appropriate expectations is particularly relevant in developmental disorders such as ASD (Anderson et al., 2001). Currently, it is suggested that ASD is associated with early disturbances in brain maturation processes. This abnormal development is even noticeable in prenatal life (Palmen et al., 2004) and continues postnatally with an atypical

pattern of acceleration in brain growth as indicated by head circumference, probably due to initial extensive generation of synapses or later inadequate synaptic pruning (Courchesne & Pierce, 2005; Palmen & Van Engeland, 2004). As stated by Anderson (2001), such an early interference in maturation of the brain presumably has its consequences for the progressive emergence of cognitive deficits later in life, such as reflected in the intelligence profile.

### **Schizophrenia spectrum pathology in ASD**

Although some individuals with ASD show successful adaptation to daily life, many others are at risk of severe deterioration of daily functioning during development, and some are at risk of very serious psychopathology, such as psychosis, later in life (e.g., Stahlberg, Soderstrom, Rastam, & Gillberg, 2004). Results of studies focussing on risk of psychosis suggest that specific developmental abnormalities in childhood, such as dysregulation of affective state and primitive anxieties, can be observed before those children meet the criteria for psychotic disorder or schizophrenia later in life (e.g., Van der Gaag et al., 1995). It is therefore relevant to examine to what extent autistic and schizotypal symptoms already coincide during adolescence in order to be able to identify the risk of developing schizophrenia later in life.

ASD and Schizophrenia Spectrum Disorders (SSD) are both characterised by significant impairments in social functioning (American Psychiatric Association (APA), 2000). SSD are psychiatric disorders involving reality distortion: disorders of thinking where a person's ability to recognize reality, his or her emotional responses, thinking processes, judgements and ability to communicate deteriorates so much that daily life functioning is seriously impaired. Symptoms such as hallucinations (false perceptions), delusions (false personal beliefs about the world), and disorganised speech and thinking are common. The greatest costs to the person affected by these experiences are the social and psychological consequences. Unemployment, social drift, social adversity, loss of confidence, drive, and even loss of the skills of independent living are among the most serious of these social and psychological effects (Birchwood & Jackson, 2001). Although according to DSM-IV-standards ASD and SSD have distinct classification criteria, the similarity of the clinical presentation of the two neurodevelopmental disorders has been a topic

of scientific dispute for many decades. Kolvin (1971) and Rutter (1972) have regarded ASD and SSD as mutually exclusive categorical diagnoses (APA, 2000) with clearly distinct developmental pathways. The term 'autism', however, was coined by Bleuler (1911) to characterise social impairments seemingly characteristic of schizophrenia. In addition, Bender (1947) argued that ASD could be an age-specific expression of a developmental disorder characterised by schizotypal symptoms in adulthood.

Recent reports have provided empirical support for a conceptual overlap in diagnostic criteria between both spectrum disorders (Hurst et al., 2007; Konstantareas & Hewitt, 2001; Sheitman et al., 2004). In their review Padgett, Miltsiou, and Tiffin (2010) argued that ASD could be a risk factor of psychosis. In a prevalence study on SSD in 241 adults diagnosed with ASD in childhood, up to 7.8% were found to meet criteria for schizophrenia or another psychotic disorder in adulthood (Stahlberg et al., 2004). The authors conclude that the risk of psychosis in ASD is clearly higher than in the general population (which is about 1%) (McGrath et al., 2004), and in other developmental disorders (such as in ADHD, which is about 5%) (Stahlberg et al., 2004). High risk of adult schizophrenia in ASD was also reported by Mouridsen, Rich, and Isager (2008). In their follow up study they found that children with ASD are particularly at risk of SSD, as 34.8% of the ASD population in their study was diagnosed with SSD symptoms as adults, of which 28.1% with schizophrenia. Other studies focussing on the presence of ASD in SSD found that in 25%-50% of patients with childhood-onset schizophrenia, the SSD was preceded by and comorbid with ASD in their study (Rapoport, Chavez, Greenstein, Addington, & Gogtay, 2009; Sporn et al., 2004).

As Padgett et al. (2010) argued, a relation between ASD and SSD may be explained by (1) ASD predisposes to SSD, (2) they are different expressions of the same disorder, or (3) they are separate but related disorders, due to shared genetic or environmental risk factors. The link between ASD and SSD symptoms is emphasized by findings of increased prevalence of SSD in parents of children with ASD, suggesting genetic associations (Larsson et al., 2005; Daniels et al., 2008). In genetic studies, a great deal of effort has been spent attempting to determine whether or not ASD and SSD are genetically two distinct disorders. Various studies reported that a growing number of risk genes and/or rare small chromosomal variants (deletions or duplications) are shared by ASD and SSD (e.g., Burbach & Van der Zwaag, 2009; Rapoport et

al., 2009), indicating that the two disorders may arise from a similar neurodevelopmental vulnerability. However, a recent study by Schwarz et al. (2011), examining biomarkers for schizophrenia, reported that SSD patients could be distinguished from patients with Asperger's syndrome with a specificity of 96%. In contrast with the other genetic studies, this outcome suggests that a genetic distinction can be drawn between ASD and SSD, indicating that the discussion on shared genetic vulnerability is still ongoing. If ASD and SSD share genetic risk factors, overlap in brain abnormalities should be found. Brain imaging studies report increased brain volume due to increased cerebral and cerebellar volume in ASD, this was not found in SSD. Increased ventricular volume and decreased corpus callosum area are consistently found in both disorders (Palmen & Van Engeland, 2004; Stanfield et al., 2008; Wright et al., 2000). So, imaging studies on ASD and SSD suggest partial overlap in brain abnormalities.

From a clinical perspective, behavioural symptoms are important cues by which the risk of SSD in ASD is determined. Despite differences in clinical presentation and age of onset, both disorders share deficits in social behaviour, unusual responsiveness to the environment, oddness of speech, and inappropriate affect. Social withdrawal, communication impairments and poor eye contact seen in ASD seem similar to the negative symptoms (constricted affect and social anxiety) seen in SSD. Recent studies have pointed to the co-occurrence of autistic and schizophrenic symptomatology in individuals. A number of these studies have focused on the presence of schizophrenia spectrum pathology in patients with ASD. Negative symptoms and to a lesser extent disorganised symptoms (odd speech and eccentric behaviour), have been reported in adults and adolescents with ASD (Dykens et al., 1991; Konstantareas & Hewitt, 2001; Rumsey et al., 1986). Signs of positive symptoms of SSD (distorted thought and perception) have not been consistently found in individuals with ASD (Craig et al., 2004; De Bruin et al., 2007; Solomon et al., 2008; Van der Gaag et al., 2005). Other studies have focused on the presence of high levels of autistic traits in patients with SSD (Bender, 1970; Esterberg et al., 2008; Sheitman et al., 2004). Moreover, follow-up studies have indicated that a substantial proportion of children diagnosed with an ASD developed SSD later in life, with conversion rates reported up to 34.8% (Mouridsen et al., 2008; Stahlberg et al., 2004; Van Engeland & Van der Gaag, 1994). This suggests that in some children with ASD a developmental shift towards psychosis or schizo-

phrenia might occur, with schizotypal traits in the prodromal phase of SSD. Schizotypy refers to a continuum of personality characteristics and experiences ranging from normal dissociative states to more extreme states that are related to psychosis. Individuals who manifest elevated levels of schizotypy demonstrate several features that resemble schizophrenia symptoms. Despite symptoms such as idiosyncratic speech or distorted perceptions, they do not experience the hallucinations, delusions, or thought disorder that characterises schizophrenia. Although they might experience some unusual sensations, they usually can be made aware of the difference between their distorted ideas and reality (Lenzenweger, 2010). When children diagnosed with ASD developed SSD later in life, it is likely that (subclinical) schizotypal traits were already present in adolescence, and it is therefore relevant to examine to what extent autistic and schizotypal symptoms already coincide during adolescence.

#### **Neurocognitive markers underlying vulnerability to SSD in ASD**

Because of the increasing body of evidence suggesting an overlap in prevalence of ASD and SSD and a link between symptoms of these neurodevelopment spectrum disorders, it is considered crucial to identify developmental markers of high vulnerability to SSD in children and adolescents with ASD. This is important for two reasons; (1) to understand developmental mechanisms that might lead to severe psychopathology (SSD) in ASD, and by understanding the neurocognitive mechanisms underlying behavioral symptoms (2) to be able to identify highly vulnerable individuals early in life and possibly limit their developmental risk by protective interventions.

Regarding the neurocognitive mechanisms of vulnerability, there is extensive literature concerning executive function (EF) problems for both ASD and SSD. EF deficits such as problems with mental flexibility and failures to inhibit inappropriate actions may be associated with rigidity and perseveration in ASD (e.g., Hill, 2004a). Likewise, the same EF deficits might also explain difficulties in regulating thoughts and feelings (Gioia & Isquith, 2004) and so contribute to the risk of developing SSD (e.g., Solomon et al., 2008). Therefore, it is relevant to investigate whether or not EF deficits are related to SSD symptomatology in ASD and to identify specific cognitive control deficits as

markers of vulnerability to SSD pathology in ASD.

The executive dysfunction theory (Ozonoff, 1997) attempts to explain autistic symptomatology, and although the claim that EF is a singular causal factor is controversial and evidence for an unique EF profile in ASD is weak (Kenworthy et al., 2008), many reviews confirm that EF deficits are found in ASD, including abnormalities in cognitive flexibility, generation of ideas, planning, and working memory (e.g., Hill, 2004a; 2004b; Kenworthy et al., 2008). The investigation of response inhibition in ASD has yielded conflicting results. Meta-analytic studies reported that it is specifically inhibition of prepotent responses that is impaired, whereas other inhibition functions, such as negative priming and neutral inhibition conditions, are less affected (e.g., Hill 2004a; 2004b). Evidently, EF is a broad concept comprising a variety of disparate functions (Miyake et al., 2000), and it is important to consider which specific EF deficits may underlie autistic symptoms. For example, deficits in specific EF domains such as verbal fluency and generation of ideas are associated with communication symptoms in ASD (Dichter et al., 2009). Difficulties in other EF domains, such as semantic fluency, are linked to social interaction problems (Kenworthy et al., 2009). Impairments in core EF domains: cognitive flexibility, working memory, and response inhibition are associated with repetitive, stereotyped behaviour in ASD (e.g., Hill, 2004a; Yerys et al., 2009).

EF deficits are also considered core neurocognitive abnormalities regarding SSD (e.g., Nieuwenstein et al., 2001), and are suggested as putative endophenotypic markers for schizophrenia (e.g., Eisenberg & Berman, 2010). Meta-analyses relating EF to SSD symptoms indicate that poor EF is related predominantly to negative symptoms (e.g., Dibben et al., 2009) and to disorganisation symptoms (e.g., Nieuwenstein et al., 2001). A meta-analysis by Johnson-Selfridge and Zalewski (2001) reported correlations between poor EF and positive symptomatology, but these earlier findings were not confirmed in later reviews of studies (Dibben et al., 2009; Ventura et al., 2009). To clarify these inconsistencies it would be useful to examine whether or not SSD symptoms are associated with specific EF deficits (Nieuwenstein et al., 2001; Vollema & Postma, 2002). Following Dibben et al. (2009), it is argued that negative symptoms should be associated particularly with difficulties in generating ideas, whereas disorganisation should be associated with response inhibition problems. In addition, findings of Guillem, Rinaldi, Pampoulova, and Stip (2008), who focused on positive symptomatology, suggest that com-

plex relations between specific aspects of positive symptoms and discrete EF processes can be found.

There is no known study on the relation between EF and both ASD and SSD symptomatology. Therefore, in order to identify vulnerability to SSD at an early stage, this dissertation focusses on identifying associations between specific EF deficits and SSD symptoms of adolescents diagnosed with ASD in childhood.

### **Aims and outline of this thesis**

ASD are lifelong conditions and the impairments in reciprocal social interactions and communication are severe, it is therefore relevant to examine how children and adolescents with ASD develop throughout their life and to investigate which factors have an advantageous or an unfavourable contribution to their development. This is best addressed by follow-up of individuals diagnosed with ASD. Studies of this thesis are part of a longitudinal study, designed to monitor the cognitive and social-emotional development of patients, referred during 1984 to 2004, to the Department of Child and Adolescent Psychiatry at the University Medical Centre Utrecht, the Netherlands. In order to gain more insight into the severity of long-term consequences of ASD to a person's well being, QoL in ASD was evaluated in young adulthood in comparison to the outcome of children with other psychiatric disorders (Chapter 2). Because of the severe impairments in social adaptation in ASD, it was hypothesized that young adults with ASD would show a worse QoL profile when compared to adults diagnosed with other main child psychiatric disorders; ADHD, disruptive behaviour disorders (DISR; i.e., Oppositional Defiant Disorders and Conduct Disorders), and affective disorders (AFF; i.e., mood and anxiety disorders). In this follow-up study, objective life conditions as well as the subjective life satisfaction were examined of 169 high-functioning adults, diagnosed in childhood with ASD (19 to 30 years) and contrasted with QoL data of age matched adults diagnosed with ADHD ( $N=85$ ), DISR ( $N=83$ ), and AFF disorders ( $N=85$ ) in childhood. The mean follow-up period of the ASD patients was 13.9 years. Objective QoL included marital status, living arrangements, level of education, employment, and usage of mental health care. Subjective QoL included satisfaction concerning living arrangements, work or

education, physical condition, partner relationship, social relationships, state of mind, and future perspective.

In addition, the identification of cognitive impairments related to developmental disorders, such as ASD should be done in consideration of the pattern of hierarchical progression of cognitive abilities consistent with brain maturation processes. Therefore, the study in chapter 3 addressed the impact of age on Wechsler intelligence profiles in a large sample of 6-to-15-year-old children and adolescents with ASD. Intelligence profiles were compared between four consecutive age cohorts (children aged 6.17-8.03 years, children aged 8.04-9.61 years, children aged 9.68-11.50 years, and adolescents aged 11.54-15.85 years) of 237 high-functioning boys with ASD. Because brain maturational disturbances in ASD are assumed to have a developmental impact, it is expected that the characteristic strengths and weaknesses are more profound in older children when compared to younger children.

Furthermore, some individuals with ASD are at risk of very serious psychopathology, such as psychosis, later in life. In order to explore the possible correspondence in symptomatology, the study in chapter 4 compared autistic symptoms to schizotypal traits in a sample of 11-to-18-year-old adolescents, already diagnosed with ASD in childhood. A group of 27 high-functioning adolescents with ASD and 30 typically developing adolescents, matched for age and gender, participated in this follow-up study. Autistic and schizotypal traits were identified by means of the Autism Questionnaire and Schizotypal Personality Questionnaire-Revised. The main hypothesis was that there is an overlap between autistic symptoms and schizotypal traits in adolescents with ASD.

In addition, the study in chapter 5 is aimed to identify specific neurocognitive markers for vulnerability to SSD pathology in ASD. In this study we addressed the relation between specific deficits in cognitive control and schizotypal symptomatology in ASD. Symptoms of autism and the risk of schizotypal symptomatology were assessed in 29 10-to-18-year-old adolescents with ASD diagnosed in childhood and compared with 40 typically developing adolescents. Based on findings so far especially response inhibition and other core EF functions (i.e., mental flexibility, visuo-motor control, interference control, and perseveration) were evaluated, representing various aspects of cognitive control. It is expected that specific EF deficits are associated with the susceptibility of SSD in ASD, not executive dysfunction in general.

Finally, the discussion in chapter 6 comprises the integration of the main findings of this thesis, the clinical implications and suggestions for future research.

## References introduction

American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR)*. Washington DC: American Psychiatric Association.

Anderson, V., Northam, E., Hendy, J., & Wrennall, J. (2001). *Developmental neuropsychology, a clinical approach*. Hove: Psychology Press Ltd.

Asarnow, R.F., Tanguay, P.E., Bott, L., Freeman, B.J. (1987). Patterns of intellectual functioning in non-retarded autistic and schizophrenic children. *Journal of Child Psychology and Psychiatry, 28* (2) 273-280.

Bastiaansen, D., Koot, H.M., Ferdinand, R.F., Verhulst, F.C. (2004). Quality of life in children with psychiatric disorders: self, parent, and clinician report. *Journal of American Academy Child Adolescent Psychiatry, 43*, 221-30.

Beauchamp, M.H., Anderson V. (2010). SOCIAL: an integrative framework for the development of social skills. *Psychological Bulletin, 136*, 39-64.

Bender, L. (1947). Childhood schizophrenia: clinical study of one hundred schizophrenic children. *American Journal Orthopsychiatry, 17*, 40-56.

Bender, L. (1970). The life course of schizophrenic children. *Biological Psychiatry, 2* (2) 165-172.

Bleuler, E. (1911). *Dementia Praecox oder Gruppe der Schizophrenien*, in: Van Aschaffenburg, G. (Ed.), *Handbuch der Psychiatrie*. Duticke, Leipzig.

Birchwood, M., & Jackson C. (2001). *Schizophrenia*. Hove: Psychological Press

Calhoun, S.L., Mayes, S.D. (2005). Processing speed in children with clinical disorders. *Psychology in the Schools, 42* (4) 333-343.

Cederlund, M., Hagberg, B., Billstedt, E., Gillberg, I.C., Gillberg, C. (2008). Asperger syndrome and autism: a comparative longitudinal follow-up study more than 5 years after original diagnosis. *Journal of Autism and Developmental Disorders, 38*, 72-85.

Charkrabati, S., & Fombonne, E. (2001). Pervasive developmental disorders in preschool children. *Journal of American Medical Association, 285* (24) 3093-3099.

Charman, T., Pickles, A., Simonoff, E., Chandler, S., Loucas, T., Baird, G. (2011). IQ in children with autism spectrum disorders: data from the Special Needs and Autism Project (SNAP). *Psychological Medicine, 41*, 619-927.

Courchesne, E. & Pierce, K. (2005). Brain overgrowth in autism during a critical time in development: implications for frontal pyramidal neuron and interneuron development and connectivity. *International Journal of Developmental Neuroscience, 23*, 153-170.

Craig, J.S., Hatton, G., Craig, F.B., Bentall, R.P. (2004). Persecutory beliefs, attributions and theory of mind: comparison of patients with paranoid delusions, asperger's syndrome and healthy controls. *Schizophrenia Research, 69* (1) 29-33.

De Bruin, E.I., Ferdinand, R.F., Meester, S., De Nijs, P.F.A., Verheij, F. (2007). High rates of psychiatric co-morbidity in PDD-NOS. *Journal Autism and Developmental Disorders, 37* (5) 877-886.

De Bruin, E. I., Verheij, F., & Ferdinand, R. F. (2006). WISC-R subtest but no overall VIQ-PIQ difference in Dutch children with PDD-NOS. *Journal of Abnormal Child Psychology, 34*, 263-271.

Daniels, J.L., Forssen, U., Hultman, C.M., Cnattingius, S., Savitz, D.A., Feychting, M., & Sparen, P. (2008). Parental psychiatric disorders associated with autism spectrum disorders in the offspring. *Pediatrics, 121*, 1357-1162.

Dibben, C.R.M., Rice, C., Laws, K., & McKenna, P.J. (2009). Is executive impairment associated with schizophrenic syndromes? A meta-analysis. *Psychological Medicine, 39*, 3, 381-392.

Dichter, G.S., Lam, K.S.L., Turner-Brown, L.M., Holtzclaw, T.N., & Bodfish, J.W. (2009). Generativity abilities predict communication deficits but not repetitive behaviors in autism spectrum disorders. *Journal of Autism and Developmental Disorders, 39*, 1298-1304.

Dykens, E., Volkmar, F., Glick, M. (1991). Thought disorder in high-functioning autistic adults. *Journal of Autism and Developmental Disorders, 21* (3) 291-301.

Eisenberg, D.P., & Berman, K.F. (2010). Executive function, neural circuitry, and genetic mechanisms in schizophrenia. *Neuropsychopharmacology, 35* (1) 258-277.

Esterberg, M.L., Trotman, H.D., Brasfield, J.L., Compton, M.T., Walker, E.F. (2008). Childhood and current autistic features in adolescents with schizotypal personality disorder. *Schizophrenia Research, 104*, 265-273.

Gillberg, C. (1991) Outcome in autism and autistic-like conditions. *Journal of American Academy of Child Adolescent Psychiatry, 30*, 375-82.

Gioia, G.A., & Isquith, P.K. (2004). Ecological assessment of executive function in traumatic brain injury. *Developmental Neuropsychology, 2* (1&2) 135-158.

Goin-Kochel, R.P., Peters, S.U., Treadwell-Deering, D. (2008). Parental reports on the prevalence of co-occurring intellectual disability among children with autism spectrum disorders. *Research in Autism Spectrum Disorders, 2*, 546-556.

Guillem, F., Rinaldi, M., Parnpoulova, T., & Stip, E. (2008). The complex relationships between executive functions and positive symptoms in schizophrenia. *Psychological Medicine, 38* (6) 853-860.

Green, J., Gilchrist, A., Burton, D., Cox, A. (2000). Social and psychiatric functioning in adolescents with Asperger syndromes compared with conduct disorder. *Journal of Autism and Developmental Disorders, 30*, 279-93.

Happé, F. G. (1994). Wechsler IQ profile and theory of mind in autism: a research note. *Journal of Child Psychology and Psychiatry, 35*, 1461-1471.

Hill, E.L. (2004a). Executive dysfunction in autism. *Trends in Cognitive Sciences, 8* (1) 26-32.

Hill, E.L. (2004b). Evaluating the theory of executive dysfunction in autism. *Developmental Review, 24* (2) 189-233.

Howlin, P. (2000). Outcome in adult life for more able individuals with autism or Asperger syndrome. *Autism, 4*, 63-83.

Howlin, P. (2003). Outcome in high-functioning adults with autism with and without early language delays: implications for the differentiation between autism and asperger syndrome. *Journal of Autism and Developmental Disorders, 33*, 3-13.

Hurst, R.M., Nelson-Gray, R.O., Mitchell, J.T., Kwapil, T.R., 2007. The relationship of Asperger's characteristics and schizotypal personality traits in a non-clinical adult sample. *Journal of Autism and Developmental Disorders, 37* (9) 1711-1720.

Johnson-Selfridge, M., & Zalewski, C. (2001). Moderator variables of executive functioning in schizophrenia: meta-analytic findings. *Schizophrenia Bulletin, 27* (2) 305-316.

Joseph, R.M., Tager-Flusberg, H., Lord, C. (2002). Cognitive profiles and social-communicative functioning in children with autism spectrum disorders. *Journal of Child Psychology and Psychiatry, 43*, 807-821.

Kaufman, A. (1990). *Assessing adolescents and adult intelligence*. Boston: Allyn and Bacon.

Kenworthy, L., Yerys, B.E., Anthony, L.G., & Wallace, G.L. (2008). Understanding executive control in autism spectrum disorders in the lab and in the real world. *Neuropsychology Review, 18* (4) 320-338.

Kolvin, I. (1971). Studies in the childhood psychoses. I. Diagnostic criteria and classification. *British Journal of Psychiatry, 118* (545) 381-384.

Konstantareas, M.M., Hewitt, T. (2001). Autistic disorder and schizophrenia: Diagnostic overlaps. *Journal of Autism and Developmental Disorders, 31* (1) 19-28.

Larsson, H.J., Eaton, W.W., Madsen, K.M., Vestergaard, M., Olesen, A.V., Agerbo, E., ... Mortensen, P.B. (2005). *American Journal of Epidemiology, 161* (10) 916-925.

Lee, L.C., Harrington, R.A., Louie, B.B., Newschaffer, C.J. (2008). Children with autism: quality of life and parental concerns. *Journal of Autism and Developmental Disorders, 38*, 1147-60.

Lenzenweger, M.F. (2010). *Schizotypy and schizophrenia: the view from experimental psychopathology*. New York: Guilford Press.

Lincoln, A. J., Allen, M. H., & Kilman, B. A. (1995). *The Assessment and Interpretation of Intellectual Abilities in People with Autism*. In E. Schopler & G.B. Mesibov (Eds.), *Learning and cognition in autism* (pp. 89-117). New York: Plenum Press.

Lincoln, A. J., Courchesne, E., Kilman, B. A., Elmasian, R., & Allen, M. (1988). A study of intellectual abilities in high-functioning people with autism. *Journal of Autism and Developmental Disorders, 18*, 505-524.

Manjiviona, J., & Prior, M. (1999). Neuropsychological profiles of children with Asperger syndrome and autism. *Autism, 3* (4) 327-356.

Mayes, S.D., Calhoun, S.L. (2003a). Ability profiles in children with autism. Influence of age and IQ. *Autism, 6* (4) 65-80.

Mayes, S.D., Calhoun, S.L. (2003b). Analysis of WISC-III, Stanford-Binet: IV, and Academic Achievement Test Scores in children with autism. *Journal of Autism and Developmental Disorders, 33* (3) 329-341.

Mayes, S.D., Calhoun, S.L. (2004). Similarities and differences in Wechsler Intelligence Scale for Children – Third edition (WISC-III) profiles: support for subtest analysis in clinical referrals. *Clinical Neuropsychology, 18* (4) 559-572.

- McGrath, J., Saha, S., Welham, J., El Saadi, O., MacCauley, C., & Chant, D. (2004). A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Medicine*, 2, 13.
- Miyake, A., Friedman, N.P., Emerson, M.J., Minshew, N.J., Witzki, A.H., Howeter, A., Wager, T.D. (2000). The unity and diversity of executive functions and their contributions to complex 'frontal lobe' tasks: a latent variable analysis. *Cognitive Psychology*, 41, 49-100.
- Mouridsen, S.E., Rich, B., Isager, T. (2008). Psychiatric disorders in adults diagnosed as children with atypical autism. A case control study. *Journal of Neural Transmission*, 115 (1) 135-138.
- Nieuwenstein, M.R., Aleman, A., & De Haan, E.H.F. (2001). Relationship between symptom dimensions and neurocognitive functioning in schizophrenia: a meta-analysis of WCST and CPT studies. *Journal of Psychiatric Research*, 35 (2) 119-125.
- Ozonoff, S. (1997). *Components of executive function in autism and other disorders*. In J. Russell (ed.), *Autism as an executive disorder* (pp.179-211). Oxford: Oxford University Press.
- Padgett, F.E., Miltsiou, E., & Tiffin, P.A. (2010). The co-occurrence of nonaffective psychosis and the pervasive developmental disorders: a systematic review. *Journal of Intellectual and Developmental Disability*, 35 (3) 187-198.
- Palmen, S.J.M.C., & Van Engeland, H. (2004). Review on structural neuroimaging findings in autism. *Journal of Neural Transmission*, 111, 903-929.
- Palmen, S.J.M.C., Van Engeland, H., Hof, P.R., & Schmitz, C. (2004). Neuropathological findings in autism. *Brain*, 127, 2572-2583.
- Palmen, S.J., & Van Engeland, H. (2004). Review on structural neuroimaging findings in autism. *Journal of Neural Transmission*, 111 (7) 903-929.
- Rapoport, 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 American Academy of Child and Adolescent Psychiatry*, 48 (1) 10-18.
- Rumsey, J.M. (1992). *Neuropsychological studies of high-level autism*. In E. Schopler & G.B. Mesibov (Eds), *High-functioning individuals with autism* (pp. 41-64). New York: Plenum Press
- Rumsey, J.M., Andreasen, N.C., Rapoport, J.L. (1986). Thought, language, communication, and affective flattening in autistic adults. *Archives of General Psychiatry*, 43 (8) 771-777.
- Rutter, M., 1972. Childhood schizophrenia reconsidered. *Journal of Autism Child Schizophrenia* 2 (4) 315-337.
- Seltzer, M.M., Shattuck, P., Abbeduto, L., Greenberg, J.S. (2004). Trajectory of development in adolescents and adults with autism. *Mental Retardation and Developmental Disabilities Research Review*, 10, 234-47.
- Shah, A., Frith, U. (1993). Why do autistic individuals show superior performance on the block design task? *Journal of Child Psychology and Psychiatry*, 34 (8) 1351-1364.
- Sheitman, B.B., Bodfish, J.W., Carmel, H. (2004). Are the negative symptoms of schizophrenia consistent with an autistic spectrum illness? *Schizophrenia Research*, 69 (1) 119-120.
- Siegel, D. J., Minshew, N. J., & Goldstein, G. (1996). Wechsler IQ profiles in diagnosis of high-functioning autism. *Journal of Autism and Developmental Disorders*, 26, 389-406.
- Sigman, M., Spence, S.J., Ting Wang, A. (2006). Autism from developmental and neuropsychological perspectives. *Annual Review of Clinical Psychology*, 2, 327-55.
- 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, 1474-1484.
- 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, 1474-1484.
- Sporn, A.L., Addington, A.M., Gogtay, N., Odonez, A.E., Gornick, M., Clasen, L., ... Rapoport, J.L. (2004). Pervasive developmental disorder and childhood-onset schizophrenia: comorbid disorder or a phenotypic variant of a very early onset illness? *Biological Psychiatry*, 55, 989-994.
- Stahlberg, O., Soderstrom, H., Rastam, M., Gillberg, C. (2004). Bipolar disorder, schizophrenia, and other psychotic disorders in adults with childhood onset AD/HD and/or autism spectrum disorders. *Journal of Neural Transmission*, 111 (7) 891-902.
- Stanfield, A.C., McIntosh, A.M., Spencer, M.D., Philip, R., Gaur, S., Lawrie, S.M., (2008). Towards a neuroanatomy of autism: a systematic review and meta-analysis of structural magnetic resonance imaging studies. *European Psychiatry*, 23 (4), 289-299.
- Stokes, M., Newton, N., Kaur, A. (2007). Stalking and social and romantic functioning among adolescents and adults with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, 37, 1969-86.
- Swaab, H. (2013). *Pervasive ontwikkelingsstoornissen [pervasive developmental disorders]*. In: Basisboek Psychopathologie, I. Franken, P. Muris, & D. Denys (ed). Chapter 4, pag. 62-74. Utrecht: De Tijdstroom.
- Van der Gaag, R.J., Caplan, R., Van Engeland, H., Loman, F., Buitelaar, J.K. (2005). A controlled study of formal thought disorder in children with autism and multiple complex developmental disorders. *Journal of Child Adolescent Psychopharmacology*, 15 (3) 465-476.
- Van Rijn, S. (2011). *Emotie en sociale cognitie [emotion and social cognition]*. In: klinische kinderneuropsychologie, H. Swaab, A. Bouma, J. Hendriksen, C. Konig (ed). Chapter 8, pag. 189-211. Amsterdam: Uitgeverij Boom.
- Venter, A., Lord, C., & Schopler, E. (1992). A follow-up study of high-functioning autistic children. *Journal of Child Psychology and Psychiatry*, 33, 489-507.
- Ventura, J., Helleman, G.S., Thames, A.D., Koellner, V., & Nuechterlein, K.H. (2009). Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis. *Schizophrenia Research*, 113 (2-3) 189-199.
- Vollema, M.G., & Postma, B. (2002). Neurocognitive correlates of schizotypy in first degree relatives of schizophrenia patients. *Schizophrenia Bulletin*, 28 (3) 367-377.
- Wechsler, D. (1974). *Manual for the Wechsler Intelligence Scale for Children Revised (WISC-R)*. New York.
- Wright, I.C.S., Rabe-Hesketh, S., Woodruff, P.W.R., David, A.S., Murray, R.M., Bullmore, E.T. (2000). Meta-analysis of regional brain volumes in schizophrenia. *The American Journal of Psychiatry*, 157, 16-25.
- Yerys, B.E., Wallace, G.L., Harrison, B., Celano, M.J., Giedd, J.N., & Kenworthy, L.E. (2009). Set-shifting in children with autism spectrum disorders: Reversal shifting deficits on the Intradimensional/ Extradimensional Shift Test correlate with repetitive behaviors. *Autism*, 13 (5) 523-538.

# CHAPTER 2

Barneveld, P.S., Swaab, H., Fagel, S., Van Engeland, H., & De Sonneville, L.M.J.

Paper based on this chapter is in press in *Comprehensive Psychiatry*.

## Quality of life: A case-controlled long-term follow-up study, comparing young high-functioning adults with autism spectrum disorders with adults with other psychiatric disorders diagnosed in childhood.

### Abstract

**Background:** Long term outcome in childhood autism spectrum disorders (ASD) was evaluated by studying quality of life (QoL) in young adulthood in comparison to the outcome of other child psychiatric disorders.

**Methods:** In this follow-up study, objective and subjective QoL of 169 high-functioning (IQ>70) adults with ASD (19 to 30 years) was contrasted with QoL data of age matched adults diagnosed with attention deficit/hyperactivity disorder ( $N=85$ ), disruptive behaviour disorders ( $N=83$ ), and affective disorders ( $N=85$ ) diagnosed during childhood. The mean follow-up period of the ASD patients was 13.9 years. Objective QoL included marital status, living arrangements, level of education, employment, and usage of mental health care. Subjective QoL included satisfaction concerning living arrangements, work or education, physical condition, partner relationship, social relationships, state of mind, and future perspective.

**Results:** QoL was more compromised in adults diagnosed with ASD in childhood than in adults with other psychiatric disorders in childhood. A relatively large proportion of the adults with ASD were single, few lived with a partner or a family and many of them were institutionalized. Adults with ASD had lower educational levels, relatively few had paid employment and many were social security recipients, as compared to the other psychiatric patients. In case the adults with ASD used medication, 47% used anti-psychotics. Regarding the subjective QoL, the adults with ASD were less satisfied about their work or education, partner relationship, and future perspective than the other groups. Even when highly educated adults with ASD were compared to highly educated adults diagnosed with other childhood disorders, the QoL appeared to be more disadvantageous in adults with ASD.



Conclusion: Many studies have shown that QoL is threatened in psychiatric patients, but findings of this study indicate that young high-functioning adults diagnosed with ASD in childhood are at relatively high risk of poor QoL compared to other childhood psychiatric disorders.

## Introduction

Children with autism spectrum disorders (ASD) are characterized by marked impairments in social interaction and communication as well as by restricted interests and repetitive behaviour. [1] These deficiencies increasingly hamper daily life functioning as demands for social relationships and independent living become larger and more prominent when growing older. [2] Reviews [3-6] of functioning in adulthood indicate that the prognosis of ASD is generally poor, albeit considerable heterogeneity in social outcomes. A minority of individuals with ASD live independently, few individuals have social and intimate relationships, and education and employment levels are low, even when general intelligence is within the normal range. [3-6] The majority of studies examining the outcome of childhood ASD, have compared the quality of life (QoL) of individuals with ASD to normally developing individuals [e.g.,7], or made comparisons between different subtypes of ASD. [e.g.,8,9] Whereas social development in ASD is specifically challenged, only a few studies have studied whether the outcome of individuals with ASD is less favourable than that of individuals with other child psychiatric disorders. A cross-sectional study of Lee et al examined QoL in a national American survey of 483 children with autism in comparison to the well-being of 6,319 children with attention deficit hyperactivity disorders (ADHD) and unaffected controls in the age range of 3 to 17 years.[10] Families with children with ASD reported more profound QoL effects than families of children with ADHD or typically developing children. Children with autism were more likely to miss school, more often repeated a grade and were less likely to participate in organized activities. In addition, Bastiaansen et al examined whether or not child psychiatric disorders have a different impact on QoL. [11] In this study of 6-to-18-year-old children referred for psychiatric problems to an outpatient child psychiatric clinic, children, their parents and attending clinicians reported on QoL indicators. Objective QoL indicators were examined, comprising living conditions, employment or school

functioning, and social relationships. They reported that 28 children with ASD had fewer friends and received more special education than 107 children with ADHD or disruptive behaviour disorders, 57 children with mood disorders, 57 children with anxiety disorders, 22 children with other disorders, and 67 children without disorders. Besides objective outcome criteria, they also studied subjective QoL, involving the perspective of the child, parents and clinician of the child's physical, emotional, social, and school functioning. Across multiple raters, the subjective QoL appeared to be poorest in those areas of life that are most affected by the symptoms specific to the diagnosis; social functioning in children with ASD, school and social functioning in children with ADHD or DISR, and emotional functioning in children with anxiety and mood disorders. [11] Finally, Green et al examined the QoL of 20 11-to-19-year-old high-functioning adolescents with Asperger syndrome, alongside a comparison psychiatric group of 20 adolescents with Conduct disorders in a cross-sectional study. [12] The adolescents with Asperger syndrome showed severe impairments in social functioning as compared to the adolescents with Conduct disorders. They showed a profound lack of the ability for independent living and difficulties in social relationships, despite good cognitive ability and absence of significant early language delay. These findings suggest that the QoL of children and adolescents with ASD is more disadvantageous than for those with other childhood disorders. To date, there are no known follow-up studies that have investigated adult outcome on objective and subjective QoL of patients with ASD, as compared to patients with other psychiatric disorders diagnosed in childhood. Such a follow-up study would be worthwhile, since consequences for social functioning may become more prominent throughout the lifespan with increasing demands for personal independence. Since ASD is a condition in which there is, almost by definition, a profound impairment in social adaptation in adulthood, it can be expected that the QoL of individuals with ASD is worse compared to the QoL of individuals with other main child psychiatric disorders. This study therefore focuses on the severity of long-term consequences of ASD to a person's well-being (QoL), in comparison to groups of adults representing three main psychiatric disorders diagnosed in childhood; ADHD, disruptive behaviour disorders (DISR, i.e., Oppositional Defiant Disorders and Conduct Disorders), and affective disorders (AFF, i.e., mood and anxiety disorders).

There is a general consensus of factors related to late outcome in

ASD. Besides the development of early language skills before the age of 6, the most significant predictor of QoL appeared to be the level of intellectual functioning in ASD. As compared to ASD individuals with an IQ level beneath 70, those individuals with an IQ of at least 70 appeared to have a much better prognosis in adulthood. [3,13,14] However, above this cut-off IQ level outcome can be very variable and difficult to predict. [14,15] Whereas intelligence can be defined as the capacity to acquire and apply knowledge and deal effectively with the environment [16], a person's educational level is argued to reflect the realized potential, i.e. to constitute a more appropriate measure of the acquisition of knowledge and skills later in life. Because the influence of education on QoL in ASD is not examined so far, this will be done in the present study.

This study is about comparison of outcomes between psychiatric patients that were diagnosed in childhood or adolescence, specifically, QoL of adults diagnosed with ASD compared to adults diagnosed with other major psychiatric disorders. The focus is on the person's marital status, living arrangements, education, employment, and mental health care to portray the QoL in a large sample of young adults diagnosed with ASD in childhood as compared to age matched groups of adults with ADHD, DISR, or AFF, with exclusion of mutual co-morbidity of the respective disorders. Objective life conditions as well as the subjective life satisfaction will be examined. It is hypothesized that young adults with ASD will show a worse QoL profile when compared to adults diagnosed with ADHD, DISR, or AFF in childhood. In addition, it is expected that low-educated adults with ASD have poorer QoL when compared to high-educated adults with ASD. Comparisons of highly educated ASD individuals to other highly educated psychiatric patients will be explored.

## Methods

### *Procedure and participants*

This study is part of a longitudinal study, designed to monitor the cognitive and social-emotional development of patients, referred during 1984 to 2004, to the Department of Child and Adolescent Psychiatry at the University Medical Centre Utrecht, the Netherlands. The study was approved by the medical ethics committee (number 05-319/K) and written informed consent was ob-

tained according to the declaration of Helsinki. Patients who were diagnosed with ASD, ADHD, DISR, or AFF and reached the young adult age (19 to 30 years of age) were approached for participation in the follow-up study during 2007 to 2010. The DSM-diagnoses of the patients in this study were based on full agreement between two board-certified psychiatrists. Semi-structured DSM-focused interviews, observations, medical records, and structured questionnaires (Child Behavior Checklist and Teacher's Report Form) were included in the diagnostic process.

Criteria for inclusion were (1) age between 19 to 30 years, (2) no axis II DSM-diagnosis of mental retardation (IQ<70) in childhood, and for the comparison groups (3) no co-morbid ADHD, DISR, or AFF disorder on Axis I of the DSM-III, DSM-III-R or DSM-IV that were customary at the time of referral. A total of 396 patients diagnosed with ASD in childhood were suitable candidates for follow-up. They were sent a letter informing them about the aims of the study and asking them to participate. A total of 169 (43%) adults (141 male, 28 female) diagnosed with ASD at a mean age of 9.80 (SD 3.73) years participated in this study, whereas 227 adults refused participation or could not be traced despite thorough search procedures involving family doctors and local government registration files. The ASD group consisted of 20 patients diagnosed in childhood with autistic disorder (299.00), 18 with Asperger's disorder (299.81) and 131 with Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS, 299.80). Mean age at follow-up was 23.70 (SD 3.33) years, the mean follow-up period was 13.90 (SD 4.44) years.

With regard to the comparison groups, after exclusion of co-morbid DISR or AFF, 85 ADHD patients were matched on age and the group consisted of 77 adults who were diagnosed in childhood with ADHD of the combined subtype (314.01), seven adults with the predominantly inattentive subtype (314.00) and one adult with the predominantly hyperactive-impulsive subtype (314.01). In addition, after exclusion of co-morbid ADHD or AFF, 83 patients with DISR were matched on age of which 61 adults were diagnosed in childhood with ODD (313.81), 10 with CD (312.81) and 12 with other disruptive behaviour disorders (ICD9/10 diagnosis 312.xx). Finally, after exclusion of co-morbid ADHD or DISR, 85 patients diagnosed with AFF in childhood were matched on age, 48 of them with a mood disorder (15 adults with depressive disorder 296.xx, and 33 adults with dysthymic disorder 300.40) and 37 with an anxiety disorder (300.xx or 309.21).

No differences in age were found between the adults with ASD, ADHD, DISR, or AFF ( $p=.983$ ). The gender distribution differed by group (ASD: 83% male, 17% female; ADHD: 88% male, 12% female; DISR: 70% male, 30% female; AFF: 38% male, 62% female) ( $p<.001$ ).

## Materials

### *Objective QoL*

The questionnaire developed for this study to administer objective life conditions, consisted of questions about the patients' marital status, living arrangements, highest educational qualification, employment, mental health care, and medication usage. The questionnaire covers customary domains of QoL. [e.g.,13] The level of education of the patients was reported on the basis of the SOI-2006 (Standaard Onderwijs Indeling [Standard Classification of Education]; see Central Bureau for Statistics) [17], which is based on the ISCED (International Standard Classification of Education; see UNESCO). [18] Low educational qualifications are defined by the level of education that fits in the categories 'Soi 1. Pre-primary education', 'Soi 2. Primary education', and 'Soi 3. Upper secondary education'. The last type of education is designed to prepare students for entering the labour market or as a preparation for further education. High educational qualifications are defined by the level of education that fits in the categories 'Soi 4. Upper secondary education' and higher levels. These types of education are aimed at specialisation with a certain field of knowledge by the acquisition of a specific profession with a direct entry into the labour market or higher professional studies with bachelor's or master's programs, doctoral studies and post-doctoral tracks. The inquiry is a self-report questionnaire, but patients could also be assisted by parents or caregivers to complete the questionnaire. ASD patients needed more assistance to answer the questions (67% self reports) than patients with ADHD (69%), DISR (82%), or AFF (92%) ( $p<.001$ ).

### *Subjective QoL*

A composite rating on a 6-point scale (1=very dissatisfied, 6=well satisfied) of life satisfaction was based on questions concerning satisfaction about living arrangements, work or education, physical condition, having or not having a

partner and social relationships, the state of mind (general mood), and future perspective (life prospects).

### *Statistical analysis*

Descriptive statistics were used to characterize the objective and subjective QoL (patients' marital status, living arrangements, education, employment, and mental health care) of all groups.

Differences between diagnostic groups on the objective and subjective QoL measures were analyzed using chi-square ( $\chi^2$ ) tests (categorical data), or multivariate, or univariate analyses of variance (ANOVA's) (ordinal data). To examine the influence of level of education on QoL, similar group comparisons between adults with QoL of low (SOI 1-3) and high (SOI 4-7) education were performed using  $\chi^2$ -tests. When significant differences were found, differences in distributions of the QoL variables of highly educated adults with ASD versus highly educated adults with ADHD, DISR or AFF were tested by  $\chi^2$ -analyses. For the  $\chi^2$ -tests, adjusted residuals were calculated in order to identify which category is over- or under-represented in the specific diagnostic category, compared to the expected frequency based on data of the total psychiatric sample. The adjusted residual is distributed according to the standard normal distribution and when it has a magnitude greater than 1.96, the corresponding category is considered a major contributor to the significance. [19] For the ANOVA's, simple contrast analyses were computed to determine whether the QoL measures differ significantly between the ASD group and comparison groups. Alpha was set to 0.05 and partial eta squared ( $\eta_p^2$ ) was computed to estimate effect sizes (weak effect:  $\eta_p^2 \sim 0.03$ ; moderate:  $\eta_p^2 \sim 0.06$ ; large:  $\eta_p^2 \geq 0.14$ ). [20]

## Results

*QoL of adults with ASD as compared to adults with ADHD, DISR or AFF.*

### *Marital status*

The majority (88%) of the adults with ASD was single, 4% of the adults had a relationship, and 8% were married or cohabiting. This distribution was significantly different in the comparison groups ( $\chi^2(6)=39.552$ ,  $p<.001$ ) with

singles being over-represented ( $z=5.8$ ) in the ASD group, and under-represented in the DISR ( $z=-3.6$ ) and AFF groups ( $z=-3.2$ ). Conversely, adults who were married or cohabiting were under-represented ( $z=-5.2$ ) in the ASD group, but over-represented in the DISR group ( $z=3.2$ ) and in the AFF group ( $z=3.0$ ) (Table 1).

#### Living arrangements

The largest proportion (45%) of the adults with ASD lived with their parents or other family members and 21% were institutionalized (supported or residential living). Twenty-seven percent of the adults with ASD lived self-reliant (independent living), and 7% lived with a partner or a family (partner and children). This distribution was significantly different in the adults with ADHD, DISR, or AFF ( $\chi^2(9)=75.420, p<.001$ ). Within the ASD group, adults who were institutionalized ( $z=5.6$ ) were over-represented, whereas those were under-represented in the DISR ( $z=-2.2$ ) and AFF ( $z=-2.8$ ) groups. In contrast, adults living with a partner or family were under-represented ( $z=-5.7$ ) in the ASD group, but over-represented in the DISR ( $z=3.6$ ) and AFF ( $z=3.2$ ) groups (Table 1).

#### Highest educational qualification

The highest qualification was primary education for 20% of the adults with ASD and lower secondary education for 17% of the adults with ASD. The majority (55%) completed upper secondary education, only 3% post-secondary non-tertiary education, and 5% completed the first stage of tertiary education (Table 1). This distribution differed by group ( $\chi^2(12)=24.768, p=.016$ ). The mean level of the highest educational qualification differed significantly by group ( $F(3,399)=3.949, p=.009, \eta_p^2=.029$ ). The highest educational level was significantly lower in the ASD group ( $M=3.57, SD=1.00$ ) compared to the DISR group ( $M=3.86, SD=.80$ ) ( $p=.026$ ) and the AFF group ( $M=3.98, SD=.95$ ) ( $p=.001$ ). There were no group differences between the ASD and ADHD ( $M=3.71, SD=.90$ ) group.

#### Employment

Most of the adults with ASD had paid employment (49%), but 36% of the adults with ASD were social security recipients. Fifteen percent of the adults with ASD had employment related training. The distribution of current employment situations differed by group ( $\chi^2(6)=27.189, p<.001$ ). The adults with paid employment were under-represented in the ASD group ( $z=-3.9$ ), whereas the social security recipients were over-represented ( $z=4.8$ ) when compared to the other groups (Table 1). For those adults with paid employment, the number of hours of paid employment did not differ by group ( $p=.055$ ).

**Table 1. Objective quality of life of adults with autism spectrum disorders (ASD) as compared to adults with attention deficit/hyperactivity (ADHD), disruptive behaviour (DISR), and affective disorders (AFF). \*  $p \leq 0.05$**

	ASD	%	z	ADHD	%	z	DISR	%	z	AFF	%	z
<b>MARITAL STATUS</b>	N=16			N=81			N=83			N=82		
Single	143	88.3	5.8*	58	71.6	-0.2	47	56.6	-3.6*	48	58.5	-3.2*
Relationship	6	3.7	-1.9	6	7.4	0.3	8	9.6	1.2	7	8.5	0.8
Married, cohabiting	13	8.0	-5.2*	16	21.0	0.0	28	33.7	3.2*	27	32.9	3.0*
<b>LIVING ARRANGEMENTS</b>	N=165			N=83			N=79			N=84		
Self-reliant	45	27.3	-0.2	18	21.7	-1.4	17	21.5	-1.4	34	40.5	2.9*
With partner or family	11	6.7	-5.7*	18	21.7	0.3	28	35.4	3.6*	28	33.3	3.2*
With parents or other family members	74	44.8	1.3	43	51.8	2.3*	31	39.2	-0.3	20	23.8	-3.6*
Institutionalized	35	21.2	5.6*	4	8.9	-1.9	3	3.8	-2.2*	2	2.4	-2.8*
<b>HIGHEST EDUCATIONAL QUALIFICATION</b>	N=157			N=82			N=79			N=85		
SOI 2. primary education	31	19.7	3.6*	8	9.8	-0.8	5	6.3	-1.8	6	7.1	-1.7
SOI 3. lower secondary education	26	16.6	-0.8	20	24.4	1.7	14	17.7	-0.1	13	15.3	-0.8
SOI 4. upper secondary education	87	55.4	-0.8	46	56.1	-0.4	49	62.0	0.8	51	60.0	0.5
SOI 5. post-secondary non-tertiary education	5	3.2	-2.0*	4	4.9	-0.6	9	11.4	2.1*	7	8.2	0.9
SOI 6. First stage of tertiary education	8	5.1	-0.3	4	4.9	-0.3	2	2.5	-1.3	8	9.4	1.8
<b>EMPLOYMENT</b>	N=159			N=82			N=80			N=84		
Paid employment	78	49.1	-3.9*	57	69.5	1.8	59	73.8	2.7*	52	61.9	0.2
In training	24	15.1	-0.4	12	14.6	-0.4	11	13.8	-0.6	18	21.4	1.5
Social security recipient	57	35.8	4.8*	13	15.9	-1.8	10	12.5	-2.5*	14	16.7	-1.6
<b>MENTAL HEALTH CARE</b>	N=161			N=82			N=83			N=85		
None	100	62.1		52	63.4		44	53.0		45	52.9	
None, but counselling in the past	27	16.8		14	17.1		23	27.7		19	22.4	
Counselling	24	14.9		13	15.9		13	15.7		16	18.8	
Hospitalized	10	6.2		3	4.2		3	3.6		5	5.9	
<b>TYPE OF MEDICATION</b>	N=55			N=40			N=20			N=30		
Psycho stimulants	11	20.0	-4.0*	34	85.0	6.7*	10	50.0	0.9	4	13.3	-3.4*
Anti depressives	10	18.2	-1.6	2	5.0	-3.5*	6	30.0	0.5	19	63.3	5.3*
Anti psychotics	26	47.3	5.1*	4	10.0	-2.5*	2	10.0	-1.6	3	10.0	-2.0*
Anxiety stabilizers	5	9.1	0.8	0	0	-2.0*	1	5.0	-0.4	4	13.3	1.6
Remaining	3	5.5	1.5	0	0	-1.3	1	5.0	0.7	0	0	-1.0

### *Mental health care*

The majority of the adults with ASD (62%) did not receive any form of mental health care, but 17% of the adults had some counselling in the past. Fifteen percent of the adults with ASD received mental treatment, 6% were hospitalized (day treatment or fully committed to a specialized mental institution). There were no group differences considering mental health care ( $p=.622$ ) (Table 1). For the adults who received any form of mental health care, the mean duration of the treatment (ASD:  $M=3.89$ ,  $SD=4.14$ ) did not differ by group ( $p=.603$ ).

Considering medication treatments for mental problems, 20% of the adults with ASD were using medication, 15% of the adults with ASD were not using medication but used some in the past, and the majority (64%) was not using any medication. This distribution differed by group ( $p=.032$ ), the adults who did not use any medication are over-represented in the DISR ( $z=2.1$ ) group, but under-represented in the ADHD ( $z=-2.5$ ) group. In this group the adults who were not using medication but used some in the past are over-represented ( $z=3.3$ ). When the adults were using or used medication, the type of medication differed by group ( $\chi^2(12)=84.202$ ,  $p<.001$ ). Almost half (47%) of the adults with ASD used anti-psychotics and this type of medication is over-represented in the ASD group ( $z=5.1$ ), while the usage of psycho stimulants was under-represented in this group ( $z=-4.0$ ) (Table 1).

### *Subjective QoL*

The adults with ASD were significantly less satisfied about their QoL than the adults with ADHD, DISR, or AFF ( $F(21,1083)=2.904$ ,  $p<.001$ ,  $\eta_p^2=.053$ ). Group differences were found considering satisfaction of work or education, physical condition, partner relationships, and future perspective (Table 2). Considering work or education the adults with ASD were less satisfied than the ADHD adults ( $p=.006$ ), DISR adults ( $p=.008$ ), and AFF adults ( $p=.021$ ). The adults with ASD were also less satisfied about their relationships with a partner than adults with ADHD ( $p=.027$ ), DISR ( $p=.003$ ), or AFF ( $p=.003$ ). Finally, the adults with ASD were less satisfied considering their future perspective than the DISR adults ( $p=.016$ ), and AFF adults ( $p=.029$ ). In contrast, the adults with ASD were significantly more satisfied about their physical condition than adults with DISR ( $p=.013$ ), and AFF ( $p=.036$ ). No group differences were found in satisfaction of living arrangements, social relationships, and state of mind.

*QoL of adults with ASD with low (SOI 1-3) versus high (SOI 4-7) educational qualifications.*

No difference in mean age was found between the adults with ASD with low educational qualifications (ASD LOW) ( $M=23.81$ ,  $SD=3.56$ ), as compared to adults with ASD with high educational qualifications (ASD HIGH) ( $M=23.63$ ,  $SD=3.19$ ) ( $p=.743$ ).

With respect to living arrangements differences were found ( $\chi^2(3)=23.029$ ,  $p<.001$ ). Within the ASD LOW group, self-reliant living adults were under-represented ( $z=-2.4$ ), whereas institutionalized adults were over-represented ( $z=4.7$ ). In contrast, in the ASD HIGH group, self-reliant living adults were over-represented but institutionalized adults were under-represented ( $z=-4.7$ ). The distribution of current employment situations also differed by group ( $\chi^2(2)=18.208$ ,  $p<.001$ ). The adults with paid employment were under-represented ( $z=-3.2$ ) in the ASD LOW group, whereas the social security recipients were over-represented ( $z=4.3$ ). However, the social security recipients were under-represented in the ASD HIGH group ( $z=-4.3$ ), whereas the adults with paid employment are over-represented ( $z=3.2$ ). No group differences were found for marital status ( $p=.607$ ), use of mental health care ( $p=.395$ ), type of medication treatment ( $p=.185$ ), and subjective QoL ( $p=.256$ ).

*QoL in high-educated adults with ASD versus high-educated adults with ADHD, DISR, and AFF.*

The mean levels of high educational qualifications ( $p=.227$ ) and age ( $p=.321$ ) did not differ by group.

### *Marital status*

The majority (87%) of the ASD HIGH adults was single, 5% of the adults had a relationship, and 8% were married or cohabiting. This distribution was significantly different in the comparison groups ( $\chi^2(6)=26.463$ ,  $p<.001$ ), with singles in the ASD HIGH group being over-represented ( $z=4.8$ ) whereas those who were married or cohabiting were under-represented ( $z=-4.7$ ) (Table 3).

### *Living arrangements*

The majority (51%) of the highly educated adults with ASD lived with their parents or other family members and 8% were institutionalized. Thirty-five percent of the ASD HIGH adults lived self-reliant, and 6% lived with a partner or a

**Table 2. Subjective quality of life of adults with autism spectrum disorders (ASD) as compared to adults with attention deficit/hyperactivity (ADHD), disruptive behaviour (DISR), and affective disorders (AFF). \*  $p \leq 0.05$**

SATISFACTION CONCERNING	ASD		ADHD		DISR		AFF		$F(3,365)$	$p$	$\eta_p^2$
	$N=139$		$N=73$		$N=77$		$N=80$				
Living arrangements	4.83	(1.12)	5.10	(10.2)	4.90	(1.20)	5.01	(1.03)	1.137	.334	.009
Work/education	4.25	(1.28)	4.75	(1.19)	4.73	(1.19)	4.66	(1.35)	3.945	<b>.009*</b>	.031
Physical condition	4.59	(1.01)	4.70	(1.06)	4.19	(1.24)	4.26	(1.20)	4.061	<b>.007*</b>	.032
Relationship partner	4.13	(1.37)	4.56	(1.29)	4.70	(1.44)	4.70	(1.28)	4.582	<b>.004*</b>	.036
Social relationships	4.40	(1.22)	4.75	(1.10)	4.55	(1.27)	4.81	(1.21)	2.582	.053	.021
State of mind	4.47	(1.21)	4.78	(1.11)	4.39	(1.17)	4.54	(1.10)	1.655	.176	.013
Future perspective	4.41	(1.19)	4.68	(1.32)	4.82	(1.13)	4.77	(1.13)	2.673	<b>.047*</b>	.021

**Table 3. Objective quality of life of adults with autism spectrum disorders and high educational qualifications (SOI 4-7) (ASD HIGH) as compared to highly educated adults with attention deficit/hyperactivity (ADHD HIGH), disruptive behaviour (DISR HIGH), and affective disorders (AFF HIGH). \*  $p \leq 0.05$**

	ASD HIGH			ADHD HIGH			DISR HIGH			AFF HIGH		
	$N$	%	$z$	$N$	%	$z$	$N$	%	$z$	$N$	%	$z$
<b>MARITAL STATUS</b>	$N=97$			$N=53$			$N=60$			$N=66$		
Single	84	86.6	4.8*	35	66.0	-0.4	32	53.3	-2.9*	38	57.6	-2.2*
Relationship	5	5.2	-0.8	3	5.7	-0.4	6	10.0	1.1	5	7.6	0.3
Married, cohabiting	8	8.2	-4.7*	15	28.3	0.7	22	36.7	2.4*	23	34.8	2.2*
<b>LIVING ARRANGEMENTS</b>	$N=99$			$N=54$			$N=59$			$N=66$		
Self-reliant	35	35.4	0.6	13	24.1	-1.6	16	27.1	-1.1	28	42.4	1.8
With partner or family	6	6.1	-5.3*	16	29.6	1.0	22	37.3	2.6*	24	36.4	2.6*
With parents or other family members	50	50.5	3.1*	24	44.4	1.0	20	33.9	-0.8	13	19.7	-3.6*
Institutionalized	8	8.1	2.6*	1	1.9	-0.9	1	1.7	-1.0	1	1.5	-1.2
<b>EMPLOYMENT</b>	$N=98$			$N=52$			$N=58$			$N=66$		
Paid employment	59	60.2		36	69.2		43	74.1		44	66.7	
In training	18	18.4		10	19.2		8	13.8		15	22.7	
Social security recipient	21	21.4		6	11.5		7	12.1		7	10.6	
<b>MENTAL HEALTH CARE</b>	$N=98$			$N=54$			$N=60$			$N=66$		
None	63	64.3		38	70.4		29	48.3		36	54.5	
None, but counselling in the past	16	16.3		8	14.8		20	33.3		13	19.7	
Counselling	16	16.3		7	13.0		10	16.7		13	19.7	
Hospitalized	3	3.1		1	1.9		1	1.7		4	6.1	
<b>TYPE OF MEDICATION</b>	$N=55$			$N=40$			$N=20$			$N=30$		
Psycho stimulants	8	28.6	-1.7	16	80.0	4.0*	8	53.3	1.1	3	13.6	-3.0*
Anti depressives	6	21.4	-1.9	2	10.0	-2.7*	6	40.0	0.4	16	72.7	4.3*
Anti psychotics	9	32.1	3.0*	2	10.0	-0.8	1	6.7	-1.0	1	4.5	-1.6
Anxiety stabilizers	3	10.7	1.3	0	0.0	-1.3	0	0.0	-1.1	2	9.1	0.7
Remaining	2	7.1	2.0*	0	0.0	-0.8	0	0.0	-0.7	0	0.0	-0.8

family. This distribution differed significantly from the highly educated adults with ADHD, DISR, or AFF ( $\chi^2(9)=43.145, p<.001$ ). Within the ASD HIGH group, the adults who lived with their parents ( $z=3.1$ ) or who were institutionalized ( $z=2.6$ ) were over-represented, whereas those adults living with a partner or family were under-represented in the ASD HIGH group ( $z=-5.3$ ) (Table 3).

#### Employment

Most of the high-educated adults with ASD had paid employment (60%), but 21% of the adults with ASD were social security recipients and 18% had employment related training (Table 3). The distribution of current employment situations did not differ by group ( $p=.340$ ).

#### Mental health care

The majority of the high-educated adults with ASD (64%) did not receive any form of mental health care, but 16% of the adults had some counselling in the past. Sixteen percent of the highly educated adults with ASD received mental treatment, 3% were part-time or fulltime hospitalized. There were no differences with the comparison groups considering usage of mental health care ( $p=.622$ ) (Table 3).

Considering medication treatments for mental problems, 15% of the highly educated adults with ASD were using medication, 14% were not using medication but used some in the past, and the majority (71%) was not using any medication. This distribution did not differ by group ( $p=.496$ ). When the high-educated adults were using or used medication, the type of medication differed by group ( $\chi^2(12)=42.554, p<.001$ ). Thirty-two percent highly educated adults with ASD used anti-psychotics and this type of medication is over-represented in the ASD HIGH group ( $z=3.0$ ) (Table 3).

#### Subjective QoL

There appeared to be a significant difference concerning satisfaction about the QoL between the highly educated adults with ASD, ADHD, DISR, or AFF ( $F(21,750)=2.394, p<.001, \eta_p^2=.063$ ). With respect to social relationships, the high-educated adults with ASD were less satisfied than those with ADHD ( $p=.013$ ) and AFF ( $p=.019$ ). In contrast, the high-educated adults with ASD were significantly more satisfied about their physical condition than adults with DISR ( $p=.003$ ) (Table 4).

**Table 4. Subjective quality of life of adults with autism spectrum disorders and high educational qualifications (SOI 4-7) (ASD HIGH) as compared to highly educated adults with attention deficit/hyperactivity (ADHD HIGH), disruptive behaviour (DISR HIGH), and affective disorders (AFF HIGH). \*  $p \leq 0.05$**

SATISFACTION CONCERNING	ASD N=91	ADHD N=48	DISR N=56	AFF N=63	F (3,254)	p	$\eta_p^2$
Living arrangements	4.82 (1.11)	5.19 (0.98)	4.91 (1.07)	5.03 (1.00)	1.393	.245	.016
Work/education	4.42 (1.20)	4.94 (1.08)	4.79 (1.07)	4.76 (1.24)	2.585	.054	.030
Physical condition	4.65 (1.03)	4.54 (1.13)	4.05 (1.26)	4.30 (1.23)	3.503	.016*	.040
Relationship partner	4.24 (1.40)	4.75 (1.28)	4.66 (1.46)	4.76 (1.25)	2.548	.056	.029
Social relationships	4.52 (1.16)	5.00 (0.85)	4.68 (1.10)	4.94 (1.12)	2.957	.033*	.034
State of mind	4.64 (1.08)	4.88 (1.16)	4.46 (1.11)	4.62 (1.08)	1.208	.308	.014
Future perspective	4.59 (1.10)	5.02 (1.06)	4.84 (1.13)	4.92 (1.02)	2.071	.105	.024

## Discussion

This follow-up study examined the specific impact of childhood ASD on QoL during young adulthood as compared to young adults who suffered from the other most prevalent psychiatric disorders in childhood; ADHD, DISR, and AFF disorders. Results showed that QoL of high-functioning adults diagnosed with ASD in childhood was more compromised than QoL of adults with other child psychiatric diagnoses. This applies for both objective and subjective QoL. In contrast with the outcome in adults with ADHD, DISR, or AFF, relatively many adults with ASD were single and only some of them were cohabiting or married. Most of the adults with ASD lived with their parents, relatively few lived with a partner or family and many of them were institutionalized. The highest educational level of the adults with ASD was significantly lower, relatively few had paid employment, and relatively many were social security recipients, as compared to adults with ADHD, DISR, and AFF disorders. When the adults with ASD were using or used medication, relatively many used anti-psychotics. The adults with ASD were less satisfied about their QoL than the adults with ADHD, DISR, or AFF disorders, they were less content about their work or education, partner relationships, and future perspective.

Several studies have shown that QoL in patients with psychiatric disorders is considerable poorer than that of typically developing individuals, but also comparable to or even poorer than that of physically ill patients, [e.g.,21,22] indicating that there is high risk of low quality of life in individuals with psychopathology. [11] Reviews reported that ADHD seriously compromises QoL, [e.g.,23,24] studies showed that patients with DISR had high rates of problems in social functioning [e.g.,25,26] and reviews also demonstrated poor QoL in patients with AFF. [e.g.,27,28,29,30] The current study revealed that ASD has a more profound negative effect on QoL in young adulthood than ADHD, disruptive, and affective disorders. Cross-sectional studies examining the relationship between the main psychiatric disorders and outcome in childhood and adolescence suggested that the QoL in ASD is more disadvantageous than in other psychiatric disorders, [10,12,21] this follow-up study showed the long-term negative impact of growing up with ASD on QoL in adulthood.

Although the objective characteristics of a patient's environment are important in evaluating QoL, the patient's subjective satisfaction of their life

conditions is also essential, but these measures are not frequently used in QoL studies with ASD adults. Subjective QoL reflects the difference between the hopes and expectations of a person and their present experience. Making a judgement on satisfaction is a comparative activity and depends on one's experiences and judgements of what is typical and possible within one's situation. These might be limited in patients with ASD, since they typically lack the ability to judge their own behaviour. In addition, subjective QoL is influenced by the personal frame of reference that in ASD patients might run counter to generally accepted standards (e.g. less need for social interactions). Moreover, it is possible that psychiatric patients in general may lower their own standards to what would be objectively not desirable levels as a consequence of adaptation to life conditions. However, in this study the high-functioning adults with ASD appeared to be less satisfied about aspects of QoL than the adults with ADHD, DISR, or AFF disorders; they were less content about their work or education, partner relationships, and future perspectives. In contrast, the adults with ASD were more satisfied about their physical condition or well-being than adults with DISR and AFF disorders. This implies that ASD adults were not generally less content about their life conditions, but they were able to differentiate between different domains of subjective QoL.

Although other studies reported that QoL can be very variable and difficult to predict in ASD populations with an IQ exceeding 70, [14,15] findings in this study showed that the level of education has an influence on QoL of adults with ASD without mental retardation. When a distinction was made between adults with ASD with low and high educational qualifications, relatively many adults with ASD with low educational qualifications lived institutionalized and were social security recipients. In contrast, relatively many adults with ASD with high education qualification lived self-reliant and had paid employment. No group differences were found concerning marital status and usage of mental health care. Remarkably, no differences considering subjective QoL were found between low- and high-educated ASD patients. Because of the variation in outcome between low- and high-educated adults with ASD, the differences of QoL were re-examined between a group of highly educated adults with ASD and groups of highly educated adults with ADHD, DISR, and AFF. In contrast with the high-educated adults with other major psychiatric diagnoses, relatively many adults with ASD were single and few were cohabiting or married. In addition, relatively few highly educated adults with ASD lived



with a partner or family and many lived with their parents or were institutionalized. The distribution of current employment situations and usage of mental health care did not differ by group. With respect to subjective QoL, the high-educated adults with ASD were less satisfied about their social relationships than those with ADHD or AFF. This indicates that even when highly educated adults with ASD were compared to highly educated adults diagnosed with the other main childhood disorders, the QoL remained to be more unfavourable in adults with ASD. This implies that high education is not a protective factor to QoL in ASD when compared to the QoL in other psychiatric disorders.

Outcomes of this study showed that a large percentage (47%) of adults with ASD were on anti-psychotics. Medication use itself, especially use of anti-psychotics, may influence QoL. Therefore, additional analyses were done to explore the differences in distributions of QoL indicators of adults with ASD who are using or used medication in the past ( $N=58$ ) versus those who are not using any medication ( $N=104$ ). Indeed, differences of both objective and subjective QoL were found. Differences were found with respect to living arrangements ( $p=.003$ ), within the ASD group with medication, institutionalized adults were over-represented and, in the contrary, under-represented in the ASD group without medication. The mean level of the highest educational qualifications differed significantly by group ( $p=.003$ ), this was significantly lower in the group of ASD adults with medication than those adults without medication. The distribution of current employment situations also differed by group ( $p<.001$ ). Within the ASD group with medication, the adults with paid employment were under-represented and the social security recipients were over-represented. No group differences were found for marital status. Group differences were also found regarding subjective QoL indicators ( $p<.001$ ). Within the ASD group with medication, the adults were less satisfied with respect to their work or education, physical condition, partner relationships, social relationships, state of mind, and their future perspective, when compared to the ASD group without medication. No group differences were found in satisfaction of their living arrangements. Moreover, within the group of ASD patients who used medication, the QoL indicators were compared between those who used anti-psychotics ( $N=26$ ) and those who used other types of medication ( $N=29$ ). However, no group differences were found, indicating that the usage of anti-psychotics has no specific influence on QoL. Nevertheless, a relation between medication usage and QoL in ASD was found. This might be ex-

plained by the medication use itself or the severity of symptoms and therefore the impact of the disorders on daily life functioning. In order to explore these hypotheses, we added comparisons between those ASD patients who use or used mental health care ( $N=61$ ) and those who did not ( $N=100$ ) and group difference were found. With respect to objective QoL indicators, the distribution of current employment situations differed by group ( $p<.001$ ), within the ASD group with mental health care, the adults with paid employment were under-represented and the social security recipients were over-represented. No other group differences were found. However, group differences were found regarding subjective QoL indicators ( $p=.002$ ). The adults within the ASD group with mental health care were less satisfied with respect to their work or education, social relationships, state of mind, and their future perspective, than those within the ASD group without mental health care. No group differences were found in satisfaction of their living arrangements, physical condition and partner relationships. In conclusion, besides the usage of medication, the usage of mental health care also did influence objective and subjective QoL. This might suggest that the severity of symptoms rather than medication use itself is a plausible explanation for compromised QoL in ASD and this should be verified in future research.

This study has a few limitations. The ASD diagnoses were not validated by the Autism Diagnostic Interview (ADI), since the subjects were diagnosed in the period between 1984 and 2004, and the Dutch translation of the ADI was not available until 2003. In addition, the exclusion of mentally retarded ASD patients and the large prevalence of PDD-NOS diagnoses limit the representativeness of the sample and, as such preclude generalizability to the whole autistic spectrum. In order to create pure comparison groups, mutual comorbidity of the control patients in the period of their referral to the Department of Child and Adolescent Psychiatry were excluded. However, some of the patients might developed co-morbid disorders until the follow-up period. This may be a possible influencing factor for their QoL. More research is required to improve our understanding of relationships between QoL and other factors besides characteristics of the diagnosis itself, like the impact of symptom severity, social skills or social network factors. This study provides a first step in demonstrating poor QoL in ASD, but the next step should be to investigate the factors that lead to this outcome. Furthermore, the pathways to poor QoL might be distinctive in the different psychiatric groups and these should be

investigated comparatively. However, this study also has several strengths. This is the first study examining the long-term impact (follow-up period of almost 14 years) of ASD for QoL in adults, using no less than three age-matched comparison groups of patients presenting with the other major childhood psychiatric disorders. This approach enables to examine the specific impact of ASD on QoL, which is not possible when including only normally developing individuals as controls as is usually done in QoL studies. In addition, this study has a relatively large sample size. Finally, an important strength of the study is the exclusion of mutual co morbidity in the three psychiatric control groups, leaving very pure comparison groups.

In conclusion, although several studies suggested that psychopathology is generally associated with poor outcome, this study revealed that the QoL of young adults diagnosed with ASD in childhood is specifically more compromised than QoL in adults with other child psychiatric disorders. They are less likely to live independently, have less intimate relationships, have lower education levels and employment levels, and their subjective life satisfaction is lower, than adults diagnosed with ADHD, DISR, or AFF in childhood. Even when highly educated adults with ASD were compared to highly educated adults diagnosed with other childhood disorders, adults with ASD and high educational qualifications are at specific risk of poor QoL.

## References

- [1] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR)*. Washington DC: American Psychiatric Association; 2000.
- [2] Beauchamp MH, Anderson V. SOCIAL: an integrative framework for the development of social skills. *Psychol Bull* 2010;136:39-64.
- [3] Gillberg C. Outcome in autism and autistic-like conditions. *J Am Acad Child Adolesc Psychiatry* 1991;30:375-82.
- [4] Howlin P. Outcome in adult life for more able individuals with autism or Asperger syndrome. *Autism* 2000;4:63-83.
- [5] Seltzer MM, Shattuck P, Abbeduto L, Greenberg JS. Trajectory of development in adolescents and adults with autism. *Ment Retard Dev Disabil Res Rev* 2004;10:234-47.
- [6] Sigman M, Spence SJ, Ting Wang A. Autism from developmental and neuropsychological perspectives. *Annu Rev Clin Psychol* 2006;2:327-55.
- [7] Stokes M, Newton N, Kaur A. Stalking, and social and romantic functioning among adolescents and adults with autism spectrum disorder. *J Autism Dev Disord* 2007;37:1969-86.
- [8] Cederlund M, Hagberg B, Billstedt E, Gillberg IC, Gillberg C. Asperger syndrome and autism: a comparative longitudinal follow-up study more than 5 years after original diagnosis. *J Autism Dev Disord* 2008;38:72-85.
- [9] Howlin P. Outcome in high-functioning adults with autism with and without early language delays: implications for the differentiation between autism and asperger syndrome. *J Autism Dev Disord* 2003;33:3-13.
- [10] Lee LC, Harrington RA, Louie BB, Newschaffer CJ. Children with autism: quality of life and parental concerns. *J Autism Dev Disord* 2008;38:1147-60.
- [11] Bastiaansen D, Koot HM, Ferdinand RF, Verhulst FC. Quality of life in children with psychiatric disorders: self, parent, and clinician report. *J Am Acad Child Adolesc Psychiatry* 2004;43:221-30.
- [12] Green J, Gilchrist A, Burton D, Cox A. Social and psychiatric functioning in adolescents with Asperger syndromes compared with conduct disorder. *J Autism Dev Disord* 2000;30:279-93.
- [13] Eaves LC, Ho HH. Young adult outcome of autism spectrum disorders. *J Autism Dev Disord* 2008;38:739-47.
- [14] Howlin P, Goode S, Hutton J, Rutter M. Adult outcome for children with autism. *J Child Psychol Psychiatry* 2004;45:212-29.
- [15] Marriage S, Wolverson A, Marriage K. Autism spectrum disorder grown up: a chart review of adult functioning. *J Canadian Acad Child Adolesc Psychiatry* 2009;18:322-27.
- [16] Wechsler D. *The measurement of adult intelligence*. Baltimore: Williams & Wilkins; 1944.
- [17] Central Bureau for Statistics. *Standaard Onderwijs Indeling (SOI) 2006. Uiteenzetting en verantwoording, editie 2006 [Standard educational classification: Explanation and justification, edition 2006]*. Voorburg, the Netherlands: CBS; 2006.
- [18] UNESCO. *International Standard Classification of Education: ISCED 1997*. Paris: UNESCO; 1997.
- [19] Haberman SJ. The analysis of residuals in cross-classified tables. *Biometrics* 1973;19:205-20.
- [20] Stevens J. *Applied multivariate statistics for the social sciences*. London: Lawrence Erlbaum Associates; 1986.
- [21] Bastiaansen D, Koot HM, Ferdinand RF. Determinants of quality of life in children with psychiatric disorders. *Qual Life Res* 2005;14:1599-1612.
- [22] Sawyer MG, Whaites L, Rey JM, Hazell PL, Graetz BW, Baghurst P. Health-related quality of life of children and adolescents with mental disorders. *J Acad Child Adolesc Psychiatry* 2002;41:530-37.
- [23] Danckaerts M, Sonuga-Burke EJS, Banaschewski T, Buitelaar J, Dopfner M, Hollis C, et al. The quality of life of children with attention deficit/hyperactivity disorder: a systematic review. *Eur Child Adolesc Psychiatry* 2010;19:83-105.
- [24] Wehmeier PM, Schacht A, Barkley RA. Social and emotional impairment in children and adolescents with ADHD and the impact on quality of life. *J Adolesc Health* 2010;46:209-17.
- [25] Greene RW, Biederman J, Zerwas S, Monuteaux MC, Goring JC, Faraone SV. Psychiatric comorbidity, family dysfunction, and social impairment in referred youth with oppositional defiant disorder. *Am J Psychiatry* 2002;159:1214-24.
- [26] Schachar R, Wachsmuth R. Oppositional disorder in children: a validation study comparing conduct disorder, oppositional disorder and normal control children. *J Child Psychol Psychiatry* 1990;31:1089-1102.
- [27] Mendlowicz MV, Stein MB. Quality of life in individuals with anxiety disorders. *Am J Psychiatry* 2000;157:669-82.
- [28] Papakostas GI, Petersen T, Mahal Y, Mischoulon D, Nierenberg AA, Fava M. Quality of life assessments in major depressive disorder: a review of the literature. *Gen Hosp Psychiatry* 2004;26:13-7.
- [29] Mogotsi M, Kaminer D, Stein DJ. Quality of life in the anxiety disorders. *Harvard Rev Psychiatry* 2000;8:273-82.
- [30] Simon GE. Social and economic burden of mood disorders. *Biol Psychiatry* 2003;54:208-15.

# CHAPTER 3

Barneveld, P.S., Swaab, H., Van Engeland, H., De Sonneville, L.M.J.  
Submitted

## Cross-sectional evidence for a decrease in cognitive function with age in children with autism spectrum disorders?

### Abstract

Background: Autism spectrum disorders (ASD) are associated with early disturbances in brain maturation processes and these interferences presumably have their consequences for the progressive emergence of cognitive deficits later in life, as expressed in intelligence profiles. In this study we addressed the impact of age on cognitive functioning of 6-to-15-year-old children and adolescents with ASD.

Method: Intelligence profiles were measured by the Wechsler Intelligence Scale for Children and compared between four consecutive age cohorts (children aged 6.17-8.03 years, children aged 8.04-9.61 years, children aged 9.68-11.50 years, and adolescents aged 11.54-15.85 years) of 237 high functioning boys with ASD.

Results: The results clearly demonstrated that the global intelligence level was lower in children aged eight years and older, when compared to 6-and-7-year-old children with ASD. This is mostly due to the Freedom From Distractibility factor, suggesting that older children were less able to sustain their attention, they were more distractible, or had more graph motor difficulties. Moreover, an effect of age was also found with respect to the relatively poor performance on the subtest Comprehension when compared to other verbal comprehension subtests, indicating that specifically the impairments in verbal comprehension and social reasoning abilities were more profound in older children when compared to 6-and-7-year-old children with ASD.

Conclusion: Findings of this cross-sectional study showed that it is relevant to take age into account when evaluating the impact of cognitive impairments on intelligence in children with ASD, since the impact of these developmental disorders might be different at different ages.

## Introduction

Autism Spectrum Disorders (ASD) are developmental disorders affecting social and communicative abilities with assumed profiles of specific characteristic cognitive functions and dysfunctions. Cognitive functioning in ASD patients is mainly evaluated by the assessment of intelligence profiles in terms of Verbal IQ (VIQ) and Performance IQ (PIQ) scale differences. Since patients with ASD are characterized by marked verbal problems (American Psychiatric Association, 2000), a widespread view is that VIQ is commonly lower than PIQ. Some studies indeed found that PIQ was significantly higher than VIQ in patients with ASD (e.g., Lincoln et al., 1988), however, other studies demonstrated that VIQ did not differ from PIQ in ASD (Verter et al., 1992; Siegel et al., 1996; Manjiviona & Prior, 1999; De Bruin et al., 2006), and some studies reported that discrepancies with VIQ significantly higher than PIQ occur nearly as often (Joseph et al., 2002; Charman et al., 2011). These conflicting results might be explained by the level of overall cognitive ability or by differences in age of assessment. Studies of the effect of overall ability on the VIQ-PIQ discrepancy indeed show that this difference tends to be smaller when general intelligence is higher (Rumsey, 1992). Furthermore, Mayes and Calhoun (2003a) concluded in their cross-sectional study that discrepancies between VIQ and PIQ tend to be smaller in a group of 73 school-aged (6 to 15 years) children with autism when compared to a group of 91 preschool (three to five years) children with autism, suggesting an effect of age. This was observed in both lower IQ (total IQ < 80) and higher IQ (total IQ ≥ 80) groups, but the VIQ-PIQ difference was not significant yet at age 6 or 7 years in children with higher IQ's, whereas the VIQ-PIQ gap was closed at a later age (9 or 10 year-old) in children with lower IQ's. These results suggest that the impact of age should be considered when investigating intelligence profiles in ASD. This is in line with cognitive-developmental theories that argue that the identification of deficits in cognitive domains related to psychopathology should be done in consideration of the pattern of hierarchical progression of cognitive abilities consistent with brain maturation processes of the central nervous system (Anderson et al., 2001a).

The VIQ versus PIQ discrepancy might not be the most sensitive way to examine cognitive abilities in ASD, since the prototypic VIQ < PIQ pattern appeared to lack consistency, as argued above, and specificity, as VIQ < PIQ differences are also seen in typically developing children and in language-dis-

ordered individuals (Lincoln et al., 1995; Siegel et al., 1996). Instead, analysis of factor profiles might be more suitable to assess intellectual strengths and weaknesses, because factor analytic studies demonstrated that the variance in Wechsler subtest scores are best explained by a three-factor solution (review Kaufman, 1990). Lincoln and colleagues (1995) reviewed studies examining the three factors: Verbal Comprehension (VC), Perceptual Organization (PO), and Freedom from Distractibility (FFD) and reported that de VC factor was depressed relative to the PO factor in individuals with autism. This indicates that persons with ASD have verbal comprehension deficits compared to their more effective visual-perception abilities. However, other studies found that the mean of the FFD factor was significantly lower than the means of the VC and PO factor in high functioning children with ASD, indicating concentration problems, distractibility and graphomotor difficulties as central cognitive problems (Mayes & Calhoun, 2003b; Calhoun & Mayes, 2005; De Bruin et al., 2006). Yet another way to investigate profiles of cognitive peaks and troughs in patients with ASD is analyzing scores at subtest level. Studies examining Wechsler subtest profiles suggest that patients with ASD perform better on tasks that require specific visuo-spatial functions and perform more poorly on tasks requiring verbal comprehension and social reasoning. This specific pattern of information processing is reflected in lower mean scores on the subtest Comprehension compared to the other verbal subtest scores, and higher mean scores on the subtest Block Design compared to the other performance subtests (Asarnow et al., 1987; Shah & Frith, 1993; Happé, 1994; Lincoln et al., 1995; Siegel et al., 1996; Mayes & Calhoun, 2003a; 2004).

At present, studies of the effect of age on different abilities as expressed in intelligence profiles are nonexistent, with the exception of the study by Mayes & Calhoun (2003a). This is remarkable since the comparison of cognitive impairments against age-appropriate expectations is particularly relevant in developmental disorders such as ASD (Anderson et al., 2001a). Currently, it is suggested that ASD is associated with early disturbances in brain maturation processes. This abnormal development is even noticeable in prenatal life (Palmen et al., 2004) and some authors found that this aberrant development continues postnatally with an atypical pattern of acceleration in brain growth as indicated by head circumference, probably due to initial extensive generation of synapses or later inadequate synaptic pruning (Palmen & Van Engeland, 2004; Courchesne & Pierce, 2005). As stated by Anderson

(2001a), such an early interference in maturation of the brain presumably has its consequences for the progressive emergence of cognitive deficits later in life, such as expressed in the intelligence profile. Children with ASD may show different cognitive dysfunctions at different ages based on changing windows of development at different ages and it is important to examine the mechanisms of dysfunction in order to determine expectations for children and adolescents with ASD throughout their development.

The current study is about the impact of age on intellectual development reflected by the Wechsler intelligence profiles in a large sample of 6-to-15-year-old high-functioning children and adolescents with ASD. Differences between VIQ and PIQ scales, between the three factors and subtest profiles are compared between four consecutive age cohorts high-functioning children with ASD. No VIQ-PIQ discrepancies were expected because only high functioning children with ASD were included. Because brain maturational disturbances in ASD were assumed to have a developmental impact, it was expected that the characteristic strengths and weaknesses on factor and subtest level were more profound in older children when compared to younger children.

## Methods

### *Procedure and participants*

Participants were selected from consecutive referrals to the patient department of Child and Adolescent Psychiatry at the University Medical Centre Utrecht, the Netherlands, from 1985 until 2004. The medical ethics committee approved the study (number 05-319/K) and written informed consent was obtained according to the declaration of Helsinki. To qualify for this study the participants had to meet the following criteria. At first, a diagnosis of ASD was required. In a case conference two board-certified psychiatrists needed to reach a 100% consensus on diagnosis and classification to insure diagnostic reliability. Semi-structured DSM-focused interviews, observations, medical records, and structured questionnaires (Child Behavior Checklist and Teacher's Report Form) (Achenbach, 1986; 1991) were included in the diagnostic process according to the standards of that period. Secondly, the age range had to be between 6 to 15 years. Thirdly, Full Scale IQ's (FSIQ) were required to be 70 or above, as measured with the Dutch adaptations of the Wechsler Intelligence

Scales for Children that were customary at the time of referral (WISC-R or WISC-III) (Wechsler, 1974; 1991). Finally, only male subjects were selected in order to rule out the possibility of interfering gender effects. A total of 237 high-functioning boys with ASD participated in the current study. The patient group was equally divided into four age cohorts by number of patients: children aged 6.17-8.03 years ( $N=59$ ), children aged 8.04-9.61 years ( $N=60$ ), children aged 9.68-11.50 years ( $N=59$ ), and adolescents aged 11.54-15.85 years ( $N=59$ ) (see Table 1).

### *Materials*

Data of intellectual functioning were available from the assessment at referral with the Dutch adaptations of the Wechsler Intelligence Scale for Children (WISC; Wechsler, 1974; 1991). The WISC-R generates a Full Scale Intelligence Quotient (FSIQ), and the VIQ and the PIQ scale scores. The VIQ scale consists of the subtests Information, Similarities, Arithmetic, Vocabulary, Comprehension, and Digit Span. The PIQ scale consists of the subtests Picture Completion, Picture Arrangement, Block Design, Object Assembly, Coding, and Mazes (Wechsler, 1974). The Kaufman factors include the Verbal Comprehension factor (VC; subtests Information, Similarities, Vocabulary, and Comprehension), the Perceptual Organization factor (PO; subtests Picture Completion, Block Design, Object Assembly, and Mazes) and the Freedom from Distractibility factor (FFD; subtests Arithmetic, Digit Span, and Coding) (Kaufman, 1975). Because different versions of the WISC have been used over the years, comparability is obtained by use of standardized scores only. A total of 223 subjects were assessed by the WISC-R and 14 subjects by the WISC-III.

### *Statistical analyses*

Group differences in FSIQ were analyzed by univariate analysis of variance (ANOVA). Simple contrasts were used for the comparison between FSIQ of the four age groups, with the youngest age group being the reference level. VIQ-PIQ scale differences between the age cohorts were analyzed by a repeated measures ANOVA, with VIQ and PIQ differences as levels of the within subjects factor and the age groups as the between subjects factor. Similarly, differences between the four age cohorts were examined with the factors VC, PO, and FFD as levels of the within subjects factor. For the comparison between the factor means, the factors were contrasted with each other. Simple contrasts were

used for the comparison between the four age groups, the youngest age group being the reference level. Finally, differences between the age cohorts were examined on the subtests Comprehension and Block Design, the subtests on which ASD patients characteristically show low and high mean scores, respectively. To investigate these subtest profiles within the VC and PO factors in relation to age, repeated measures ANOVAs were conducted. The differences between the mean scores on the subtest Comprehension and the means of the other subtests belonging to the VC factor (Information, Similarities, and Vocabulary) were used as levels of within subjects factors and age groups as between subjects factor. Similarly, the differences between the mean scores of the subtest Block Design and the means of the other subtests belonging to the PO factor (Picture Completion, Object Assembly, and Mazes) were used as levels of within subjects factors and age groups as between subjects factor. Because intelligence levels of the participants were assessed over a long period of time (between 1985 until 2004) a potential Flynn-effect was accounted for by using year of assessment as a covariate in all analyses. Because the effect of this covariate appeared to be not significant, the analyses were rerun without the covariate. Alpha was set to 0.05 and partial eta squared ( $\eta_p^2$ ) was computed to estimate effect sizes (weak effect:  $\eta_p^2 \sim 0.03$ ; moderate:  $\eta_p^2 \sim 0.06$ ; large:  $\eta_p^2 \geq 0.14$ ) (Stevens, 1986).

## Results

### *Descriptives*

The means and standard deviations of FSIQ, VIQ and PIQ of the four age cohorts are shown in Table 1. A total of 16.5% had a FSIQ score between 70 and 84, 69.2% of the children with ASD had an IQ score within the normal range (FSIQ 85 to 115), and 14.3% had an FIQ score above 115.

### *FSIQ and the PIQ and VIQ scales*

The FSIQ means were significantly different between the four age groups [ $F(3,233)=3.14, p=.026, \eta_p^2=.039$ ], and simple contrast analyses showed that the mean FSIQ of the youngest age cohort was significantly higher than the FSIQ means of the three older age cohorts (1st vs. 2nd age cohort:  $p=.026$ ; 1st vs. 3rd:  $p=.052$ ; and 1st vs. 4th:  $p=.004$ ). No significant VIQ-PIQ differences

were found ( $p=.293$ ) and the group by scales interactions were not significant ( $p=.408$ ) (Table 1).

### *VC, PO, and FFD factors*

Means of the factors are displayed in Figure 1. A significant difference was found between the means of the three factors ( $F(2,446)=15.94, p<.001, \eta_p^2=.067$ ) and difference contrast analyses showed that the FFD factor differed significantly from the VC and PO factor ( $F(1,223)=34.16, p<.001, \eta_p^2=.133$ ). A significant main effect of age was found ( $F(3,223)=4.03, p=.008, \eta_p^2=.051$ ). The mean of the three factors of the youngest age cohort was significantly higher than the means of the three older age cohorts (1st vs. 2nd age cohort:  $p=.013$ ; 1st vs. 3rd:  $p=.016$ ; and 1st vs. 4th:  $p=.001$ ). Moreover, an interaction effect (factors x age groups) was found at trend level ( $F(6,446)=2.02, p=.062, \eta_p^2=.026$ ). Visual inspection (see Figure 1) suggests that differences between groups were lowest on Verbal Comprehension and highest on freedom from distractibility. Post-hoc analyses showed that the differences between age groups were highest on the FFD factor when compared to the mean of the VC and PO factor ( $F(3,223)=2.97, p=.033, \eta_p^2=.038$ ).

## Subtests

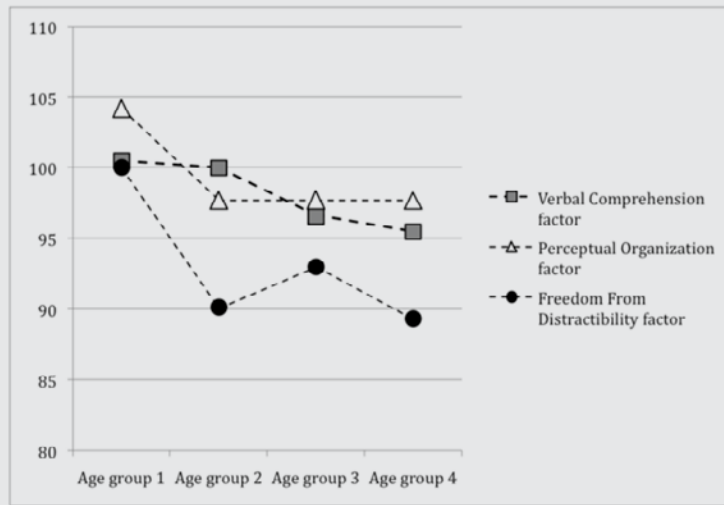
Table 2 shows the mean scaled subtest scores and standard deviations of children with ASD in the four age groups.

The means of the subtest Comprehension was significantly lower when compared to the means of the other VC subtests ( $F(1,232)=46.43, p<.001, \eta_p^2=.167$ ). An interaction effect of VC subtests (mean of Comprehension vs. mean of the other VC subtests) x age groups was found at trend level ( $F(3,232)=2.13, p=.097, \eta_p^2=.028$ ), and simple contrast analyses showed that the difference between the means of the subtest Comprehension and the means of the other VC subtests was larger in the two eldest age groups than in the youngest group (1st vs. 3rd age cohort:  $p=.080$ ; 1st vs. 4th:  $p=.018$ ) (see Figure 2).

The means of the subtest Block Design was significantly higher when compared to the means of the other PO subtests ( $F(1,233)=12.11, p=.001, \eta_p^2=.049$ ), however, no significant interaction effect (PO subtests difference x four age groups) was found ( $p=.563$ ).

**Table 1. The age range, mean age, and mean and standard deviation of Full scale IQ, Verbal IQ, and Performance IQ of the four age cohorts of the children with ASD.**

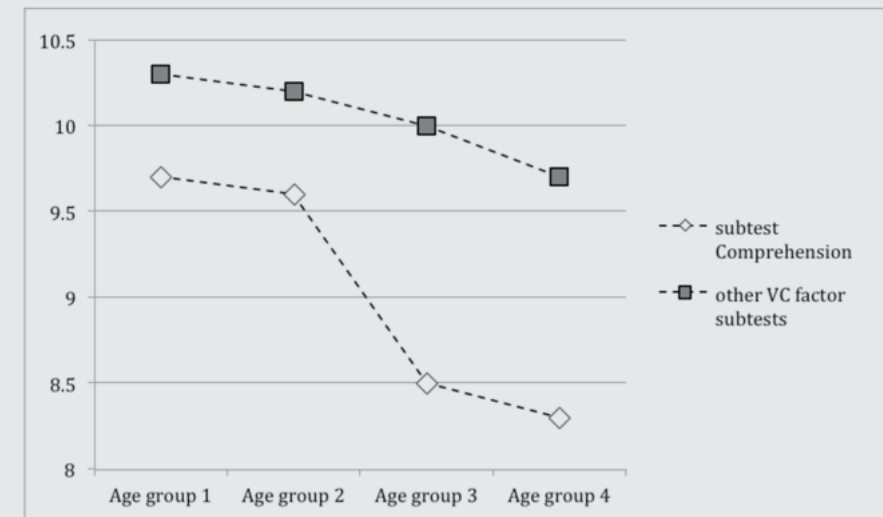
	Age range		Age		Full Scale IQ		Verbal IQ		Performance IQ	
	N	Min - Max	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age group 1	59	6.17 - 8.03	7.26	(.56)	102.93	(13.5)	101.81	(14.2)	103.81	(15.1)
Age group 2	60	8.04 - 9.61	8.78	(.45)	97.08	(13.6)	98.12	(12.6)	96.58	(15.7)
Age group 3	59	9.68 - 11.50	10.51	(.53)	97.80	(15.9)	97.29	(16.3)	98.07	(16.9)
Age group 4	59	11.54 - 15.85	13.27	(1.29)	95.25	(13.9)	94.42	(11.9)	97.25	(15.9)



**Figure 1. Means of the factors (Verbal Comprehension, Perceptual Organization, and Freedom from Distractibility) of the four age cohorts of the children with ASD.**

**Table 2. Mean scaled subtest scores and standard deviations of children with ASD in four age groups.**

	Age group 1 N=59	Age group 2 N=60	Age group 3 N=59	Age group 4 N=59
<b>Subtests VC factor</b>	M (SD)	M (SD)	M (SD)	M (SD)
Comprehension	9.66 (2.5)	9.55 (2.3)	8.54 (2.7)	8.34 (2.1)
Information	10.63 (2.9)	10.35 (3.0)	10.17 (3.3)	9.76 (2.6)
Similarities	10.00 (3.3)	10.40 (2.7)	10.42 (3.3)	10.48 (2.6)
Vocabulary	10.20 (3.3)	9.93 (2.8)	9.41 (3.4)	8.83 (2.5)
<b>Subtests PO Factor</b>				
Block Design	11.33 (3.1)	9.98 (3.4)	10.44 (3.1)	10.77 (3.6)
Picture Completion	10.53 (3.5)	9.53 (3.2)	9.38 (3.2)	9.29 (2.9)
Object Assembly	10.49 (3.3)	9.49 (3.3)	9.60 (3.3)	9.98 (3.9)
Mazes	10.60 (3.1)	10.35 (3.4)	10.56 (3.3)	10.07 (3.1)
<b>Subtests FFD factor</b>				
Arithmetic	10.60 (3.1)	8.98 (3.1)	9.37 (3.6)	9.47 (3.0)
Digit Span	10.34 (3.7)	8.93 (3.3)	9.42 (2.8)	8.12 (2.8)
Coding	9.29 (2.9)	8.03 (3.3)	8.49 (3.2)	7.71 (2.9)



**Figure 2. Means of the subtest Comprehension compared to the means of the other Verbal Comprehension (VC) subtests (Information, Similarities, and Vocabulary) of the four age groups.**

## Discussion

Measurements of cognitive abilities against age-appropriate expectations are highly relevant in studies of developmental disorders such as ASD. In this study we examined the relation between age and intelligence profiles of children and adolescents with ASD in the age range of 6 to 15 years old. The results clearly demonstrate lower general intelligence levels in children aged eight years and older compared to younger children with ASD. Similarly, the analyses of the three factors showed that the FFD factor was relatively lower in children aged eight years and older when compared to 6-and-7-year-old children with ASD. Moreover, an effect of age was also found with respect to the relatively poor performance on the subtest Comprehension, the difference between this subtest and the other VC subtests is larger in the eldest age groups than in the youngest age group.

Although the results have to be interpreted with caution because only cross-sectional data were analyzed and the extent to which IQ scores for individual children with ASD actually decrease with time is not known, the findings suggest a progressive impairment of cognitive functioning in children with ASD. Children from eight years and older have more difficulties to sustain their attention, are more distractible, or have more graph motor difficulties when compared to younger children, as reflected on the differences of the FFD factor. The apparent decline in intelligence around eight years might be associated with a possible absence of the typically expected growth spurt in executive functioning aligned with maturation of the frontal lobe, as seen in typically developing children (Anderson, 2002). Associated with ongoing maturation, children and adolescents may gradually acquire the capacity for more efficient processing, because transmission of nerve impulses is more rapid with increasing myelination of nerve tracks (Anderson et al., 2001b). The development of executive functions might especially be affected in ASD by abnormal growth processes, because of the relatively late and prolonged period of maturation of the putative underlying cortical areas (Courchesne & Pierce, 2005). The impaired development of executive functions might play an important mediating role in the development of intelligence. Furthermore, since executive functions such as attentional control and response inhibition are required when performing tasks of the FFD factor, presumed impairment of executive functions might also contribute to a less harmonious distribution

of factor profiles in older children when compared to younger ones.

As expected, no VIQ versus PIQ discrepancies were found in this sample of high functioning ASD children, and there were also no differences between age groups. However, a clear distinction can be made between factor level performances, with relatively better performance on the Verbal Comprehension and Perceptual Organization factors and relatively poorer performance on the Freedom from Distractibility factor. In addition, it was found that children aged eight years and older scored lower on the factors compared to the younger children with ASD. More specifically, the differences between age groups were highest on the Freedom from Distractibility factor. These results suggest that discrimination on the basis of factor profiles is more sensitive when examining the impact of age on intellectual strengths and weaknesses in high-functioning children with ASD than the use of the VIQ and PIQ scales.

When profiles of peaks and troughs in children with ASD were examined at subtest level, this study showed that the patients with ASD performed worse on the subtest Comprehension when compared to the other subtests of the Verbal Comprehension factor. This finding is in correspondence with studies that showed lower mean scores on Comprehension compared to other verbal scale scores (e.g., Siegel et al., 1996; Mayes & Calhoun, 2003b; 2004; De Bruin et al., 2006; Charman et al., 2011). With respect to this subtest, the distinction with the performance on the other VC subtests is larger in the eldest age groups than in the youngest group. This might indicate that specifically the impairments in verbal comprehension and social reasoning abilities are more profound in older children when compared to 6-and-7-year-old children with ASD. Since the ability of social reasoning is believed to be mediated by the frontal regions (Walker & Bollini, 2002), the specific age-effect of performance on Comprehension possibly suggests more profound executive dysfunction in older children with ASD. Typically developing children show increased reasoning and problem-solving abilities and the capacity to think in multiple dimensions at approximately seven years of age (Anderson, 2001b). These executive functions are required for social reasoning as measured by the subtest Comprehension and inefficient acquisition of these skills in children with ASD might result in deviations from expected patterns of development. Besides the characteristic trough in patients with ASD as indicated by the low performance on Comprehension, the typical peak in children with



ASD as indicated by the high performance on the subtest Block Design (e.g., Asarnow et al., 1987; Shah & Frith, 1993; Happé, 1994; Siegel et al., 1996) was also found in this study. The children with ASD scored higher on this subtest when compared to the other subtests of the Perceptual Organization factor, indicating superior abstract visuo-spatial abilities in children with ASD. As described in the weak central coherence theory, the peak of performance on Block Design can be explained as the development of a relatively local, as opposed to global, processing style of children with ASD (Shah & Frith, 1993; Happé, 1994). However, no effect of age was found with respect to abstract visuo-spatial abilities.

In conclusion, findings of this study show that intelligence levels are lower in children aged eight years and older, when compared to 6-and-7-year-old children with ASD, specifically for the FFD factor, indicating difficulties to sustain their attention, higher distractibility, or more graph motor difficulties. Moreover, an effect of age was also found with respect to the relatively poor performance on the subtest Comprehension when compared to other verbal comprehension subtests, indicating that specifically the impairments in verbal comprehension and social reasoning abilities are more profound in older children when compared to 6-and-7-year-old children with ASD. These findings show that it is relevant to take age into account when evaluating cognitive impairments on intelligence in children with ASD, since the impact of these developmental disorders might be different at different ages and become more noticeable later in life. Longitudinal studies are desirable to verify whether or not children with ASD actually have progressive impairments during development, as shown by intelligence profiles.

## References

- Achenbach, T. M. (1986). *Manual for the Teacher Report Form and the Child Behavior Profile*. Burlington: University of Vermont Department of Psychiatry.
- Achenbach, T. M. (1991). *Integrative Guide for the 1991 CBCL, YSR and TRF Profiles*. Burlington: University of Vermont Department of Psychiatry.
- American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR)*. Washington DC: American Psychiatric Association.
- Anderson, V.A., Anderson, P., Northam, E., Jacobs, R., & Catroppa, C. (2001b). Development of executive functions through late childhood and adolescence in an Australian Sample. *Developmental Neuropsychology, 20*, 1, 385-406.
- Anderson, V., Northam, E., Hendy, J., & Wrennall, J. (2001a). *Developmental neuropsychology, a clinical approach*. Hove: Psychology Press Ltd.
- Anderson, P. (2002). Assessment and development of executive function (EF) during childhood. *Child Neuropsychology, 8*, 2, 71-82.
- Asarnow, R.F., Tanguay, P.E., Bott, L., Freeman, B.J. (1987). Patterns of intellectual functioning in non-retarded autistic and schizophrenic children. *Journal of Child Psychology and Psychiatry, 28*, 2, 273-280.
- Calhoun, S.L., Mayes, S.D. (2005). Processing speed in children with clinical disorders. *Psychology in the Schools, 42*, 4, 333-343.
- Charman, T., Pickles, A., Simonoff, E., Chandler, S., Loucas, T., Baird, G. (2011). IQ in children with autism spectrum disorders: data from the Special Needs and Autism Project (SNAP). *Psychological Medicine, 41*, 619-927.
- Courchesne, E. & Pierce, K. (2005). Brain overgrowth in autism during a critical time in development: implications for frontal pyramidal neuron and interneuron development and connectivity. *International Journal of Developmental Neuroscience, 23*, 153-170.
- De Bruin, E. I., Verheij, F., & Ferdinand, R. F. (2006). WISC-R subtest but no overall VIQ-PIQ difference in Dutch children with PDD-NOS. *Journal of Abnormal Child Psychology, 34*, 263-271.
- Happé, F. G. (1994). Wechsler IQ profile and theory of mind in autism: a research note. *Journal of Child Psychology and Psychiatry, 35*, 1461-1471.
- Joseph, R.M., Tager-Flusberg, H., Lord, C. (2002). Cognitive profiles and social-communicative functioning in children with autism spectrum disorders. *Journal of Child Psychology and Psychiatry, 43*, 807-821.
- Kaufman, A. (1990). *Assessing adolescents and adult intelligence*. Boston: Allyn and Bacon.
- Kaufman, A. S. (1975). Factor Analysis of the WISC-R at 11 age levels between 6,5 and 16,5 years. *Journal of Consulting and Clinical Psychology, 52*, 74-79.
- Lincoln, A. J., Allen, M. H., & Kilman, B. A. (1995). *The Assessment and Interpretation of Intellectual Abilities in People with Autism*. In E. Schopler & G.B. Mesibov (Eds.), *Learning and cognition in autism* (pp. 89-117). New York: Plenum Press.
- Lincoln, A. J., Courchesne, E., Kilman, B. A., Elmasian, R., & Allen, M. (1988). A study of intellectual abilities in high-functioning people with autism. *Journal of Autism and Developmental Disorders, 18*, 505-524.
- Manjiviona, J., & Prior, M. (1999). Neuropsychological profiles of children with Asperger syndrome and autism. *Autism, 3*, 4, 327-356.
- Mayes, S.D., Calhoun, S.L. (2003a). Ability profiles in children with autism. Influence of age and IQ. *Autism, 6*, 4, 65-80.
- Mayes, S.D., Calhoun, S.L. (2003b). Analysis of WISC-III, Stanford-Binet: IV, and Academic Achievement Test Scores in children with autism. *Journal of Autism and Developmental Disorders, 33*, 3, 329-341.
- Mayes, S.D., Calhoun, S.L. (2004). Similarities and differences in Wechsler Intelligence Scale for Children – Third edition (WISC-III) profiles: support for subtest analysis in clinical referrals. *Clinical Neuropsychology 18* (4) 559-572.
- Palmen, S.J.M.C., & Van Engeland, H. (2004). Review on structural neuroimaging findings in autism. *Journal of Neural Transmission, 111*, 903-929.
- Palmen, S.J.M.C., Van Engeland, H., Hof, P.R., & Schmitz, C. (2004). Neuropathological findings in autism. *Brain, 127*, 2572-2583.
- Rumsey, J.M. (1992). *Neuropsychological studies of high-level autism*. In E. Schopler & G.B. Mesibov (Eds.), *High-functioning individuals with autism* (pp. 41-64). New York: Plenum Press
- Shah, A., Frith, U. (1993). Why do autistic individuals show superior performance on the block design task? *Journal of Child Psychology and Psychiatry, 34*, 8, 1351-1364.
- Siegel, D. J., Minshew, N. J., & Goldstein, G. (1996). Wechsler IQ profiles in diagnosis of high-functioning autism. *Journal of Autism and Developmental Disorders, 26*, 389-406.
- Stevens, J. (1986). *Applied multivariate statistics for the social sciences*. London: Lawrence Erlbaum Associates.
- Venter, A., Lord, C., & Schopler, E. (1992). A follow-up study of high-functioning autistic children. *Journal of Child Psychology and Psychiatry, 33*, 489-507.
- Walker, E. & Bollini, A. M. (2002). Pubertal neurodevelopment and the emergence of psychotic symptoms. *Schizophrenia Research, 54*, 17-23.
- Wechsler, D. (1974). *Manual for the Wechsler Intelligence Scale for Children Revised (WISC-R)*. New York.
- Wechsler, D. (1991). *Manual for the Wechsler Intelligence Scale for Children - Third Edition (WISC-III)*. San Antonio, TX.

# CHAPTER 4

Barneveld, P.S., Pieterse, J., De Sonnevle, L., Van Rijn, S., Lahuis, B., Van Engeland, H., & Swaab, H. (2011). Overlap of autistic and schizotypal traits in adolescents with autism spectrum disorders. *Schizophrenia Research*, 126, 231-236.

## Overlap of autistic and schizotypal traits in adolescents with autism spectrum disorders

### Abstract

This study addresses the unraveling of the relationship between autism spectrum and schizophrenia spectrum traits in a population of adolescents with Autism Spectrum Disorder (ASD). Recent studies comparing isolated symptoms of both spectrum disorders as well as diagnostic criteria for each (DSM-IV-TR) suggest resemblances in the clinical phenotype. A group of 27 adolescents with ASD (11-18 years) and 30 typically developing adolescents, matched for age and gender, participated in this study. Within the ASD group 11 adolescents satisfied DSM-IV-TR criteria for schizotypal personality disorders. Autistic and schizotypal traits were identified by means of well validated questionnaires (Autism Questionnaire, AQ and Schizotypal Personality Questionnaire-Revised, SPQ). Significantly more schizotypal traits in adolescents with ASD were found than in typically developing controls. Besides high levels of negative symptoms, adolescents with ASD also displayed high levels of positive and disorganized symptoms. There appeared to be a relationship between the mean level of autistic symptoms and schizotypal traits, as well as specific associations between autistic symptoms and negative, disorganized and positive schizotypal symptoms within individuals. Schizotypal symptomatology in all sub dimensions that are reflected by the SPQ scores, was most prominently associated with attention switching problems of the autism symptoms from the AQ. These findings indicate that patients diagnosed with an ASD show schizophrenia spectrum traits in adolescence. Although other studies have provided empirical support for this overlap in diagnostic criteria between both spectrum disorders, the present findings add to the literature that behavioral overlap is not limited to negative schizotypal symptoms, but extends to disorganized and positive symptoms as well.

## 1. Introduction

Autism Spectrum Disorders (ASD) and Schizophrenia Spectrum Disorders (SSD) are both characterized by significant impairments in social functioning (American Psychiatric Association (APA), 2000). Although these spectrum disorders have distinct classification criteria according to the current DSM-IV-TR standards, the extent of overlap with respect to the clinical presentation of the disorders and the underlying mechanisms of each, have been topics of scientific discussion for many decades. In the early '40s, Kanner (1943) adopted the term 'autism' from Eugene Bleuler (1911), who had coined it to describe the self-absorbed withdrawn behaviors that were characteristic of adults with schizophrenia. Bender (1947) argued that ASD could be an age specific expression of a developmental disorder that in adulthood is characterized by schizotypal symptoms. Recent reports have provided empirical support for a conceptual overlap in diagnostic criteria between both spectrum disorders (Hurst et al., 2007; Konstantareas & Hewitt, 2001; Sheitman et al., 2004). Kolvin (1971) and Rutter (1972), however, have regarded ASD and SSD as mutually exclusive categorical diagnoses (APA, 2000) with clearly distinct developmental pathways. Despite the clear differences in clinical presentation and age of onset, recent studies have pointed to the co-occurrence of autistic and schizophrenic symptomatology in individuals. A number of these studies have focused on the presence of schizophrenia spectrum pathology in patients with ASD, further illuminating the possible overlap between both disorders. Negative symptoms and to a lesser extent disorganized symptoms, have been reported in adults and adolescents with ASD (Dykens et al., 1991; Konstantareas & Hewitt, 2001; Rumsey et al., 1986). Signs of positive symptoms of SSD have not been consistently found in individuals with ASD (Craig et al., 2004; De Bruin et al., 2007; Solomon et al., 2008; Van der Gaag et al., 2005).

Other studies have focused on the presence of high levels of autistic traits in patients with SSD (Bender, 1970; Esterberg et al., 2008; Sheitman et al., 2004). Moreover, follow-up studies have indicated that a substantial proportion of children diagnosed with an ASD developed SSD later in life, with conversion rates reported up to 34.8% (Mouridsen et al., 2008; Stahlberg et al., 2004; Van Engeland & Van der Gaag, 1994). This suggests that in some children with ASD a developmental shift towards schizotypy might occur. In these cases, it is likely that (subclinical) schizotypal traits were already present in

adolescence, and it is relevant to examine to what extent autistic and schizotypal symptoms already coincide during adolescence.

A major factor affecting the clarity of previous findings stems from the categorical approach employed in the majority of studies. Only a small number of studies have explored the relation between the behavioral expressions of both disorders from a dimensional perspective. As Konstantareas and Hewitt (2001) have argued, this allows for a degree of overlap of specific symptom expression, and can therefore provide more insight into the putative common grounds in symptomatology. Hurst and colleagues (2007) have incorporated this dimensional approach and have found strong positive associations between autistic and schizotypal features in a large non-clinical population. However, it is obviously important to study these relations in clinical samples that meet diagnostic criteria for either ASD or SSD.

In the present study we add to the literature by direct comparison of autistic symptoms to schizotypal traits in a sample of adolescents, already diagnosed with ASD in childhood, in order to explore the possible correspondence in symptomatology. It is hypothesized that adolescents with ASD show more schizotypal traits than typically developing adolescents. The main hypothesis is that there is an overlap between autistic symptoms and schizotypal traits in adolescents with ASD.

## 2. Methods

### 2.1. Subjects

Twenty-seven adolescents with ASD (11-18 years) and 30 typically developing controls, matched on age and gender participated in the study. The participants with ASD consisted of a group of consecutive referrals to the inpatient Department of Child and Adolescent Psychiatry at the University Medical Centre Utrecht, the Netherlands (1998-2004). A total of 55 inpatients diagnosed with ASD were sent a letter informing them about the aims of the study and checking their willingness to participate in the study. Twelve adolescents refused participation. Forty-three adolescents and their parents decided to participate in the study of which three cancelled their participation later on. A written informed consent was collected prior to entry in the study.

To qualify for the current study the participants had to meet the fol-

lowing inclusion criteria. First, a diagnosis of ASD at childhood was required, based on 100% diagnostic agreement with regard to the DSM-IV-TR classification between two board-certified psychiatrists. During the follow-up period, the ASD diagnoses were validated using the Dutch translation of the Autism Diagnostic Interview – Revised (ADI-R) (Lord et al., 1994). A diagnosis of ASD was considered if the adolescent obtained a score meeting or exceeding the cut-off criteria on two domains, including the ADI-R reciprocal social interaction domain and a score within one point of the cut-off on either the communication or restricted activities/interests domain. Second, adolescents were included if they had an estimated Full Scale IQ of 70 or higher, based on the subtests Vocabulary and Block Design of the Dutch adaptation of the Wechsler Intelligence Scales for Children (WISC-IIIINL; Wechsler, 2002) or Adults (WAIS-IIIINL; Wechsler, 2005). Following these two criteria, eight adolescents were excluded because they did not meet the ADI cut-off criteria and three were excluded because they had a Full Scale IQ below 70. Two adolescents were excluded because of too much missing data. Reliable scores for 27 adolescents with ASD (20 boys, 7 girls) were obtained. Eleven adolescents with ASD (40.7%) met the criteria for a schizotypal personality disorder (DSM-IV-TR 301.22). In addition, 23 adolescents met criteria for affective or anxiety disorders, three for somatic disorders, nine for attention deficit/hyperactivity disorders, and five for oppositional defiant disorders or conduct disorders.

The typically developing (TD) group consisted of 30 adolescents (23 boys, 7 girls) with ages 10-18 years. They were recruited by contacting regular public secondary schools. All individuals were screened for global intelligence (Full Scale IQ of 70 or higher, based on the subtests Vocabulary and Block Design of the WISC-IIIINL or WAIS-IIIINL). None of the typically developing controls satisfied the criteria for ASD or schizotypal personality disorder. Moreover, all individuals needed to be free of problem behavior as indicated by total problem scores below the clinical range of 70 on the CBCL (Achenbach, 1986).

## 2.2. Measures

Autism traits were evaluated using the Autism Questionnaire (AQ, Baron-Cohen et al., 2001). The AQ is a 50 item self-report questionnaire and assesses the degree to which an individual of normal intelligence might show features of the core autistic phenotype: poor social skills (e.g., 'I find it hard to make new friends'), poor attention switching (e.g., 'I prefer to do the same thing

over and over again'), exceptional attention to detail (e.g., 'I tend to notice details that others do not'), poor communication skills (e.g., 'I frequently find that I don't know how to keep a conversation going') and poor imagination (e.g., 'When I'm reading a story, I find it difficult to work out the characters' intentions').

Schizophrenia spectrum pathology was measured using the revised Schizotypal Personality Questionnaire (SPQ, Raine, 1991; Vollema & Hoijtink, 2000). The SPQ is a 74 item self-report measure of schizotypal traits, which have shown to be normally distributed in the general population. Factor analytical studies have revealed three dimensions of schizotypy: positive schizotypy (e.g., referential thinking and delusional atmosphere), negative schizotypy (e.g., constricted affect and social anxiety) and disorganization (odd speech and eccentric behavior) (Vollema & Hoijtink, 2000). Raine (1991) described the development of the SPQ which is modeled on DSM-III-R criteria for schizotypal personality disorder. A chi-square analysis indicated a significant association between 'group membership' based on scores on the SPQ (high/low) and clinical diagnosis (yes/no) of schizotypal personality disorder ( $\chi^2=7.3, p=.007$ ). The point-biserial correlation between diagnosis of schizotypal personality disorders and SPQ scores was also significant ( $r=.60, p<0.001$ ) (Raine, 1991). These analyses demonstrate that high scores on the SPQ are indicative of a diagnosis of schizotypal personality disorder. In addition, in a study of Vollema et al. (2002) the SPQ was used as an indicator of the vulnerability to schizophrenia. First-episode schizophrenia patients and relatives of schizophrenia patients were compared with respect to SPQ scores. Schizophrenia patients differed largely from the relatives on all three SPQ dimensions. Based on these studies, the SPQ is regarded as an indicator of the genetic vulnerability of schizophrenia and it is sensitive to gradient levels of schizophrenia proportional to the risk of schizophrenia associated with the degree of kinship with schizophrenic family members. The SPQ was slightly modified to better accommodate a young population (e.g., items referring to work were changed into referring to school) (Sprong et al., 2008).

## 2.3. Statistical analyses

Group differences were tested using univariate (total AQ and SPQ scores) and multivariate (subscales of the AQ and SPQ) analyses of variance, controlling for IQ. Partial eta squared ( $\eta_p^2$ ) was used to estimate effect sizes (weak effect:

$\eta_p^2 \sim 0.03$ ; moderate:  $\eta_p^2 \sim 0.06$ ; large:  $\eta_p^2 \geq 0.14$ ) (Stevens, 1986). The degree of relationships between total scores and dimensions of the AQ and SPQ were examined by Spearman's bivariate correlations ( $r$ ) (small effect size:  $r=0.1-0.23$ ; medium:  $r=0.24-0.36$ ; large:  $r \geq 0.37$ ) (Cohen, 1992), which are converted into the proportion of explained variance.

### 3. Results

#### 3.1. Age, gender and IQ

Comparison of the ASD and typically developing adolescents revealed no difference in age (ASD: mean age=14.6,  $SD=2.1$ ; TD mean age=15.4,  $SD=2.1$ ) ( $p=.157$ ) and gender ( $p=.820$ ). There was a significant difference in global intelligence level (ASD mean TIQ=93.6,  $SD=13.7$ ; TD mean TIQ=114.0,  $SD=9.6$ ) ( $t(55)=6.56$ ,  $p<.001$ ). As a consequence, IQ was used as a covariate in all analyses.

#### 3.2. Autistic traits

The mean total AQ score was significantly higher in the ASD group ( $M=22.0$ ,  $SD=7.2$ ) than in the TD group ( $M=10.1$ ,  $SD=5.9$ ) ( $F(2,54)=16.96$ ,  $p<.001$ ,  $\eta_p^2=.239$ ). As shown in Figure 1, the adolescents with ASD displayed more autistic traits than typically developing adolescents in four domains, with moderate to large effect sizes: Social skills ( $F(2,54)=7.65$ ,  $p=.008$ ,  $\eta_p^2=.124$ ), Attention switching ( $F(2,54)=9.78$ ,  $p=.003$ ,  $\eta_p^2=.153$ ), Attention to detail ( $F(2,54)=13.08$ ,  $p=.001$ ,  $\eta_p^2=.195$ ) and Communication ( $F(2,54)=11.59$ ,  $p=.001$ ,  $\eta_p^2=.177$ ). No significant difference was found on Imagination ( $p=.363$ ).

#### 3.3. Schizotypal traits

The mean total SPQ score was significantly higher in adolescents with ASD ( $M=32.2$ ,  $SD=16.4$ ) than in typically developing adolescents ( $M=10.9$ ,  $SD=8.3$ ) ( $F(2,54)=13.76$ ,  $p<.001$ ,  $\eta_p^2=.203$ ). The scores on all three dimensions were significantly higher in adolescents with ASD than in typically developing controls, with moderate to large effect sizes (see Figure 2): Negative symptoms (ASD:  $M=15.33$ ,  $SD=8.4$ ; TD:  $M=4.87$ ,  $SD=3.4$ ) ( $F(2,54)=11.06$ ,  $p=.002$ ,  $\eta_p^2=.170$ ), Positive symptoms (ASD:  $M=9.59$ ,  $SD=7.2$ ; TD:  $M=3.57$ ,  $SD=3.9$ ) ( $F(2,54)=7.83$ ,  $p=.007$ ,  $\eta_p^2=.127$ ) and Disorganized behavior (ASD:  $M=7.22$ ,  $SD=4.4$ ; TD:  $M=2.80$ ,  $SD=3.2$ ) ( $F(2,54)=6.90$ ,  $p=.011$ ,  $\eta_p^2=.113$ ).

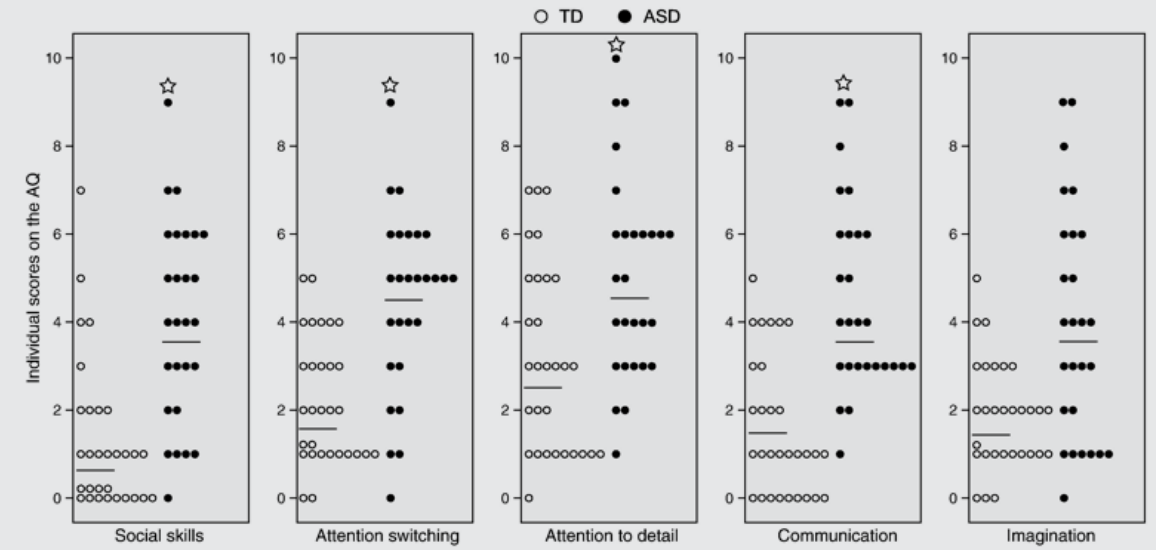


Figure 1. Levels of autism traits as measured with the Autism Questionnaire (AQ; individuals scores and median) in adolescents with autism spectrum disorders (ASD) as compared to typically developing (TD) adolescents. \*  $p<.05$

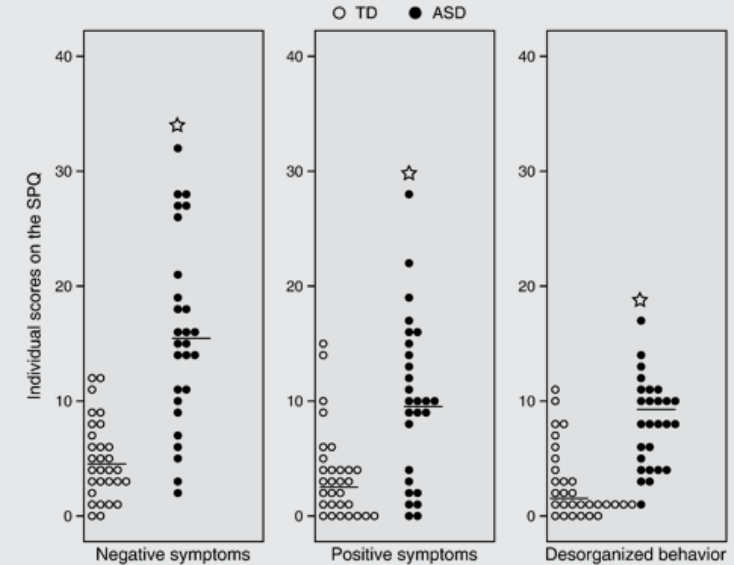


Figure 2. Levels of schizotypal traits as measured with the Schizotypal Personality Questionnaire (SPQ; individuals scores and median) in adolescents with Autism Spectrum Disorders (ASD) as compared to typically developing (TD) adolescents. \*  $p<.05$

### 3.4. Overlap between autistic and schizotypal traits

Within the ASD group, a significant correlation was found between the mean level of autistic and schizotypal traits ( $r=.38, p=.024$ ), with a proportion of explained variance of 14%. The SPQ total score was significantly correlated with the autistic traits Attention switching ( $r=.57, p=.001$ ) and Communication ( $r=.45, p=.009$ ), resulting in respectively 32% and 20% explained variance.

The SPQ negative dimension was significantly correlated with the AQ domains Social skills ( $r=.57, p=.001$ ), Attention switching ( $r=.60, p<.001$ ), Communication ( $r=.68, p<.001$ ), and Imagination ( $r=.56, p=.001$ ), with respectively 32%, 36%, 46% and 31% proportions of explained variance. The SPQ disorganized dimension was significantly correlated with the AQ domains Attention switching ( $r=.43, p=.013$ ) and Communication ( $r=.36, p=.031$ ), accounting for respectively 19% and 13% of the explained variance. The SPQ positive dimension was significantly correlated with the AQ domain Attention switching ( $r=.37, p=.027$ ), with a proportion of explained variance of 14%.

## 4. Discussion

The objective of this study was to examine to what extent patients diagnosed with an ASD in early childhood show schizophrenia spectrum traits in adolescence in order to explore the correspondence between autistic and schizotypal symptoms. The outcome revealed higher scores on all dimensions of the schizophrenia phenotype in adolescents with ASD than in typically developing adolescents. Besides high levels of negative symptoms, adolescents with ASD also displayed high levels of positive symptoms and disorganized symptoms.

Although autism spectrum and schizophrenia spectrum disorders have distinct classification criteria according to the current DSM-IV-TR, and have clearly different developmental pathways, our findings demonstrate a striking resemblance of their clinical phenotypes. That is, there appears to be an overlap between autistic symptoms and schizotypal traits. When considering the different dimensions of schizotypy separately, an overlap between negative traits and autistic features in terms of explained variance ranged from 31% to 46%. Autistic features were also related to disorganized symptoms (13% to 16% explained variance) and positive symptoms (14% explained variance). Our finding that an overlap between autistic traits and negative

schizotypal symptoms was found is equivalent to the vision of Bleuler (1911) and supports the idea of correspondence in diagnostic criteria between both spectrum disorders (Hurst et al., 2007; Konstantareas & Hewitt, 2001; Sheitman et al., 2004).

The present findings suggest that behavioral overlap is not limited to negative schizotypal symptoms but extends to disorganized and positive symptoms as well. These results were consistent with other studies by Dykens et al. (1991) and Rumsey et al. (1986) who reported shared symptoms in ASD and schizophrenia, like poverty of speech. Considering positive symptoms, Blackshaw et al. (2001) and Craig et al. (2004) indicated some degree of paranoid ideation in adults who were diagnosed with Asperger syndrome. In addition, Solomon et al. (2008) and Van der Gaag et al. (2001) described illogical thinking and loose associations in children with ASD.

It may be emphasized that the associations between autistic and schizotypal symptomatology in the present study were almost exclusively accounted for by two autistic traits, i.e., attention switching problems and communication difficulties. High levels of communication problems were associated with more negative and disorganized symptoms. The autistic feature attention switching stands out prominently, as it appeared to be related to all three dimensions of schizotypy. This suggests that inattentive behavior might be a common denominator underlying the manifestation of a broad range of schizotypal behaviors. Examples of behavioral abnormalities as measured by the AQ domain of attention switching include: 'New situations make me anxious', 'I like to carefully plan any activities I participate in', or 'I prefer to do the same thing over and over again'. These items reflect rigidity and perseveration. In the autism literature, it has often been suggested that these impairments are related to underlying executive dysfunctions, such as difficulties with planning, cognitive inflexibility, and the failure to inhibit inappropriate actions (Hill, 2004). These executive functions, however, are also needed to control, organize and regulate thoughts and feelings. When impaired, they might contribute to positive and disorganized schizotypal features, as demonstrated by earlier studies (Diwadkar et al., 2006; Solomon et al., 2008). Indeed, neurocognitive dysfunctions have been reported for schizophrenia within the domain of executive functioning and attention (e.g., Frangou, 2010; Mesholam-Gately et al., 2009; Ventura et al., 2009). Future studies are needed to identify putative common underlying cognitive mechanisms that contribute

to both autism spectrum and schizophrenia spectrum pathologies.

Although speculative, the current findings might have clinical implications. As high levels of schizotypy appear to reflect a higher risk of developing schizophrenia (Mata et al., 2000; Miller et al., 2002; Vollema et al., 2002), the significant association of positive symptoms in the ASD group might implicate an increased risk of schizophrenia spectrum pathology in some of these patients. To better appreciate the degree of schizotypal symptoms in our population, SPQ scores of the study of Vollema et al. (2002) and the mean scores of the adolescents in our ASD group were compared. The SPQ dimension scores of our group (negative schizotypy:  $M=15.3$ ; positive schizotypy:  $M=9.6$ ; disorganization:  $M=7.2$ ) were equal to the mean scores of 51 first-episode schizophrenia patients of the study of Vollema and colleagues (negative:  $M=15.2$ , Cohen's  $d=.01$ ; positive:  $M=11.9$ ,  $d=.29$ ; disorganization:  $M=6.0$ ,  $d=.25$ ). Moreover, the total score of our patient group ( $M=22.0$ ) was equal to that of the patient group of 93 schizophrenic adults ( $M=36.2$ ,  $d=.24$ ) in the study of Rossi and Daneluzzo (2000). These findings indicate that the behavioral problems as measured in our ASD sample have a high degree of schizotypal characteristics, which might imply vulnerability of schizophrenia. However, this hypothesis should be further explored in a longitudinal design. So far, this idea is supported by some longitudinal studies, showing shifts from an autism spectrum diagnosis in childhood towards a schizophrenia spectrum diagnosis in adulthood, with risk percentages amounting to 34.8% (Mouridsen et al., 2008; Stahlberg et al., 2004; Van Engeland & Van der Gaag, 1994). However, results from Esterberg et al. (2008) illustrated that, although a strong association was found between autistic features and schizotypal symptoms in adolescents with schizotypal personality disorder, the autistic symptoms appeared not to be predictive of later conversion to a psychotic disorder. Due to the cross-sectional character of this study we cannot yet make implications about the prognostic value of specific childhood autistic traits for developing adult schizophrenia later in life.

It should be noted that the present study has several limitations. Firstly, the information obtained from the questionnaires was subject to limitations inherent in self-report. Secondly, the relatively small sample size precluded the examination of the possible influence of age on schizotypal behaviors. Thirdly, the inclusion of an inpatient ASD population limits the representativeness of the sample and, as such, reduces the generalizability to

the whole autistic spectrum. Future studies are needed to identify common underlying cognitive mechanisms that account for co-occurring behavioral abnormalities. Moreover, it is recommended that these studies incorporate a developmental context, since the exact manifestation of behaviors may be dependent on the dynamics of underlying cognitive development. Finally, longitudinal studies are recommended for making statements about the prognostic value of autistic behaviors for later conversion to SSD. In conclusion we still feel that we should draw attention to the overlap of autistic and schizotypal symptomatology.

## References

- Achenbach, T.M., 1986. *Manual for the teacher report form and the child behavior profile*. Burlington: University of Vermont, Department of Psychiatry.
- American Psychiatric Association, 2000. *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR)*. American Psychiatric Association, Washington DC.
- Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., Clubley, E., 2001. The autism-spectrum quotient (AQ): Evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *J. Autism Dev. Disord.* 31 (1) 5-17.
- Bender, L., 1947. Childhood schizophrenia: clinical study of one hundred schizophrenic children. *Am. J. Orthopsychiatry* 17, 40-56.
- Bender, L., 1970. The life course of schizophrenic children. *Biol. Psychiatry* 2 (2) 165-172.
- Blackshaw, A.J., Kinderman, P., Hare, D.J., Hatton, C., 2001. Theory of mind, causal attribution and paranoia in asperger syndrome. *Autism* 5 (2) 147-163.
- Bleuler, E., 1911. *Dementia Praecox oder Gruppe der Schizophrenien*, in: Van Aschaffenburg, G. (Ed.), *Handbuch der Psychiatrie*. Duticke, Leipzig.
- Cohen, J., 1992. A power primer. *Psychol. Bull.* 112, 155-159.
- Craig, J.S., Hatton, G., Craig, F.B., Bentall, R.P., 2004. Persecutory beliefs, attributions and theory of mind: comparison of patients with paranoid delusions, asperger's syndrome and healthy controls. *Schizophr. Res.* 69 (1) 29-33.
- De Bruin, E.I., Ferdinand, R.F., Meester, S., De Nijs, P.F.A., Verheij, F., 2007. High rates of psychiatric co-morbidity in PDD-NOS. *J. Autism Dev. Disord.* 37 (5) 877-886.
- Diwadkar, V.A., Montrose, D.M., Dworakowski, D., Sweeney, J.A., Keshavan, M.S., 2006. Genetically predisposed offspring with schizotypal features: An ultra high-risk group for schizophrenia? *Prog. Neuropsychopharmacol. Biol. Psychiatry* 30 (2) 230-238.
- Dykens, E., Volkmar, F., Glick, M., 1991. Thought disorder in high-functioning autistic adults. *J. Autism Dev. Disord.* 21 (3) 291-301.
- Esterberg, M.L., Trotman, H.D., Brasfield, J.L., Compton, M.T., Walker, E.F., 2008. Childhood and current autistic features in adolescents with schizotypal personality disorder. *Schizophr. Res.* 104, 265-273.
- Frangou, S., 2010. Cognitive function in early onset schizophrenia: a selective review. *Frontiers in Hum. Neurosci.* 3, 1-6.
- Hill, E.L., 2004. Executive dysfunction in autism. *Trends in cognitive sciences* 8 (1) 26-32.
- Hurst, R.M., Nelson-Gray, R.O., Mitchell, J.T., Kwapil, T.R., 2007. The relationship of Asperger's characteristics and schizotypal personality traits in a non-clinical adult sample. *J. Autism Dev. Disord.* 37 (9) 1711-1720.
- Kanner, L., 1943. Autistic disturbances of affect contact. *Nervous Child* 2, 217-250.
- Kolvin, I., 1971. Studies in the childhood psychoses. I. Diagnostic criteria and classification. *Br. J. Psychiatry* 118 (545) 381-384.
- Konstantareas, M.M., Hewitt, T., 2001. Autistic disorder and schizophrenia: Diagnostic overlaps. *J. Autism Dev. Disord.* 31(1) 19-28.
- 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. *J. Autism Dev. Disord.* 24 (5) 659-685.
- Mata, I., Sham, P.C., Gilvarry, C.M., Jones, P.B., Lewis, S.W., Murray, R.M., 2000. Childhood schizotypy and positive symptoms in schizophrenic patients predict schizotypy in relatives. *Schizophr. Res.* 44 (2) 129-136.
- Mesholam-Gately, R.I., Giuliano, A.J., Goff, K.P., Faraone, S.V., Seidman, L.J., 2009. Neurocognition in first-episode schizophrenia: a meta-analytic review. *Neuropsychol.* 23 (3) 315-336.
- Miller, P., Byrne, M., Hodges, A., Lawrie, S.M., Owens, D.G., Johnstone, E.C., 2002. Schizotypal components in people at high risk of developing schizophrenia: Early findings from the Edinburgh high-risk study. *Br. J. Psychiatry* 180, 179-184.
- Mouridsen, S.E., Rich, B., Isager, T., 2008. Psychiatric disorders in adults diagnosed as children with atypical autism. A case control study. *J. Neural Transm.* 115 (1) 135-138.
- Raine, A., 1991. The SPQ: A scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophr. Bull.* 17 (4) 555-564.
- Rossi, A., Daneluzzo, E., 2002. Schizotypal dimensions in normals and schizophrenic patients: a comparison with other clinical samples. *Schizophr. Res.* 54, 67-75.
- Rumsey, J.M., Andreasen, N.C., Rapoport, J.L., 1986. Thought, language, communication, and affective flattening in autistic adults. *Arch. Gen. Psychiatry.* 43 (8) 771-777.
- Rutter, M., 1972. Childhood schizophrenia reconsidered. *J. Autism Child Schizophr.* 2 (4) 315-337.
- Sheitman, B.B., Bodfish, J.W., Carmel, H., 2004. Are the negative symptoms of schizophrenia consistent with an autistic spectrum illness? *Schizophr. Res.* 69 (1) 119-120.
- Solomon, M., Ozonoff, S., Carter, C., Caplan, R., 2008. Formal thought disorder and the autism spectrum: Relationship with symptoms, executive control, and anxiety. *J. Autism Dev. Disord.* 38, 1474-1484.
- Sprong, M., Becker, H.E., Schothorst, P.F., Swaab, H., Ziermans, T.B., Dingemans, P.M., Linszen, D., Van Engeland, H., 2008. Pathways to psychosis: A comparison of the pervasive developmental disorder subtype Multiple Complex Developmental Disorder and the "at risk mental state". *Schizophr. Res.* 99 (1-3) 38-47.
- Stahlberg, O., Soderstrom, H., Rastam, M., Gillberg, C., 2004. Bipolar disorder, schizophrenia, and other psychotic disorders in adults with childhood onset AD/HD and/or autism spectrum disorders. *J. Neural Transm.* 111 (7) 891-902.
- Stevens, J., 1986. *Applied multivariate statistics for the social sciences*. London: Lawrence Erlbaum Associates.
- Van der Gaag, R.J., Caplan, R., Van Engeland, H., Loman, F., Buitelaar, J.K., 2005. A controlled study of formal thought disorder in children with autism and multiple complex developmental disorders. *J. Child Adolesc. Psychopharmacol.* 15 (3) 465-476.
- Van Engeland, H., Van der Gaag, R.J., 1994. MCDD in childhood: a precursor of schizophrenic spectrum disorders. *Schizophr. Res.* 11 (2) 197-197.
- Ventura, J., Helleman, G.S., Thames, A.D., Koellner, V., Nuechterlein, K.H., 2009. Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: A meta-analysis. *Schizophr. Res.* 113, 189-199.
- Vollema, M.G., Hoijtink, H., 2000. The multidimensionality of self-report schizotypy in a psychiatric population: An analysis using multidimensional Rasch models. *Schizophr. Bull.* 26 (3) 565-575.
- Vollema, M.G., Sitskoorn, M.M., Appels, M.C., Kahn, R.S., 2002. Does the schizotypal personality questionnaire reflect the biological-genetic vulnerability to schizophrenia? *Schizophr. Res.* 54 (1-2) 39-45.
- Wechsler, D., 2002. *Wechsler Intelligence Scale for Children-III NL: Handleiding en verantwoording [Manual]*. The Psychological Corporation Ltd., Harcourt Assessment.
- Wechsler, D., 2005. *Wechsler Adult Intelligence Scale-III: Nederlandstalige bewerking, technische handleiding [Manual]*. Lisse: Harcourt Test Publishers.



# CHAPTER 5

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## Impaired response inhibition in autism spectrum disorders, a marker of vulnerability to schizophrenia spectrum disorders?

### Abstract

In this study we addressed the relation between specific deficits in cognitive control and schizotypal symptomatology in adolescents with autism spectrum disorders (ASD) diagnosed in childhood. We aimed to identify cognitive control deficits as markers of vulnerability to the development of schizophrenia spectrum pathology in ASD. Symptoms of autism and the risk of schizotypal symptomatology were assessed in 29 high-functioning adolescents with ASD, and compared with 40 typically developing adolescents. Cognitive control (response inhibition, mental flexibility, visuo-motor control, interference control, and perseveration) was evaluated for specific association with schizotypal symptomatology. Impaired response inhibition appeared to be strongly and specifically associated with schizotypal symptomatology in adolescents with ASD, especially those with positive and disorganized symptoms. Response inhibition problems could indicate vulnerability to the development of schizotypal symptomatology in ASD.

### Introduction

Autism spectrum disorders (ASD) are lifelong conditions characterized by severe impairments in social interaction and dysfunctional communication, with serious impact on daily life (American Psychiatric Association (APA), 2000). Although some individuals with ASD show successful adaptation to daily life, many others are at risk of severe deterioration of daily functioning during development (APA, 2000), and some are at risk of very serious psychopathology, such as psychosis, later in life (e.g., Stahlberg, Soderstrom, Rastam, & Gillberg,

2004). Results of studies focussing on this risk suggest that specific developmental abnormalities in childhood, such as dysregulation of affective state and primitive anxieties, occur before those children meet the criteria for psychotic disorder or schizophrenia later in life (e.g., Van der Gaag et al., 1995). In their review Padgett, Miltsiou, and Tiffin (2010) argued that ASD could be a risk factor for psychosis. In a prevalence study on Schizophrenia Spectrum Disorders (SSD) in 241 adults diagnosed with ASD in childhood, up to 7.8% were found to meet criteria for schizophrenia or another psychotic disorder in adulthood (Stahlberg et al., 2004). The authors conclude that the risk of psychosis in ASD is clearly higher than in the general population (about 1%) (McGrath et al., 2004), and in other developmental disorders (such as ADHD, about 5%) (Stahlberg et al., 2004). Moreover, Raja and Azzoni (2010) reported that 84.6% of 26 adults with ASD showed psychotic symptoms, and 72.7% had a concurrent diagnosis of schizophrenia. In an earlier study, Volkmar and Cohen (1991) concluded on the basis of case records of 163 adolescents and adults with autism that the frequency of SSD in ASD is comparable to that in the general population. However, the comparability of their findings to those of more recent studies is restricted, since approximately 50% of their patients were mute. Other studies focussing on the presence of ASD in SSD found that in 25%-50% of patients childhood-onset schizophrenia was preceded by and comorbid with ASD (Rapoport, Chavez, Greenstein, Addington, & Gogtay, 2009; Sporn et al., 2004). The link between ASD and SSD symptoms is emphasized by findings of increased prevalence of SSD in parents of children with ASD, suggesting genetic associations (Larsson et al., 2005; Daniels et al., 2008). Therefore, it is considered crucial to identify developmental markers of high vulnerability to SSD in children and adolescents with ASD in order to (1) understand developmental mechanisms that might lead to severe psychopathology (SSD), and by understanding these mechanisms (2) to be able to identify highly vulnerable individuals early in life and possibly limit their developmental risk by protective interventions.

Although according to DSM-IV-standards ASD and SSD have distinct classification criteria, the similarity of the clinical presentation of the two neurodevelopmental disorders has been a topic of scientific dispute for many decades. Kolvin (1971) and Rutter (1972) argued that ASD and SSD are mutually exclusive categorical diagnoses with distinct developmental pathways. The term 'autism', however, was coined by Bleuler (1911) to characterize social

impairments seemingly characteristic of schizophrenia. In addition, Bender (1947) argued that ASD could be an age-specific expression of a developmental disorder characterized by schizotypal symptoms in adulthood. As Padgett et al. (2010) argued, a relation between ASD and SSD may be explained by the possibility that ASD predisposes to SSD, they are different expressions of the same disorder, or they are separate but related disorders, due to shared genetic or environmental risk factors. From a clinical perspective, behavioral symptoms are important cues by which the risk of psychosis in ASD is determined. Both disorders share deficits in social behavior, oddness of speech, unusual responsiveness to the environment, and inappropriate affect. A study of the similarities and differences at a phenotypical level may reveal risk factors for SSD in ASD. Recently, Barneveld et al. (2011) reported that it was specifically attention switching problems in ASD that were associated with identified positive (distorted thought and perception) and negative symptoms (constricted affect and social anxiety), as well as disorganized schizotypal behavior (odd speech and eccentric behavior), suggesting that deficits in cognitive control functions, such as attention regulation, might signal a risk of SSD in ASD.

Regarding neurocognitive mechanisms of vulnerability, it is argued that problems with attention regulation in ASD may indicate reduced abilities to switch to alternative cognitive strategies (Fugard, Stewart, & Stenning 2011), possibly reflecting mental inflexibility and failures to inhibit inappropriate actions. These executive function (EF) deficits may be associated with rigidity and perseveration in ASD (e.g., Hill, 2004a). EF deficits might also explain difficulties in regulating thoughts and feelings (Gioia & Isquith, 2004), and so contribute to the risk of SSD (e.g., Solomon, Ozonoff, Carter, & Caplan, 2008). Therefore, we examined whether or not EF deficits are related to SSD symptomatology in ASD, and sought to identify specific cognitive control deficits as markers of vulnerability to SSD pathology in ASD.

There is extensive literature concerning EF dysfunction for both ASD and SSD. The executive dysfunction theory (Ozonoff, 1997) attempts to explain autistic symptomatology, and although the claim that EF is a singular causal factor is controversial and evidence for an unique EF profile in ASD is weak (Kenworthy, Yerys, Anthony, & Wallace, 2008), many reviews confirm that EF deficits are found in ASD, including abnormalities in cognitive flexibility, generation of ideas, planning, and working memory (e.g., Hill, 2004a; 2004b; Kenworthy et al., 2008). The investigation of response inhibition in ASD has

yielded conflicting results. Meta-analytic studies reported that it is specifically inhibition of prepotent responses that is impaired, whereas other inhibition functions are affected less, such as negative priming and neutral inhibition conditions (e.g., Hill 2004a; 2004b). Evidently, EF is a broad concept comprising a variety of disparate functions (Miyake et al., 2000), and it is important to consider which specific EF deficits might underlie autistic symptoms. For example, deficits in specific EF domains such as verbal fluency and generation of ideas are associated with communication symptoms in ASD (Dichter, Lam, Turner-Brown, Holtzclaw, & Bodfish, 2009). Difficulties in other EF domains, such as semantic fluency, are linked to social interaction problems (Kenworthy, Black, Harrison, Della Rosa, & Wallace, 2009). Impairments in core EF domains: cognitive flexibility, working memory, and response inhibition are associated with repetitive, stereotyped behavior in ASD (e.g., Hill, 2004a; Yerys et al., 2009).

EF deficits are also considered core neurocognitive abnormalities regarding SSD (e.g., Nieuwenstein, Aleman, & De Haan, 2001), and are suggested as putative endophenotypic markers for schizophrenia (e.g., Eisenberg & Berman, 2010). Meta-analyses relating EF to SSD symptoms indicate that poor EF is related predominantly to negative symptoms (e.g., Dibben, Rice, Laws, & McKenna, 2009) and to disorganization symptoms (e.g., Nieuwenstein et al., 2001). A meta-analysis by Johnson-Selfridge and Zalewski (2001) reported correlations between poor EF and positive symptomatology, but these findings were not confirmed in other reviews (Nieuwenstein et al., 2001; Dibben et al., 2009; Ventura, Helleman, Thames, Koellner, & Nuechterlein, 2009). To clarify these inconsistencies it would be useful to examine whether or not SSD symptoms are associated with specific EF deficits (Nieuwenstein et al., 2001; Vollema & Postma, 2002). Following Dibben et al. (2009), it is argued that negative symptoms should be associated particularly with difficulties in generating ideas, whereas disorganization should be associated with response inhibition problems. In addition, Guillem, Rinaldi, Parnpoulova, and Stip (2008) focused on positive symptomatology and also found complex relations between specific aspects of positive symptoms and discrete EF processes.

There is no known study on the relation between EF functions and both ASD and SSD symptomatology. However, Solomon et al. (2008) investigated whether illogical thinking, which refers to schizophrenia-related pragmatic language impairments and unusual verbal behavior, is related to EF in

ASD children. They reported relations between response inhibition problems and illogical thinking, suggesting that response inhibition might be a candidate marker of SSD vulnerability in ASD. In our study we also aimed to identify specific cognitive markers for vulnerability to SSD pathology in ASD, especially response inhibition and other core EF domains (i.e., mental flexibility, visuo-motor control, interference control, and perseveration) representing various aspects of cognitive control. This was examined in adolescents with ASD, so that we could identify vulnerability to SSD at an early stage (e.g. Frangou, 2010). Therefore, the focus is on identifying associations between EF deficits and schizotypal symptoms that could already emerge during adolescence as a precursor of the risk of SSD.

## Methods

### *Design*

This study is part of a longitudinal study on the cognitive and social-emotional development of patients referred to the Department of Child and Adolescent Psychiatry at the University Medical Centre Utrecht, the Netherlands, between 1998 to 2004. Patients were admitted for a short period for observation and elaborate diagnostic assessment and diagnosed with ASD at childhood. They were re-examined at adolescence during 2007 and 2008 with a mean follow-up period of six to seven years. The study was approved by the medical ethics committee (number 05-319/K), and written informed consent was obtained according to the declaration of Helsinki.

### *Participants*

Twenty-nine adolescents with ASD (10 to 18 years) and 40 typically developing (TD) controls, matched on age and gender, participated in the study. Fifty-five patients diagnosed with ASD at childhood were sent a letter informing them about the aims of the study and asking them to participate. Fifteen adolescents refused participation, leaving 40 adolescents eligible for the study. No differences in gender distribution ( $p=.070$ ) and age at referral ( $p=.113$ ) were found between the potential participants and those who refused participation. Reasons for nonparticipation were: no interest or time (47%), a wish not to put too much stress on the adolescent (40%), or parents divorcing (13%).

The participants had to meet the following inclusion criteria. First, a diagnosis of ASD at childhood was required, based on full agreement between two board-certified psychiatrists. Semi-structured DSM-focused interviews, observations, medical records, and structured questionnaires were included in the diagnostic process. During the follow-up period, the ASD diagnoses were validated by the Autism Diagnostic Interview – Revised (ADI-R) (Lord, Rutter, & Le Couteur, 1994). A diagnosis of ASD required a score meeting the cut-off criteria on a minimum of two domains, including the ADI-R reciprocal social interaction domain and either the communication or the restricted activities/interests domain (Bölte, Westerwald, Holtmann, Freitag, & Poustka, 2011). The second inclusion criterion was an IQ of 70 or higher. Eight adolescents were excluded because they failed to meet the ADI cut-off criteria, and three adolescents were excluded because they had an IQ below 70, leaving 29 adolescents with ASD (21 boys, 8 girls) participating. The mean age was 14.72 ( $SD=2.1$ ,  $min=10.94$ ,  $max=18.45$ ). The mean ADI social interaction score was 19.73 ( $SD=5.1$ ), for communication 13.97 ( $SD=3.6$ ), and for restricted activities/interests 3.86 ( $SD=2.7$ ). Seventeen participants (59%) met ADI cut-off criteria on all three domains, 12 adolescents (41%) met criteria on two domains. Although the DSM discourages diagnosing anyone before 18 years with a personality disorder, when a board-certified psychiatrist described the schizotypal symptoms (instability of functioning, affect dysregulation and high levels of anxieties) in the ASD group at time of referral it was found that 12 participants (41%) would have met the criteria for a schizotypal personality disorder (DSM-IV-TR 301.22), which indicates serious developmental risks in these children.

The TD group consisted of 40 adolescents (32 boys, 8 girls; Age:  $M=15.22$ ,  $SD=2.5$ ,  $min=10.27$ ,  $max=18.80$ ), recruited by contacting regular public secondary schools. All individuals had an IQ of 70 or higher and had to be free of problem behavior (i.e., total problem scores must be below the clinical cut-off score of 70 on the Child Behavior Checklist; Achenbach, 1986). No difference in age ( $p=.384$ ) and gender distribution ( $p=.461$ ) was found between the ASD and TD groups.

## Measures

### *Group descriptives*

Global IQ was estimated via the Vocabulary and Block Design subtests of the Wechsler Intelligence Scales for Children (WISC-III<sup>NL</sup>; Wechsler, 2002) or Adults (WAIS-III<sup>NL</sup>; Wechsler 2005).

### *Schizotypal symptoms*

SSD symptomatology was appraised using the revised Schizotypal Personality Questionnaire with proven reliability and validity (SPQ; Raine, 1991). The SPQ is a 74-item self-report measure modelled on DSM-III-R criteria for schizotypal personality disorder, with high scores being indicative of a diagnosis of schizotypal personality disorder (Raine, 1991) and of genetic vulnerability to schizophrenia (Vollema & Postma, 2002). Score distribution in the general population is normal and therefore suitable for correlation analyses with cognitive performance scores. A factor-analytic study conducted in a psychiatric population revealed three dimensions: positive schizotypy (e.g., referential and delusional thinking), negative schizotypy (e.g., constricted affect and social anxiety), and disorganization (odd speech and eccentric behavior) (Vollema & Hoijtink, 2000). Although a different factor solution was found in a student population (Chmielewski & Watson, 2008), we chose the factor structure that is commonly used in studies assessing the presence of SSD (Vollema & Hoijtink, 2000).

### *Autism symptoms*

ASD symptomatology was assessed via the Autism-Spectrum Quotient (AQ; Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001), a 50-item self-report questionnaire assessing the degree to which an individual may have features of ASD: poor social skills, poor attention switching, exceptional attention to detail, poor communication skills, and poor imagination. Several studies have indicated that the AQ is effective at distinguishing individuals with ASD from TD individuals (e.g., Baron-Cohen et al., 2001). Score distribution in the general population is normal (Hurst, Mitchell, Kimbrel, Kwapil, & Nelson-Gray, 2007b). Psychometric properties and validity have been established in several studies (e.g., Hurst, Nelson-Gray, Mitchell, & Kwapil, 2007a). However, the use of self-reports for ASD patients may involve limitations due to difficul-

ties in self-reflection. Baron-Cohen et al. (2001) addressed this issue and found sufficient support for the assumption that high-functioning ASD patients are able to report their own preferences and describe what they find easy or difficult. Therefore, the AQ is evaluated as a valuable instrument for quantifying autistic symptomatology of high-functioning ASD patients, although findings should be interpreted with caution.

#### *Cognitive control measures*

The EF processes of response inhibition, mental flexibility, and visuo-motor control under conditions varying in EF demands, were measured by performances on computerized tasks taken from the Amsterdam Neuropsychological Tasks (ANT) (De Sonneville, 2005). The ANT is used extensively to examine EF processes in various patient populations, which points to the sensitivity of this assessment battery to deficits in neuropsychological functions (e.g., Slaats-Willems, De Sonneville, Swaab-Barneveld, & Buitelaar, 2005) and its reliability and validity (e.g., Huijbregts, Swaab-Barneveld, & De Sonneville, 2010). In addition, the EF processes of interference control and perseveration were assessed via the Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993).

#### *Response inhibition*

Inhibition of a prepotent response was assessed by the ANT subtest 'Shifting attentional Set'. A coloured square jumps randomly on a bar to the right or left. Depending on the colour of the square, the participant has to execute a compatible (pressing the key in the same direction) or an incompatible response (opposite direction). This test consists of three parts. The first part requires compatible responses (fixed compatible condition), the second part requires incompatible responses (fixed incompatible condition), for which it is imperative to inhibit the prepotent responses of the first part. Response inhibition leads to slower, less stable, and less accurate responses and is evaluated by contrasting parts one and two on speed (mean latency), fluctuation in speed (standard deviation of mean latency), and accuracy (percentage of errors) (e.g., Huijbregts, De Sonneville, Licht, Sergeant, & Van Spronsen, 2002).

#### *Mental flexibility*

Mental flexibility was assessed by the same ANT subtest, 'Shifting attentional

Set'. In the third part the colour varies (random condition), requiring mental flexibility by continuously adjusting the response. Flexibility is evaluated by contrasting part one and the compatible condition of part three on speed, fluctuation in speed, and accuracy (e.g., Huijbregts et al, 2002).

#### *Visuo-motor control*

Visuo-motor control was assessed by contrasting the performance of two ANT eye-hand coordination tasks, 'Tracking' and 'Pursuit'. In the tracking task the participant has to draw a circle by moving the cursor in-between two concentric circles, so that planning and execution of automatized movements can be measured. The pursuit task requires the participant to continuously track a target moving randomly across the screen. Because the trajectory is unpredictable, we assessed the concurrent planning and execution of a non-automatized movement requiring continuous adaptation in order to follow a randomly moving target. This task imposes higher EF demands than the tracking task (Slaats-Willems et al, 2005). EF-dependent visuo-motor control was assessed by contrasting the performance on the tasks on accuracy (mean distance to the target) and fluctuation in accuracy (standard deviation of the mean distance) (Rommelse et al., 2007).

#### *Interference control and perseveration*

Interference control and perseveration were assessed by the computerized version of the WCST (Heaton et al., 1993), based on a rule-learning paradigm. Interference control was operationalized by the failure to maintain set (i.e., the number of failures to complete a card-sorting set after at least five correct consecutive sorts), as this score reflects the vulnerability to interference with ongoing processing (Andrewes, 2001). Perseveration was operationalized by contrasting the numbers of perseveration errors (i.e., the participant continues sorting the previous correct category despite negative feedback) and non-perseveration errors (Loring, Lezak, & Howieson, 2004).

### **Statistical analyses**

Differences between groups on the questionnaires were tested using univariate (total SPQ and AQ) and multivariate (subscales of the SPQ and AQ)

analyses of variance (ANOVAs). The degree of relation between schizotypal symptoms (total SPQ) and autistic symptoms (total AQ) was examined within the ASD group by partial correlations, controlling for age ( $r$ ), (small effect size:  $r=0.1-0.23$ ; medium:  $r=0.24-0.36$ ; large:  $r\geq 0.37$ ) (Cohen, 1992). An exploratory factor analysis was performed on the total sample to determine how SSD and ASD symptoms are related. The AQ and SPQ subscales were entered in a principal component analysis, with oblimin rotation, allowing for some correlation between factors. Response inhibition, mental flexibility, visuo-motor control, and perseveration were operationalized as the contrast between performance on one condition (one task or part of a task) and the performance on another condition. Contrasts were entered as levels of within-subject (WS) factors in GLM repeated-measures ANOVAs. Separate runs were made with speed, flexibility in speed, accuracy, and fluctuations in accuracy on the set-shifting task or the visuo-motor coordination tasks as dependent variables. The Group\*WS factor interactions reflect the extent to which differences between groups are condition or task dependent. Differences in interference control were tested by univariate ANOVA. Because of the wide age range and because EF tends to develop progressively during this period, age was used as a covariate in all analyses. To verify whether or not our findings were consistent across age, the ASD and TD groups were (median) split into a young and an older group, and an ANCOVA repeated-measures design was run, with Group (ASD vs. TD) and Age group (young vs. old) as BS factors and Inhibition as WS factor. As recommended by Dennis et al. (2009) IQ was not used as a covariate, because controlling for IQ removes variability in the outcome measure that is related to EF. Alpha was set to 0.05, and partial eta squared ( $\eta_p^2$ ) was computed to estimate effect sizes (weak effect:  $\eta_p^2\sim 0.03$ ; moderate:  $\eta_p^2\sim 0.06$ ; large:  $\eta_p^2\geq 0.14$ ) (Stevens, 1986). The degree of relation between the EF tasks and schizotypal and autistic symptoms (SPQ and AQ subscales) was examined within the ASD group by partial correlations controlling for age. We have refrained from executing regression analyses involving all EF measures, as the number of participants is too small to yield a stable solution. To verify the impact of age, bivariate correlation analyses were run separately for the young and old patients. For these correlational analyses alpha was set to 0.01 to compensate for the effect of multiple testing. When significant correlations were found, group differences on EF tasks were re-analyzed adding total AQ and SPQ scores, respectively, as a covariate to examine the specificity of relations

between EF and schizotypal, or EF and autistic symptomatology.

## Results

There was a significant difference in global intelligence between the ASD group ( $M=94.34$ ,  $SD=13.5$ ) and the TD group ( $M=111.62$ ,  $SD=12.1$ ) ( $F(1,66)=29.49$ ,  $p<.0001$ ,  $\eta_p^2=.309$ ). Within the ASD group a significant partial correlation was found between the mean levels of schizotypal and of autistic traits ( $r=.35$ ,  $p=.038$ ), with a proportion of explained variance of 12%. This relation did not change substantially when age was not controlled for ( $r=.44$ ,  $p=.011$ ). In the factor analysis three factors were extracted, explaining 83% of the variance. Factor 1 refers to autistic symptoms, with major loadings of the AQ subscales Imagination (.91), Social skills (.91), Communication (.66), and Attention switching (.54), and one additional loading of the SPQ subscale Negative symptoms (.50). Factor 2 refers to schizotypal symptoms, with major loadings of all SPQ subscales: Positive symptoms (.94), Disorganized behavior (.87), and Negative symptoms (.65). A third factor consisted of a major loading of the AQ subscale Attention to details (.99).

### *Schizotypal symptoms*

The mean total SPQ score was significantly higher in adolescents with ASD ( $M=31.21$ ,  $SD=16.8$ ) than in TD adolescents ( $M=11.20$ ,  $SD=7.7$ ) ( $F(1,60)=31.21$ ,  $p<.0001$ ,  $\eta_p^2=.342$ ). The multivariate analysis of the SPQ subscales confirmed this outcome, more schizotypal symptomatology was found in the ASD group than in the TD group ( $F(3,58)=11.19$ ,  $p<.0001$ ,  $\eta_p^2=.367$ ), the scores on all SPQ dimensions were significantly higher in adolescents with ASD; with large effect sizes (Table 1). Total SPQ score differences between the young and old ASD patients were not significant ( $p=.269$ ).

### *Autistic symptoms*

The mean total AQ score was significantly higher in the ASD group ( $M=21.61$ ,  $SD=7.4$ ) than in the TD group ( $M=10.49$ ,  $SD=5.8$ ) ( $F(1,60)=37.08$ ,  $p<.0001$ ,  $\eta_p^2=.382$ ). The multivariate analysis of the AQ subscales confirmed this outcome in that the the adolescents with ASD displayed more autistic symptoms than TD adolescents ( $F(5,56)=7.67$ ,  $p<.0001$ ,  $\eta_p^2=.406$ ), significantly higher scores were found in all AQ domains; with moderate to large effect sizes (Table

**Table 1. Levels of schizotypal and autistic symptomatology in adolescents with ASD as compared to typically developing adolescents**

	ASD group		TD group		$F(1,60)$	$p$	$\eta_p^2$
	Mean	$SD$	Mean	$SD$			
<b>Schizotypal symptoms</b>							
Negative symptoms	14.89	(8.54)	5.00	(3.35)	31.27	<.0001	.343
Positive symptoms	9.25	(7.26)	3.74	(3.75)	11.49	.001	.161
Disorganized behavior	7.07	(4.37)	2.74	(2.91)	15.99	.0001	.210
<b>Autistic symptoms</b>							
Social skills	3.96	(2.24)	1.31	(1.64)	24.49	<.0001	.290
Attention switching	4.43	(2.03)	2.34	(1.51)	16.10	<.0001	.212
Attention to detail	4.82	(2.44)	3.11	(2.23)	8.79	.004	.128
Communication	4.43	(2.17)	1.54	(1.52)	30.83	<.0001	.339
Imagination	3.93	(2.58)	2.14	(1.39)	9.25	.003	.134

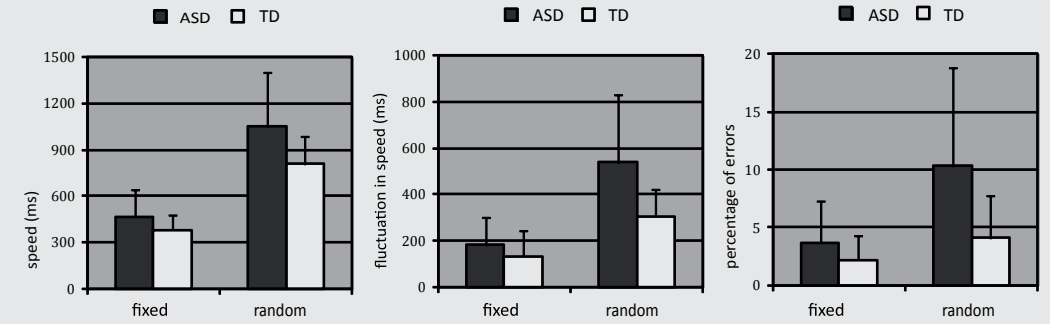


Figure 2. Mental flexibility: performance in speed (left), fluctuation in speed (middle) and accuracy (right) during the fixed and random condition on the set-shifting task by group (mean and standard deviation).

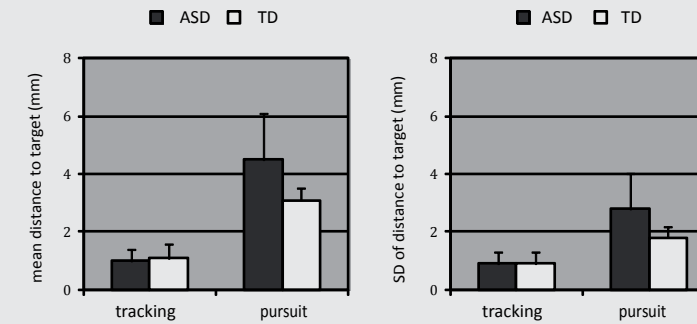


Figure 3. Visuo-motor control: performance in accuracy (left) and fluctuation in accuracy (right) on the tracking and pursuit task by group (mean and standard deviation).

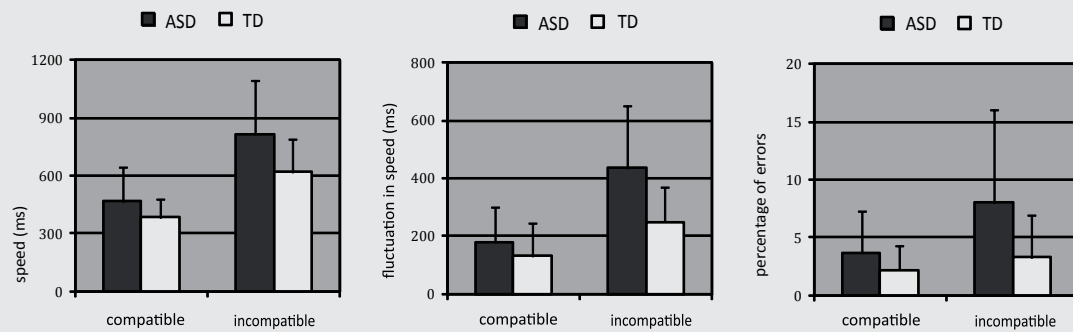


Figure 1. Response inhibition: performance in speed (left), fluctuation in speed (middle) and accuracy (right) during the compatible and incompatible condition on the set-shifting task by group (mean and standard deviation).

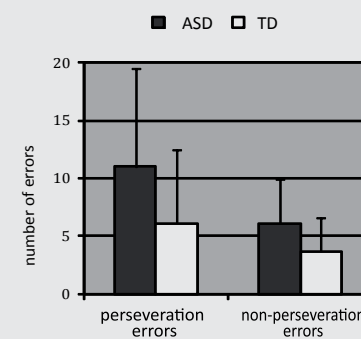


Figure 4. Perseveration: number of perseveration errors in contrast with non-perseveration errors on the WCST by group (mean and standard deviation)

1). Total AQ score differences between the young and older ASD patients were not significant ( $p=.195$ ).

#### *Response inhibition*

Group interacted with stimulus-response mapping for speed ( $F(1,60)=4.33$ ,  $p=.042$ ,  $\eta_p^2=.067$ ), fluctuation in speed ( $F(1,59)=5.40$ ,  $p=.024$ ,  $\eta_p^2=.084$ ), and accuracy ( $F(1,57)=4.29$ ,  $p=.043$ ,  $\eta_p^2=.070$ ) (Figure 1), which indicates that these differences between ASD and TD adolescents increase under incompatible conditions, reflecting problems in inhibiting prepotent responses in adolescents with ASD. Adding Age (young vs. old) as a second BS factor resulted in a significant Group\*Inhibition(speed) interaction ( $p=.011$ ,  $\eta_p^2=.10$ ), signifying that the ASD patients have problems with response inhibition, which confirms the above result. The 2nd-order interaction (Group\*Inhibition\*Age) is not significant ( $p=.39$ ), which indicates that the interaction is consistent across age. Similar results were found for fluctuation in speed and accuracy.

#### *Mental flexibility*

The interaction of stimulus-response mapping with group approached significance for speed ( $F(1,60)=3.57$ ,  $p=.064$ ,  $\eta_p^2=.056$ ) and was significant for fluctuation in speed ( $F(1,59)=6.39$ ,  $p=.014$ ,  $\eta_p^2=.098$ ), and for accuracy ( $F(1,57)=5.64$ ,  $p=.021$ ,  $\eta_p^2=.090$ ) (Figure 2), which indicates that these differences between groups increase under random conditions, demonstrating deficits in mental flexibility in adolescents with ASD.

#### *Visuo-motor control*

Significant Group\*Task interactions were found concerning accuracy ( $F(1,57)=15.47$ ,  $p<.0001$ ,  $\eta_p^2=.213$ ) and fluctuation in accuracy ( $F(1,56)=8.45$ ,  $p=.005$ ,  $\eta_p^2=.131$ ) (Figure 3). Differences in accuracy and fluctuation in accuracy between ASD and TD adolescents were larger on the pursuit task than on tracking task, reflecting the effect of higher EF demands.

#### *Interference control*

A significant group difference for interference control was found ( $F(1,65)=6.13$ ,  $p=.016$ ,  $\eta_p^2=.086$ ); adolescents with ASD failed more frequently to maintain set than TD adolescents, suggesting difficulties to control their attention.

#### *Perseveration*

Adolescents in the ASD group made more errors than TD controls ( $F(2,58)=3.82$ ,  $p=.028$ ,  $\eta_p^2=.116$ ): not only more perseverative errors ( $F(1,59)=5.51$ ,  $p=.022$ ,  $\eta_p^2=.085$ ) but also more non-perseverative errors ( $F(1,59)=6.89$ ,  $p=.011$ ,  $\eta_p^2=.105$ ). Perseveration did not interact significantly with group ( $p=.166$ ) (Figure 4), which indicates that perseveration does not discriminate between groups.

#### *Correlations of EF functions with schizotypal and autistic symptoms*

Within the ASD group no significant correlations were found between any measure of cognitive control and degree of autistic symptomatology. The same result was found with regard to schizotypal symptoms, with the exception of response inhibition. Significant partial correlations were found between response inhibition (accuracy) and Total SPQ score ( $r=.58$ ,  $p=.001$ ) as well as SPQ Positive symptoms ( $r=.52$ ,  $p=.003$ ) and Disorganized behavior ( $r=.68$ ,  $p<.001$ ), resulting in respectively 34%, 27%, and 46% explained variance. The correlation between response inhibition (accuracy) and SPQ Negative symptoms approached significance ( $r=.35$ ,  $p=.040$ ). In addition, a significant correlation was found between response inhibition (fluctuation in speed) and Disorganized behavior ( $r=.47$ ,  $p=.007$ ), with 22% explained variance. The bivariate correlation analyses, run for the young and older patients separately, resulted in similar outcomes (for example: the correlation between SPQ total score and inhibition (accuracy) was  $r=.58$  in the younger group and  $r=.51$  in the older group). Similar results were found for the other associations, which confirms that these findings are consistent across age. In addition, the results are probably unrelated to an overlap between the AQ and SPQ scores, since the correlations between response inhibition and SPQ scores remained significant after we controlled for the influence of autistic symptoms (e.g., correlation between response inhibition (accuracy) and Total SPQ score, with the Total AQ score as covariate:  $r=.59$ ,  $p=.001$ ).

To verify that response inhibition deficits in the ASD sample were related to the presence of schizotypal symptoms, we again ran the repeated measures ANOVA on response inhibition: Group\*Inhibition (accuracy) interactions disappeared when using the SPQ total ( $p=.823$ ), SPQ Positive ( $p=.425$ ), or Disorganized behavior ( $p=.787$ ) score as a covariate. The Group\*Inhibition



(fluctuation in speed) interaction also disappeared when controlling for the SPQ Disorganized behavior score ( $p=.130$ ).

## Discussion

The objective of this study was to examine whether deficits in cognitive control contribute to SSD symptomatology in ASD, and if possible to identify specific vulnerability markers indicating a risk of SSD in adolescents diagnosed with ASD in early childhood. The outcome revealed high levels of schizotypal symptomatology and a substantial level of impaired cognitive control in adolescents with ASD, i.e., problems with inhibiting prepotent responses, mental flexibility, visuo-motor control with high EF demands, and difficulties in controlling interference. Only impaired response inhibition in ASD was associated with schizotypal symptoms, whereas we did not find any significant associations between measures of cognitive control and ASD symptomatology. The specificity of this result is emphasized by the finding that, after controlling for schizotypal symptoms, response inhibition does no longer discriminate between groups, suggesting that impaired response inhibition in ASD is mainly associated with the presence of schizotypal symptoms. We therefore suggest that impaired response inhibition might be a marker of vulnerability to SSD symptoms developing in ASD.

The presence of schizotypal symptoms co-occurring with ASD symptoms emphasizes the relevance of examining comorbidity in researching ASD. This underscores that inconsistencies in the literature concerning inhibition in ASD can be explained by high numbers of comorbidity factors (Kenworthy et al., 2008). Meta-analytic studies on inhibition functions report that inhibition of prepotent responses is specifically impaired in ASD (e.g., Hill 2004a), as we also found in our study. Moreover, our findings suggest that of the EF domain, it is specifically response inhibition deficits in ASD that could indicate high risk of developing SSD symptoms. Others have related inhibition problems to degrees of schizotypal traits in other disorders associated with increased vulnerability to SSD pathology as well (Van Rijn, Aleman, De Sonneville, & Swaab, 2009).

Regarding the relation between specific EF deficits and various separate dimensions of schizotypy, deficiencies in inhibiting responses were

associated with disorganized behavior and positive symptoms, which explains 46% and 27% of variance, respectively. These findings are reflected in the results of the meta-analysis by Dibben et al. (2009), in which the failure to inhibit responses was associated with disorganized symptoms. However, where Dibben's results were found in adults with schizophrenia, our findings indicate that impaired response inhibition is related to schizotypal symptomatology within an ASD sample already in adolescence.

Our findings clearly show cognitive control deficits in adolescents with ASD with a relatively high mean IQ, so that replication of these findings for other IQ levels is necessary. However, we found no problems with perseveration, which is inconsistent with other studies. Meta-analyses report that persons with ASD (e.g., Hill, 2004a; 2004b) and SSD (e.g. Laws, 1999) are highly perseverative in their responses on the WCST. Inconsistencies in findings are probably related to differences in how perseveration is operationalized. Most studies report an absolute number of perseveration errors, whereas others, as for instance we also did, report proportional measures (i.e., perseveration errors relative to non-perseveration errors), which represents a more valid operationalization. Consistent with our results, in the meta-analysis by Laws, reviewing WCST analyses in SSD, a medium effect size for the number of perseveration errors was found, but the effect size for the proportion of perseverative errors appeared to be small (Laws, 1999).

Although we found high levels of autistic symptomatology and a substantial level of impaired cognitive control within the ASD sample, no significant correlations were found between cognitive control measures and the degree of autistic symptomatology. This is probably due to the small range of scores. An alternative explanation may be that the lack of correlation is related to the limitations of self-report in these ASD patients, so that replication of these findings by other instruments, such as observation scales, is advisable to further validate this finding.

Our results indicate that adolescents with ASD show SSD traits. A relation was found between schizotypal and autistic traits (12% explained variance), suggesting a correspondence in diagnostic criteria between both spectrum disorders. For more detailed discussion see Barneveld et al. (2011), which reports specific associations between autistic symptoms and negative, disorganized and positive schizotypal symptoms.

An exploratory factor analysis was performed to rule out the pos-

sibility that any overlap between SSD and ASD symptoms is a result of two questionnaires measuring the same construct. The AQ and SPQ appeared to differentiate between symptomatology: one factor referred to autistic symptoms and another factor to schizotypal symptoms. Negative symptoms loaded on both factors. This SPQ scale which reflects constricted affect and social anxiety, comprises symptoms that clinically correspond with autistic symptoms (Bleuler, 1911), in line with studies reporting schizotypal negative symptoms in ASD (Dykens, Volkmar, & Glick, 1991; Rumsey, Andreasen, & Rapoport, 1986).

Out of concern for the wide age range, younger and older ASD patients' AQ and SPQ scores were examined and found not to differ significantly from each other. In addition, analyses using age as a second BS factor (young vs. old) and the bivariate correlations per age group were run, and confirmed that the findings were consistent across age.

Several limitations of our study should be mentioned. The information obtained from questionnaires was affected by the limitations inherent in self-report. This specifically applies to young ASD adolescents, who may have difficulties judging their own behavior. In addition, the inclusion of a high-functioning ASD population limits the representativeness of the sample and precludes generalizability to the whole autistic spectrum. Moreover, ascertainment bias possibly influenced results in an unpredictable way (27% refused participation), although no differences on demographics were found between participants and nonparticipants. Furthermore, although high levels of schizotypal symptoms were found in ASD patients, it is impossible to determine whether schizotypal problems are qualitatively equal to those found in SSD patients. Finally, patients with ASD often show symptoms of many other psychiatric disorders besides SSD (e.g., attention deficit/hyperactivity disorder, social anxiety disorder; Simonoff et al., 2008), and EF deficits are related to other neurodevelopmental disorders. Whether response inhibition is specifically associated with schizotypal symptomatology in ASD and not with coexisting symptoms of other psychiatric disorders remains to be investigated.

In conclusion, we found high levels of schizotypal symptomatology in adolescents with ASD and considerable cognitive control deficits. Impaired response inhibition appeared to be strongly associated with positive and disorganized

schizotypal symptoms, which clearly suggests that impaired response inhibition is a vulnerability marker for the development of SSD pathology within ASD already during adolescence. We recommend a follow-up study in order to examine whether these response inhibition problems in ASD are predictors for full-threshold psychotic illness.

## References

Achenbach, T.M. (1986). *Manual for the teacher report form and the child behavior profile*. Burlington: University of Vermont, Department of Psychiatry.

American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR)*. Washington, DC: American Psychiatric Association.

Andrewes, D. (2001). *Neuropsychology: From theory to practice*. Hove, UK: Psychology Press, Ltd.

Barneveld, P.S., Pieterse, J., De Sonnevle, L., Van Rijn, S., Lahuis, B., Van Engeland, H., & Swaab, H. (2011). Overlap of autistic and schizotypal traits in adolescents with autism spectrum disorders. *Schizophrenia Research, 126*, 1-3, 231-236.

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The Autism-Spectrum Quotient (AQ): Evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *Journal of Autism and Developmental Disorders, 31*, 1, 5-17.

Bender, L. (1947). Childhood schizophrenia: clinical study of one hundred schizophrenic children. *American Journal of Orthopsychiatry, 17*, 40-56.

Bleuler, E. (1911). *Dementia Praecox oder Gruppe der Schizophrenien*. In: Handbuch der Psychiatrie (ed. G. Van Aschaffenburg). Duttcke, Leipzig.

Bölte, S., Westerwald, E., Holtmann, M., Freitag, C., & Poustka, F. (2011). Autistic traits and autism spectrum disorders: the clinical validity of two measures presuming a continuum of social communication skills. *Journal of Autism and Developmental Disorders, 41*, 66-72.

Chmielewski, M., & Watson, D (2008). The heterogeneous structure of schizotypal personality disorder: Item-level factors of the schizotypal personality questionnaire and their associations with obsessive-compulsive disorder symptoms, dissociative tendencies, and normal personality. *Journal of Abnormal Psychology, 117*, 364-376.

Cohen, J. (1992). A power primer. *Psychology Bulletin, 112*, 155-159.

Daniels, J.L., Forssen, U., Hultman, C.M., Cnattingius, S., Savitz, D.A., Feychting, M., & Sparen, P. (2008). Parental psychiatric disorders associated with autism spectrum disorders in the offspring. *Pediatrics, 121*, 1357-1162.

Dennis, M., Francis, D.J., Cirino, P.T., Schachar, R., Barnes, M.A., & Fletcher, J.M. (2009). Why IQ is not a covariate in cognitive studies of neurodevelopmental disorders. *Journal of the International Neuropsychological Society, 15*, 331-343.

De Sonnevle, L.M.J. (2005). Amsterdamse Neuropsychologische Taken: wetenschappelijke en klinische toepassingen [Amsterdam Neuropsychological Tasks: Scientific and clinical applications]. *Tijdschrift voor neuropsychologie, 0*, 27-41.

Dibben, C.R.M., Rice, C., Laws, K., & McKenna, P.J. (2009). Is executive impairment associated with schizophrenic syndromes? A meta-analysis. *Psychological Medicine, 39*, 3, 381-392.

Dichter, G.S., Lam, K.S.L., Turner-Brown, L.M., Holtzclaw, T.N., & Bodfish, J.W. (2009). Generativity abilities predict communication deficits but not repetitive behaviors in autism spectrum disorders. *Journal of Autism and Developmental Disorders, 39*, 1298-1304.

Dykens, E., Volkmar, F., Glick, M. (1991). Thought disorder in high-functioning autistic adults. *Journal of Autism and Developmental Disorders, 21*, 3, 291-301.

Eisenberg, D.P., & Berman, K.F. (2010). Executive function, neural circuitry, and genetic mechanisms in schizophrenia. *Neuropsychopharmacology, 35*, 1, 258-277.

Frangou, S. (2010). Cognitive function in early onset schizophrenia: a selective review. *Frontiers in human Neuroscience, 3*, 6, 1-6.

Fugard, A.J.B., Stewart, M.E., & Stenning, K. (2011). Visual-verbal-analytic reasoning bias as a function of self-reported autistic-like traits. *Autism, 15*, 3, 327-340.

Gioia, G.A., & Isquith, P.K. (2004). Ecological assessment of executive function in traumatic brain injury. *Developmental Neuropsychology, 25*, 1&2, 135-158.

Guillem, F., Rinaldi, M., Parnpoulova, T., & Stip, E. (2008). The complex relationships between executive functions and positive symptoms in schizophrenia. *Psychological Medicine, 38*, 6, 853-860.

Heaton, R.K., Chelune, G.J., Talley, J.L., Kay, G.G., & Curtiss, G. (1993). *Wisconsin card sorting test manual: Revised and expanded*. Odessa, FL: Psychological Assessment Resources.

Hill, E.L. (2004a). Executive dysfunction in autism. *Trends in Cognitive Sciences, 8*, 1, 26-32.

Hill, E.L. (2004b). Evaluating the theory of executive dysfunction in autism. *Developmental Review, 24*, 2, 189-233.

Huijbregts, S.C.J., Swaab-Barneveld, H., & De Sonnevle, L.M.J. (2010). Cognitive and motor control in Neurofibromatosis Type 1: Influence of maturation and hyperactivity-inattention. *Developmental Neuropsychology, 35*, 737-751.

Huijbregts, S., De Sonnevle, L., Licht, R., Sergeant, J., & Van Spronsen, F. (2002). Inhibition of prepotent responding and attentional flexibility in treated phenylketonuria. *Developmental Neuropsychology, 22*, 2, 481-499.

Hurst, R.M., Nelson-Gray, R.O., Mitchell, J.T., & Kwapil, T.R. (2007a). The relationship of Asperger's characteristics and schizotypal personality traits in a non-clinical adult sample. *Journal of Autism and Developmental Disorders, 37*, 9, 1711-1720.

Hurst, R.M., Mitchell, J.T., Kimbrel, N.A., Kwapil, T.K., & Nelson-Gray, R.O. (2007b). Examination of the reliability and factor structure of the Autism Spectrum Quotient (AQ) in a non-clinical sample. *Personality and Individual Differences, 43*, 1938-1949.

Johnson-Selfridge, M., & Zalewski, C. (2001). Moderator variables of executive functioning in schizophrenia: meta-analytic findings. *Schizophrenia Bulletin, 27*, 2, 305-316.

Kenworthy, L., Black, D.O., Harrison, B., Della Rosa, A., & Wallace, G.L. (2009). Are executive control functions related to autism symptoms in high-functioning children? *Child Neuropsychology, 15*, 5, 425-440.

Kenworthy, L., Yerys, B.E., Anthony, L.G., & Wallace, G.L. (2008). Understanding executive control in autism spectrum disorders in the lab and in the real world. *Neuropsychology Review, 18*, 4, 320-338.

Kolvin, I. (1971). Studies in the childhood psychoses. I. Diagnostic criteria and classification. *British Journal of Psychiatry, 118*, 545, 381-384.

Larsson, H.J., Eaton, W.W., Madsen, K.M., Vestergaard, M., Olesen, A.V., Agerbo, E., ... Mortensen, P.B. (2005). *American Journal of Epidemiology, 161*, 10, 916-925.

Laws, K.R. (1999). A meta-analytic review of Wisconsin Card Sort Studies in schizophrenia: general intellectual deficit in disguise? *Cognitive Neuropsychiatry, 4*, 1, 1-35.

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.

Loring, D.W., Lezak, M.D., & Howieson, D.B. (2004). *Neuropsychological assessment*. Oxford University Press.

McGrath, J., Saha, S., Welham, J., El Saadi, O., MacCauley, C., & Chant, D. (2004). A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Medicine, 2*, 13.

Miyake, A., Friedman, N.P., Emerson, M.J., Minshew, N.J., Witzki, A.H., Howeter, A., Wager, T.D. (2000). The unity and diversity of executive functions and their contributions to complex 'frontal lobe' tasks: a latent variable analysis. *Cognitive Psychology, 41*, 49-100.

Mouridsen, S.E., Rich, B., & Isager, T. (2008). Psychiatric disorders in adults diagnosed as children with atypical autism. A case control study. *Journal of Neural Transmission, 115*, 135-138.

Nieuwenstein, M.R., Aleman, A., & De Haan, E.H.F. (2001). Relationship between symptom dimensions and neurocognitive functioning in schizophrenia: a meta-analysis of WCST and CPT studies. *Journal of Psychiatric Research, 35*, 2, 119-125.

Ozonoff, S. (1997). *Components of executive function in autism and other disorders*. In J. Russell (ed.), *Autism as an executive disorder* (pp.179-211). Oxford: Oxford University Press.

Padgett, F.E., Miltsiou, E., & Tiffin, P.A. (2010). The co-occurrence of nonaffective psychosis and the pervasive developmental disorders: a systematic review. *Journal of Intellectual and Developmental Disability, 35*, 3, 187-198.

Raine, A. (1991). The SPQ: A scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophrenia Bulletin, 17*, 4, 555-564.

Raja, M., & Azzoni, A. (2010). Autistic spectrum disorders and schizophrenia in the adult psychiatric setting: diagnosis and comorbidity. *Psychiatria Danubina, 22*, 4, 514-521.

Rapoport, 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 American Academy of Child and Adolescent Psychiatry, 48*, 1, 10-18.

Rommelse, N.N.J., Altkink, M.E., Oosterlaan, J., Buschgens, C.J.M., Buitelaar, J., De Sonnevle, L.M.J., & Sergeant, J.A. (2007). Motor control in children with ADHD and non-affected siblings: deficits most pronounced using the left hand. *Journal of Child Psychology and Psychiatry, 48*, 11, 1071-1079.

Rumsey, J.M., Andreason, N.C., Rapoport, J.L. (1986). Thought, language, communication, and affective flattening in autistic adults. *Archives of General Psychiatry, 43*, 8, 771-777.

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

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 American Academy of Child and Adolescent Psychiatry, 47*, 8, 921-929.

Slaats-Willems, D., De Sonnevle, L., Swaab-Barneveld, H., & Buitelaar, J. (2005). Motor flexibility problems as a marker for genetic susceptibility to Attention-Deficit/Hyperactivity Disorder. *Biological Psychology, 58*, 233-238.

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*, 1474-1484.

Sporn, A.L., Addington, A.M., Gogtay, N., Ordonez, A.E., Gornick, M., Clasen, L., ... Rapoport, J.L. (2004). Pervasive developmental disorder and childhood-onset schizophrenia: comorbid disorder or a phenotypic variant of a very early onset illness? *Biological Psychiatry, 55*, 989-994.

Stahlberg, O., Soderstrom, H., Rastam, M., & Gillberg, C. (2004). Bipolar disorder, schizophrenia, and other psychotic disorders in adults with childhood onset AD/HD and/or autism spectrum disorders. *Journal of Neural Transmission, 111*, 891-902.

Stevens, J. (1986). *Applied multivariate statistics for the social sciences*. London: Lawrence Erlbaum Associates.

Van der Gaag, R.J., Buitelaar, J., Van den Ban, E., Bezemer, M., Nijjo, 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*, 1096-1106.

Van Rijn, S., Aleman, A., De Sonnevle, L., & Swaab, H. (2009). Cognitive mechanisms underlying disorganization of thought in a genetic syndrome (47,XXY). *Schizophrenia Research, 112*, 91-98.

Ventura, J., Helleman, G.S., Thames, A.D., Koellner, V., & Nuechterlein, K.H. (2009). Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis. *Schizophrenia Research*, 113, 2-3, 189-199.

Volkmar, F.R., & Cohen, D.J. (1991). Comorbid association of autism and schizophrenia. *The American Journal of Psychiatry*, 148, 1705-1707

Vollema, M.G., & Hoijtink, H. (2000). The multidimensionality of self-report schizotypy in a psychiatric population: An analysis using multidimensional Rasch models. *Schizophrenia Bulletin*, 26, 3, 565-575.

Vollema, M.G., & Postma, B. (2002). Neurocognitive correlates of schizotypy in first degree relatives of schizophrenia patients. *Schizophrenia Bulletin*, 28, 3, 367-377.

Wechsler, D. (2002). *Wechsler Intelligence Scale for Children-III NL: Handleiding en verantwoording [Manual]*. The Psychological Corporation Ltd., Harcourt Assessment.

Wechsler, D. (2005). *Wechsler Adult Intelligence Scale-III: Nederlandstalige bewerking, technische handleiding [Manual]*. Lisse: Harcourt Test Publishers.

Yerys, B.E., Wallace, G.L., Harrison, B., Celano, M.J., Giedd, J.N., & Kenworthy, L.E. (2009). Set-shifting in children with autism spectrum disorders: Reversal shifting deficits on the Intradimensional/Extradimensional Shift Test correlate with repetitive behaviors. *Autism*, 13, 5, 523-538.

# CHAPTER 6



## Summary and discussion

### Summary and integration of main results

Social cognition entails a vast set of abilities that allow people to live in large, complex social groups. Core deficits in people with ASD are difficulties in adapting their behaviour to the social environment which hampers or restricts the possibilities to communicate adequately and to have reciprocal relationships. The problems with adaptation to the social environment in people with ASD have a serious impact on functioning in their daily life. Since ASD are severe and lifelong conditions it is particularly relevant to examine how children and adolescents with ASD develop throughout their life and to investigate which factors constitute an advantageous or an unfavourable contribution to their development.

#### *Social outcome: Quality of Life in ASD*

Findings of this thesis provided more insight into the consequences of difficulties of adapting behaviour to the social environment in ASD, by revealing that young adults diagnosed with ASD in childhood are at specific risk of poor QoL. Several studies have shown that QoL is threatened in individuals with psychopathology in general (e.g., Bastiaansen et al., 2004), but the follow-up study of chapter 2 revealed that ASD have a more profound unfavourable effect on QoL in young adulthood than ADHD, DISR, and AFF disorders. In comparison to adults diagnosed in childhood with these disorders, relatively many adults with ASD were single and only some of them were cohabiting or married. Most of the adults with ASD lived with their parents, relatively few lived with a partner or family and many of them were institutionalized. The highest educational level of the adults with ASD was significantly lower than in the other patient groups, relatively few had paid employment, and relatively many were

social security recipients. When the adults with ASD (had) used medication, relatively many were on anti-psychotics.

Although these objective judgements of life conditions are important in evaluating QoL in ASD, the patient's own, subjective, appraisal of satisfaction with life is also essential to their well being. Outcomes of the study of subjective QoL indicated that adults with ASD were less content about their work or education, partner relationships, and future perspectives, but more satisfied about their physical condition than adults with other psychiatric disorders diagnosed in childhood. The outcome of subjective QoL is the resultant of the judgements of the hopes and expectations of a person versus present experience, influenced by the subject's personal frame of reference. One might argue that patients with developmental psychiatric disorders in general might have lowered their own standards to what would be desirable levels as a consequence of adaptation to life conditions, and specifically ASD patients might have personal frames of references that run counter to generally accepted standards (e.g., less need for social interactions and therefore more satisfaction on these matters). Nevertheless, adults with ASD appeared to be less satisfied on several QoL domains than the adults with the other psychiatric disorders, so, it is concluded that they experience relatively more distress in their life.

When examining the influence of level of education on QoL in patients without mental retardation (IQ exceeding 70), no differences in subjective outcomes were found between lower and higher educated patients with ASD, unexpectedly indicating that subjective QoL is not primarily determined by criteria related to educational level. However, findings demonstrated that lower educated adults with ASD showed poorer objective QoL concerning living arrangements and work than those with higher educational qualifications, indicating that educational levels are significant in societal outcome in ASD. Therefore, it was interesting to examine whether or not the differences in outcomes of the psychiatric disorders still exist when only higher educated adults with ASD were compared to higher educated adults with the other psychiatric disorders. Results show that both objective and subjective QoL remained to be more unfavourable in adults with ASD compared to other disorders. This indicates that, even if they appeared to be successful during education and have the same employment, higher education level is not a protective factor to QoL in ASD.

#### *Cognitive dysfunction in relation to age in ASD*

The second aim of this dissertation was investigating factors contributing to presumed progressive developmental problems when children and adolescents with ASD grow up. When we examined the impact of age on cognitive functioning of 6-to-15-year-old children and adolescents, the results clearly demonstrated lower global intelligence levels in children aged eight years and older compared to younger children with ASD (chapter 3). Although the results have to be interpreted with caution because only cross-sectional data could be analyzed, the findings suggest a progressive impairment of cognitive functioning in children with ASD. The differences in global intelligence level were mostly due to the performances on the subtests of the Freedom from Distractibility factor, indicating that older children (of eight years and older) had more difficulties to sustain their attention, were more distractible, or had more graph motor difficulties when compared to younger (6-and-7-year-old) children. The apparent decline in intelligence might be associated with a possible absence of the typically expected growth spurt in executive functioning, which runs parallel to the maturation of the frontal lobe, as seen in typically developing children (Anderson, 2002). The development of EF might especially be affected in ASD by abnormal growth processes, explained by the observation of the relatively late and prolonged period of maturation of the putative underlying cortical areas (Courchesne & Pierce, 2005). The suggested impairment of intellectual functioning over age and the specific performance on FFD might be mediated by the impaired development of EF. Furthermore, since EF, such as attentional control and response inhibition, are required when performing tasks of the FFD factor, the impairment of EF presumably contributes to a less harmonious distribution of factor profiles in older children when compared to younger ones.

When profiles of peaks and troughs of intellectual skills in children with ASD were examined at the subtest level, an effect of age was also found with respect to the relatively poor performance on the subtest Comprehension when compared to other VC subtests, suggesting that specifically the impairments in verbal comprehension and social reasoning abilities are more profound in older children when compared to younger (6-and-7-year-old) children with ASD. Since the ability of social reasoning is believed to be mediated by the frontal regions (Walker & Bollini, 2002), the specific age-effect of performance on Comprehension possibly suggests executive dysfunction in older

children with ASD. Typically developing children show increased reasoning and problem-solving abilities and the capacity to think in multiple dimensions develops at approximately seven years of age (Anderson, 2001). These EF's are required for social reasoning as measured by the subtest Comprehension, and inefficient acquisition of these skills in children with ASD might result in deviations from expected patterns of development. In contrast to the characteristic verbal comprehension and social reasoning problems in patients with ASD, the typical superior or relatively preserved abstract visuo-spatial abilities in children with ASD as reflected in the peak of performance on Block Design (e.g., Asarnow et al., 1987; Happé, 1994; Siegel et al., 1996; Shah & Frith, 1993) were also found in the present study. However, no effect of age was found with respect to abstract visuo-spatial abilities.

#### *Schizophrenia spectrum pathology in ASD*

The third aim of this thesis was to unravel the relation between autism spectrum and schizophrenia spectrum traits in adolescents diagnosed with ASD in childhood. The outcome revealed that adolescents with ASD scored higher on all symptom dimensions of the schizophrenia phenotype than typically developing adolescents (chapter 4). Besides high levels of negative symptoms, adolescents with ASD also displayed high levels of positive symptoms and disorganised symptoms. Our finding that an overlap between autistic traits and schizotypal symptoms was found is equivalent to the vision of Bleuler (1911) and supports the idea of correspondence between both spectrum disorders (Hurst et al., 2007; Konstantareas & Hewitt, 2001; Sheitman et al., 2004).

The present findings suggest that behavioural overlap is not limited to negative schizotypal symptoms but extend to disorganised and positive symptoms as well. These results were consistent with other studies by Dykens et al. (1991) and Rumsey et al. (1986) who reported shared symptoms in ASD and schizophrenia, like poverty of speech. Considering positive symptoms, Blackshaw et al. (2001) and Craig et al. (2004) indicated some degree of paranoid ideation in adults who were diagnosed with Asperger syndrome. In addition, Solomon et al. (2008) and Van der Gaag et al. (2001) described illogical thinking and loose associations in children with ASD.

It may be emphasised that the associations between autistic and schizotypal symptomatology in the present study were almost exclusively accounted for by two traits of the autistic symptoms, i.e., attention switch-

ing problems and communication difficulties. High levels of communication problems were associated with more negative and disorganised symptoms of the schizotypal dimensions. The autistic feature attention switching stands out prominently, as it appeared to be related to all three dimensions of schizotypy. This suggests that inattentive behaviour might be an underlying manifestation of a broad range of schizotypal behaviours. Therefore, further investigation was needed to identify underlying neurocognitive mechanisms that contribute to SSD in ASD.

#### *Neurocognitive markers underlying vulnerability to SSD in ASD*

The fourth aim of this dissertation was to examine whether deficits in cognitive control contribute to SSD symptomatology in ASD, and to identify specific neurocognitive vulnerability markers indicating a risk of SSD in adolescents diagnosed with ASD in early childhood. The outcome revealed high levels of schizotypal symptomatology and a substantial level of impaired neurocognitive control in adolescents with ASD, i.e., problems with inhibiting prepotent responses, mental flexibility, visuo-motor control with high EF demands, and difficulties in controlling interference (chapter 5). However, only impaired response inhibition in ASD was associated with schizotypal symptoms, whereas no significant associations between measures of other cognitive control and ASD symptomatology were found. This result was further specified when, after controlling for schizotypal symptoms, response inhibition no longer discriminated between groups, revealing that impaired response inhibition in ASD was mainly associated with the presence of schizotypal symptoms and can not be explained by autism symptoms. We therefore conclude that impaired response inhibition might be a marker of vulnerability to SSD symptoms developing in ASD.

The presence of schizotypal symptoms co-occurring with ASD symptoms emphasises the relevance of examining comorbidity in assessment of ASD. This underscores that inconsistencies in the literature concerning inhibition in ASD may be the resultant of high numbers of comorbidity factors (Kenworthy et al., 2008). Meta-analytic studies on inhibition functions report that inhibition of prepotent responses is specifically impaired in ASD (e.g., Hill 2004), as we also found in our study. Moreover, our findings suggest that specifically response inhibition above other impairments in EF in ASD is associated with high risk of developing SSD symptoms. Others have found that in-

hibition problems are related to degree of schizotypal traits in other disorders, concluding an association of inhibition problems with increased vulnerability to SSD pathology as well (Van Rijn, Aleman, De Sonneville, & Swaab, 2009).

Regarding the relation between specific EF deficits and various separate dimensions of schizotypy, deficiencies in inhibiting responses were associated with disorganised behaviour and positive symptoms. These findings are supported by the results of the meta-analysis by Dibben et al. (2009), in which the failure to inhibit responses was associated with disorganised symptoms. However, where Dibben's results were found in adults with schizophrenia, our findings indicate that impaired response inhibition is also related to schizotypal symptomatology within an ASD sample in adolescence.

### **General discussion, implications for the future and clinical implications**

In order to gain a better understanding of how children with ASD develop throughout their life and to get more insight into the consequences of difficulties in adaptation to the social environment as characteristically is seen in ASD, long-term outcome in childhood ASD was evaluated by studying quality of life in young adulthood, compared to other childhood developmental disorders (chapter 2). Although several studies suggested that developmental psychopathology is generally associated with poor outcome, this study revealed that the QoL of young adults diagnosed with ASD in childhood is specifically more compromised than QoL in adults diagnosed with other child psychiatric disorders. Even when highly educated adults with ASD were compared to highly educated adults diagnosed with ADHD, disruptive behaviour, or affective disorders, adults with ASD and high educational qualifications were at specific risk of poor QoL.

This was the first study examining the long-term impact (follow-up period of almost 14 years) of ASD for QoL in adults, using no less than three age-matched comparison groups of patients presenting with the other major childhood psychiatric disorders. This approach enabled to examine the specific impact of ASD on QoL, which is not possible when including only typically developing individuals as controls as is usually done in QoL studies. An important strength of the study was the exclusion of mutual comorbidity of the three psychiatric control groups, leaving pure comparison groups. More

research is required to enhance our understanding of relations between QoL and other factors besides characteristics of the diagnosis itself, like the impact of symptom severity, social skills or social network factors. This study provides a first step in demonstrating poor QoL in ASD, but the next step should be to further investigate the factors that lead to this outcome.

From a clinical point of view these findings are highly relevant. Parents of children with ASD need accurate information about the prognosis of their child's identified impairments (Kisler & McConachie, 2010). We can now provide a better indication of the consequences of ASD for their daily life functioning that may become more prominent when these children grow older and are faced with increasing demands for personal independence. Receiving accurate perceptions of their child's prognosis has numerous advantages (Goin-Kochel, Peters, Treadwell-Deering, 2008), including setting reasonable expectations in terms of relationships and achievements for their child and more realistic goals for interventions and therapies. For children with ASD, functioning in daily life requires support beyond what is normally needed by others at a similar age and stage of life. This underscores the relevance of further development of specific treatment to improve social skills or adjust the child's environment in order to increase their quality of life and subjective satisfaction of their life conditions. Such treatment and support may include a variety of forms such as guidance, or specially designed environmental or social arrangements. Providing these forms of support has been a major function of education, health, and human service programmes. In this process, the concept of QoL has become increasingly central in developing programmatic policies and practices as well as in evaluating the impact that programmes have on the lifestyles of their users (Schalock, 2004).

The focus of the study described in chapter 3 was on intelligence profiles in 6-to-15-year-old children and adolescents diagnosed with ASD, with particular interest in the role of age. Results of the cross-sectional study showed that it is relevant to take age into account when evaluating the developmental impact of cognitive impairments on intelligence in children with ASD, since the impact of these developmental disorders might be different at different ages. Longitudinal studies are desirable to examine whether or not children with ASD actually have progressive impairments during development, as suggested by our study. For clinicians and parents, this means that re-evaluation of cognitive function during development is recommended.



The results of the study, described in chapter 4, drew attention to this risk of SSD symptomatology in ASD. Although other studies provide empirical support for co-occurring diagnostic criteria between both spectrum disorders, the present findings add to the literature that behavioural overlap is not limited to negative schizotypal symptoms, but extends to disorganised and positive symptoms as well. Although speculative, the current findings may have clinical implications. As high levels of schizotypy appear to reflect a higher risk of developing schizophrenia (Mata et al., 2000; Miller et al., 2002; Vollema et al., 2002), finding high levels of positive symptoms and disorganised behaviour in ASD may implicate an increased risk of schizophrenia spectrum pathology later in life. Implications about the prognostic value of specific childhood symptoms in ASD to the risk of adult schizophrenia should be further explored in a longitudinal design.

The here presented findings are in line with the on-going discussion on the possible relation between ASD and SSD. Classification systems (like the DSM-IV) suggest no direct relation to the underlying aetiology of the disorders. It is, however, very plausible that psychiatric disorders show different clinical presentations at different ages as manifestations of the same underlying disorder, resulting in “cross over” of classification in some cases. The idea of age-specific manifestations of psychopathological symptomatology needs to be given more emphasis to solve on-going questions on co-morbid developing psychiatric disorders and symptoms over time and their possible relation to the aetiology (Hollis, 2001). In addition to using a dichotomous categorical classification system in which an individual does or does not possess a characteristic pattern of symptoms, the use of a dimensional symptom system in which an individual can be characterized by a level on a continuum of a specific characteristic could be helpful in subtyping the ASD spectrum disorders. The degree to which a child or adolescent with ASD shows elevated levels of autistic characteristics and elevated levels of schizotypal characteristics, (such as a large degree of instability of functioning, affect dysregulation and high levels of anxiety), can assist in recognising developmental risk.

Finally, the dynamics of underlying cognitive development of SSD symptomatology in ASD were investigated. Impaired response inhibition appeared to be strongly associated with positive and disorganised schizotypal symptoms, which clearly suggests that impaired response inhibition is a vulnerability marker for the development of SSD pathology within ASD

already during adolescence. We recommend a follow-up study in order to examine whether these response inhibition problems in ASD are predictive for full-threshold psychotic illness. Future studies should incorporate a developmental context, since the manifestations of SSD symptomatology in ASD at different ages may be dependent on developmental milestones of response inhibition.

These results indicate that clinicians should be aware of inhibition problems in adolescents with ASD because this may be associated to the risk of serious schizophrenia pathology later in life. The inhibition problems are possibly related to the difficulties in regulating thoughts and feelings in these adolescents.

### **Limitations**

In order to appraise the findings of this thesis one should take the following general limitations into account. Since the sample selection covers a long time span (between 1984 and 2004) and standardized diagnostic parent interview procedures were developed during this period (e.g. the Autism Diagnostic Interview (ADI), these interviews were not used as a validation criterion for the ASD diagnosis in the first and second study. However, in the last two follow-up studies the ASD diagnoses at childhood were validated by the Dutch translation of the ADI in adolescence. In addition, the exclusion of mentally retarded ASD patients in the first study and the inclusion of high-functioning ASD populations in the last three studies limit the representativeness of the sample and, as such, preclude generalisability to the whole autistic spectrum. Moreover, the information obtained from questionnaires in the first, third and fourth study was affected by the limitations inherent in self-report. This specifically applies to ASD adolescents and adults, who may have difficulties judging their own behavior.

## Concluding remarks

Given the four research questions of this dissertation, we can conclude the following:

Growing up, children with ASD are at specific risk of poor quality of life in adulthood when compared to other children with psychiatric disorders. Secondly, the performance of children and adolescents with ASD on specific domains of intellectual functioning is different at different ages, indicating a possible progressive impact of the developmental disorders. Therefore, re-evaluation of cognitive function during development of children and adolescents with ASD is recommended. Thirdly, children with ASD who are at risk of SSD symptomatology, may show negative schizotypal symptoms, but also disorganized and positive symptoms in addition to ASD symptomatology. These symptoms of schizotypy appear to be associated with neurocognitive inhibition problems in childhood. Parents, teachers and clinicians should be aware of inhibition problems in children and adolescents with ASD because they may be an indicator of high risk to serious schizophrenia spectrum pathology later in life.

## References

- Anderson, P. (2002). Assessment and development of executive function (EF) during childhood. *Child Neuropsychology*, 8, 2, 71-82.
- Anderson, V., Northam, E., Hendy, J., & Wrennall, J. (2001). *Developmental neuropsychology, a clinical approach*. Hove: Psychology Press Ltd.
- Asarnow, R.F., Tanguay, P.E., Bott, L., Freeman, B.J. (1987). Patterns of intellectual functioning in non-retarded autistic and schizophrenic children. *Journal of Child Psychology and Psychiatry*, 28, 2, 273-280.
- Bastiaansen, D., Koot, H.M., Ferdinand, R.F., Verhulst, F.C. (2004). Quality of life in children with psychiatric disorders: self, parent, and clinician report. *Journal of American Academy Child Adolescent Psychiatry*, 43, 221-30.
- Blackshaw, A.J., Kinderman, P., Hare, D.J., Hatton, C. (2001). Theory of mind, causal attribution and paranoia in asperger syndrome. *Autism* 5 (2) 147-163.
- Bleuler, E., 1911. *Dementia Praecox oder Gruppe der Schizophrenien*, in: Van Aschaffenburg, G. (Ed.), *Handbuch der Psychiatrie*. Duticke, Leipzig.
- Courchesne, E. & Pierce, K. (2005). Brain overgrowth in autism during a critical time in development: implications for frontal pyramidal neuron and interneuron development and connectivity. *International Journal of Developmental Neuroscience*, 23, 153-170.
- Craig, J.S., Hatton, G., Craig, F.B., Bentall, R.P. (2004). Persecutory beliefs, attributions and theory of mind: comparison of patients with paranoid delusions, asperger's syndrome and healthy controls. *Schizophrenia Research*, 69 (1) 29-33.
- Dibben, C.R.M., Rice, C., Laws, K., & McKenna, P.J. (2009). Is executive impairment associated with schizophrenic syndromes? A meta-analysis. *Psychological Medicine*, 39, 3, 381-392.
- Dykens, E., Volkmar, F., Glick, M. (1991). Thought disorder in high-functioning autistic adults. *Journal of Autism and Developmental Disorders*, 21 (3) 291-301.
- Goin-Kochel, R.P., Peters, S.U., Treadwell-Deering, D. (2008). Parental reports on the prevalence of co-occurring intellectual disability among children with autism spectrum disorders. *Research in Autism Spectrum Disorders*, 2 (3) 546-556.
- Happé, F. G. (1994). Wechsler IQ profile and theory of mind in autism: a research note. *Journal of Child Psychology and Psychiatry*, 35, 1461-1471.
- Hill, E.L. (2004). Executive dysfunction in autism. *Trends in Cognitive Sciences*, 8, 1, 26-32.
- Hollis, C. (2001). *Diagnosis and differential diagnosis*. In: Remschmidt, H. (Ed). *Schizophrenia in children and adolescents*. Cambridge: University Press.
- Hurst, R.M., Nelson-Gray, R.O., Mitchell, J.T., Kwapil, T.R. (2007). The relationship of Asperger's characteristics and schizotypal personality traits in a non-clinical adult sample. *Journal of Autism and Developmental Disorders*, 37 (9) 1711-1720.
- Kenworthy, L., Yerys, B.E., Anthony, L.G., & Wallace, G.L. (2008). Understanding executive control in autism spectrum disorders in the lab and in the real world. *Neuropsychology Review*, 18, 4, 320-338.
- Kim-Cohen, J., Caspi, A., Moffitt, T.E., Harrington, H., Milne, B.J., Poulton, R. (2003). Prior juvenile diagnoses in adults with mental disorder: developmental follow-up of a prospective-longitudinal cohort. *Archives of General Psychiatry*, 60, 709-717.
- Kisler, J., & McConachie, H. (2010). Parental reaction to disability. *Paediatrics and Child Health*, 20 (7) 309-314.
- Konstantareas, M.M., Hewitt, T. (2001). Autistic disorder and schizophrenia: Diagnostic overlaps. *Journal of Autism and Developmental Disorders*, 31 (1) 19-28.
- Mata, I., Sham, P.C., Gilvarry, C.M., Jones, P.B., Lewis, S.W., Murray, R.M. (2000). Childhood schizotypy and positive symptoms in schizophrenic patients predict schizotypy in relatives. *Schizophrenia Research*, 44 (2) 129-136.
- Miller, P., Byrne, M., Hodges, A., Lawrie, S.M., Owens, D.G., Johnstone, E.C. (2002). Schizotypal components in people at high risk of developing schizophrenia: Early findings from the Edinburgh high-risk study. *British Journal of Psychiatry*, 180, 179-184.
- Rumsey, J.M., Andreasen, N.C., Rapoport, J.L., (1986). Thought, language, communication, and affective flattening in autistic adults. *Archives of General Psychiatry*, 43 (8) 771-777.
- Schalock, R.L. (2004). The concept of quality of life: what we know and do not know. *Journal of Intellectual Disability Research*, 48 (3) 203-216.

Shah, A., Frith, U. (1993). Why do autistic individuals show superior performance on the block design task? *Journal of Child Psychology and Psychiatry*, 34, 8, 1351-1364.

Siegel, D. J., Minshew, N. J., & Goldstein, G. (1996). Wechsler IQ profiles in diagnosis of high-functioning autism. *Journal of Autism and Developmental Disorders*, 26, 389-406.

Sheitman, B.B., Bodfish, J.W., Carmel, H. (2004). Are the negative symptoms of schizophrenia consistent with an autistic spectrum illness? *Schizophrenia Research*, 69(1) 119-120.

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, 1474-1484

Van der Gaag, R.J., Caplan, R., Van Engeland, H., Loman, F., Buitelaar, J.K. (2005). A controlled study of formal thought disorder in children with autism and multiple complex developmental disorders. *Journal of Child Adolescent Psychopharmacology*, 15(3) 465-476.

Van Rijn, S., Aleman, A., De Sonneville, L., & Swaab, H. (2009). Cognitive mechanisms underlying disorganization of thought in a genetic syndrome (47,XXY). *Schizophrenia Research*, 112, 91-98.

Vollema, M.G., Sitskoorn, M.M., Appels, M.C., Kahn, R.S. (2002). Does the schizotypal personality questionnaire reflect the biological-genetic vulnerability to schizophrenia? *Schizophrenia Research*, 54 (1-2) 39-45.

Walker, E., & Bollini, A.M. (2002). Pubertal neurodevelopment and the emergence of psychotic symptoms. *Schizophrenia Research*, 54 (1) 17-23

# NEDERLANDSE SAMENVATTING

## Opgroeien met autismespectrumstoornissen: uitkomsten in de adolescentie en volwassenheid

### Inleiding

Sociale vaardigheden stellen mensen in staat om zich in grote sociale groepen te bewegen en tijdens hun ontwikkeling zijn mensen in belangrijke mate afhankelijk van hun onderlinge interacties. Sociale situaties zijn vaak complex omdat er veel informatie verwerkt moet worden en ze zijn dynamisch door de interactieve aard waarbij er vaak beperkte tijd beschikbaar is om sociale signalen te interpreteren en daar op een adequate wijze op te reageren. De kwaliteit van sociaal gedrag is afhankelijk van de vaardigheden die essentieel zijn bij het verwerken van sociaal relevante informatie in dynamische situaties en bij het flexibel kunnen afstemmen en adequaat reageren op de sociale omgeving. Verstoringen in de sociale informatieverwerking hebben nadelige gevolgen voor de mogelijkheden om sociaal adaptief te kunnen functioneren en bemoeilijken de mogelijkheid tot het aangaan van wederkerige relaties (Swaab, 2013; Van Rijn, 2011). De moeite die men heeft om gedrag adaptief af te stemmen op de sociale omgeving vormt het kernprobleem van mensen met autismespectrumstoornissen (autism spectrum disorders; ASD) en is van invloed op het aangaan en onderhouden van wederkerige relaties en de mogelijkheden om adequaat te communiceren. De problemen met adaptatie aan de sociale omgeving bij mensen met ASD hebben een groot effect op hun algemeen dagelijkse functioneren en de kwaliteit van leven. Omdat ASD ernstig zijn en een chronisch beloop hebben, is het belangrijk om te weten hoe de ontwikkeling van kinderen en adolescenten met ASD zal verlopen en welke factoren een gunstige of ongunstige bijdrage aan die ontwikkeling zullen hebben.

## Opbouw van het proefschrift

De focus van dit proefschrift betreft de uitkomsten van het opgroeien met ASD in de adolescentie en de volwassenheid. Wanneer kinderen met ASD opgroeien, wat zijn dan de gevolgen van deze ernstige ontwikkelingsstoornis voor hun ontwikkeling en welke factoren zijn daarbij van invloed? De verschillende onderzoeken behorende bij dit proefschrift maken deel uit van een longitudinale studie, opgezet om de cognitieve en sociaal-emotionele ontwikkeling van kinderen met psychiatrische stoornissen in kaart te brengen. Deze kinderen werden in de periode tussen 1984 en 2004 aangemeld bij de afdeling kinderen en jeugdpsychiatrie van het Universitair Medisch Centrum Utrecht.

Om meer inzicht te verkrijgen in de mate van ernst van de gevolgen van ASD op lange termijn, is de kwaliteit van leven geëvalueerd van jongvolwassenen die op de kinderleeftijd zijn gediagnosticeerd met ASD door middel van een follow-up studie (hoofdstuk 2). Zowel objectieve sociale uitkomsten (burgerlijke staat, woonomstandigheden, opleidingsniveau, werk en het gebruik van geestelijke gezondheidszorg), als subjectieve uitkomsten (tevredenheid over deze aspecten van kwaliteit van leven en toekomstperspectief) zijn onderzocht. Vanwege de specifieke, ernstige problemen met sociale adaptatie binnen ASD, werd verwacht dat het welzijn van jong volwassenen met ASD slechter is dan dat van jong volwassenen gediagnosticeerd met andere kinderpsychiatrische stoornissen. In deze follow-up studie werd de kwaliteit van leven (Quality of Life; QoL) van 169 hoog-functionerende volwassenen met ASD (19 tot 30 jaar) vergeleken met, op leeftijd geselecteerde, volwassenen die gedurende hun kindertijd gediagnosticeerd zijn met aandachtstekortstoornissen met of zonder hyperactiviteit (attention deficit hyperactivity disorders; ADHD;  $N=85$ ), disruptieve of normoverschrijdende gedragsstoornissen (disruptive behaviour disorders; DISR; oppositieel-opstandige gedragsstoornissen en anti-sociale gedragsstoornissen;  $N=83$ ) en affectieve stoornissen (affective disorders; AFF; angst- en stemmingsstoornissen ( $N=85$ )).

Problemen met adaptief functioneren bij individuen met ASD kunnen worden verklaard door de inadequate manier waarop ze informatie uit hun sociale omgeving waarnemen en verwerken. Door middel van intelligentieonderzoek werd het vermogen om informatie te verwerken en daar betekenis aan te verlenen onderzocht en werden cognitieve problemen geïdentificeerd die ten grondslag liggen aan de ontwikkelingsstoornissen. Er moet bij ASD

rekening gehouden worden met beperkingen van of stagnaties in de hiërarchische vooruitgang van cognitieve vermogens die parallel lopen met de ontwikkeling van het brein. In hoofdstuk 3 is het onderzoek beschreven naar intelligentieprofielen binnen een grote groep 6- tot en met 15-jarige kinderen en adolescenten met ASD, met speciale aandacht voor de rol van leeftijd. Er werd verwacht dat de impact van de ontwikkelingsstoornis op het intelligentieprofiel bij oudere kinderen duidelijker naar voren zou komen dan bij jongere kinderen met ASD. De intelligentieprofielen van 237 hoog-functionerende jongens met ASD werden vergeleken in vier opeenvolgende leeftijdsgroepen (kinderen in de leeftijd van 6.17 tot en met 8.03 jaar; 8.04 tot 9.61 jaar; 9.68 tot 11.50 jaar, en adolescenten in de leeftijd van 11.54 tot en met 15.85 jaar).

Hoewel sommige individuen met ASD zich voldoende kunnen aanpassen in het dagelijks leven en tegen weinig problemen aanlopen, hebben velen een risico op ernstige verstoringen in hun dagelijks functioneren tijdens hun ontwikkeling en voor sommigen bestaat er een verhoogde kans op zeer ernstige psychopathologie, zoals het krijgen van psychotische symptomen later in hun leven. Als kinderen worden gediagnosticeerd met ASD, later in hun leven een stoornis ontwikkelen in het schizofrene spectrum (schizophrenia spectrum disorders; SSD), is het waarschijnlijk dat ze schizotypische kenmerken laten zien tijdens de adolescentie. Het is dan van belang om deze schizotypische kenmerken zo vroeg mogelijk te herkennen, om behandeling en begeleiding in te kunnen zetten en daarmee de invloed van deze kenmerken op het beloop van de stoornis en op het dagelijkse leven zoveel mogelijk te beperken. In hoofdstuk 4 staat de mogelijke overlap centraal tussen symptomen van ASD en van schizotypie in het gedrag bij adolescenten met ASD. De relatie tussen autistische en schizotypische kenmerken is onderzocht in een groep van 27 adolescenten (11 tot en met 18 jaar), die werden vergeleken met 30 normaal ontwikkelende adolescenten.

In verband met het verhoogde risico op SSD bij ASD is het van belang om indicatoren voor dit risico vroeg in de ontwikkeling te onderkennen, om de ontwikkeling van onderliggende mechanismen te begrijpen die leiden tot deze ernstige psychopathologie en om daarmee de individuen met dit verhoogde risico vroeg in hun ontwikkeling te identificeren. Mogelijk kan dit leiden tot de ontwikkeling van interventies die preventief kunnen worden ingezet. Doel van het onderzoek dat is beschreven in hoofdstuk 5, was het identificeren van specifieke neurocognitieve kenmerken van kwetsbaarheid voor SSD patholo-

gie binnen ASD. Het onderzoek werd met name gericht op het vermogen om controle over het gedrag uit te oefenen (het vermogen tot inhibitie van ongewenst gedrag) en op andere kerndomeinen van executieve functies (mentale flexibiliteit, visuo-motorische controle, afleidingsgevoeligheid en perseverantie). Dit is onderzocht bij 29 adolescenten (in de leeftijd van 10 tot en met 18 jaar) met ASD.

## Onderzoeksbevindingen

### *Sociale uitkomsten: kwaliteit van leven bij ASD*

Resultaten van het onderzoek naar kwaliteit van leven laten zien dat jongvolwassenen met ASD een hoog risico hebben op beperkte QoL. Uit verschillende onderzoeken blijkt dat QoL bedreigd is voor mensen met psychopathologie (e.g., Bastiaansen, Koot, & Ferdinand, 2005; Sawyer et al., 2002), maar de follow-up studie van hoofdstuk 2 impliceert dat er sprake is van een lagere QoL bij volwassenen die in de kindertijd zijn gediagnosticeerd met ASD, dan bij volwassenen die in de kinderleeftijd werden gediagnosticeerd met ADHD, met disruptieve stoornissen en met affectieve stoornissen. In vergelijking met de sociale uitkomsten van volwassenen met ADHD, DISR of AFF stoornissen, bleken relatief veel volwassenen met ASD vrijgezel en relatief weinig volwassenen woonden samen of waren getrouwd. De meeste volwassenen met ASD woonden bij hun ouders, relatief weinig van hen woonden met een partner of een gezin en velen woonden in een instelling of woonvoorziening. Het hoogste opleidingsniveau van de volwassenen met ASD was lager, relatief weinig van hen hadden een betaalde baan en relatief velen hadden een uitkering, in vergelijking met volwassenen met ADHD, DISR of AFF stoornissen. Als de ASD volwassenen medicatie gebruikten, slikten relatief veel van hen antipsychotica. Omdat problemen met sociale adaptatie het onderscheidende criterium is voor ASD in vergelijking met de andere kinderpsychiatrische stoornissen, kan men concluderen dat deze problemen specifiek geassocieerd zijn met de meest beperkte kwaliteit van leven.

Objectieve leefsituaties van de patiënt zijn belangrijk bij het evalueren van QoL, maar ook de subjectieve beleving van hun levensomstandigheden is essentieel, waarbij kan worden opgemerkt dat dit laatstgenoemde aspect in het algemeen nog maar weinig aandacht heeft gekregen in het on-

derzoek naar QoL bij volwassenen met psychiatrische problemen. In het huidige onderzoek bleken de hoog-functionerende volwassenen met ASD minder tevreden over hun kwaliteit van leven dan de volwassenen met ADHD, DISR of AFF stoornissen; ze waren minder tevreden over hun opleiding of werk, over hun partnerrelaties en over hun toekomstperspectief. De volwassenen met ASD waren echter meer tevreden over hun fysieke conditie dan volwassenen met ADHD, DISR of AFF stoornissen. De uitkomsten van de subjectieve QoL betreft het verschil tussen de hoop en verwachtingen van het individu en zijn of haar gerealiseerde omstandigheden. Subjectieve QoL wordt daarmee beïnvloed door een persoonlijk referentiekader. Het is mogelijk dat psychiatrische patiënten in het algemeen lagere standaarden hanteren, als consequentie van gewenning aan aanpassingen in hun levensomstandigheden. Specifiek bij ASD patiënten is het mogelijk dat zij een ander referentiekader hebben dan gebruikelijk (bijvoorbeeld minder behoefte aan sociale interactie) en daarmee is de evaluatie van hun tevredenheid in dit opzicht mogelijk afwijkend. Uiteindelijk bleken volwassenen met ASD echter minder tevreden over verschillende domeinen van QoL dan volwassenen met andere psychiatrische stoornissen en is er dus sprake van relatief meer lijdensdruk.

Bij het onderzoeken van de invloed van opleidingsniveau op QoL bij patiënten met ASD zonder verstandelijke beperking (IQ boven de 70), blijkt er onverwacht geen verschil in subjectieve QoL tussen laag- en hoogopgeleide volwassenen met ASD. Hieruit valt op te maken dat subjectieve QoL niet bepaald wordt door factoren die verband houden met opleidingsniveau. Opleidingsniveau bleek wel van invloed op objectieve sociale uitkomsten bij volwassenen met ASD. Vanwege een gevonden verschil met betrekking tot woon- en werkomstandigheden tussen laag- en hoogopgeleide volwassenen met ASD, werd het vervolgens interessant om te onderzoeken of de verschillen in QoL tussen de psychiatrische patiënten bleven bestaan als hoogopgeleide volwassenen met ASD werden vergeleken met hoogopgeleide volwassenen met ADHD, DISR en AFF stoornissen. Hieruit bleek dat volwassenen met ASD lagere scores van objectieve en subjectieve QoL hadden, ondanks vergelijkbare werkomstandigheden. Dit impliceert dat een hoog opleidingsniveau geen beschermende factor is voor QoL bij ASD.

### *Cognitieve disfuncties in relatie tot leeftijd bij ASD*

Bij het onderzoek naar de relatie tussen leeftijd en intelligentieprofielen bij kinderen en adolescenten met ASD in de leeftijd tussen 6 en 15 jaar, bleek dat de algemene intelligentieniveaus van oudere kinderen (acht jaar en ouder) lager waren dan die van jongere kinderen met ASD (hoofdstuk 3). Hoewel deze bevindingen voorzichtig geïnterpreteerd moeten worden, aangezien het hier gaat om cross-sectionele evidentie, suggereren de resultaten dat er sprake is van een progressieve ontwikkeling van cognitieve problemen bij kinderen met ASD. De leeftijdsverschillen in algemeen intelligentieniveau konden vooral worden toegeschreven aan verschillen in prestaties die horen bij de subtests uit de factor Verwerkingssnelheid. Oudere kinderen (acht jaar en ouder) hadden meer problemen om hun aandacht vast te houden, waren meer afleidbaar of hadden meer grafo-motorische problemen dan de jongere kinderen (zes- en zevenjarigen). Rond de leeftijd van zeven of acht jaar wordt bij normaal ontwikkelende kinderen een versnelde ontwikkeling gezien van executieve functies (EF) (Anderson, 2002). De ontwikkeling van EF zal vooral ongunstig zijn beïnvloed bij ASD door abnormale groeiprocessen in het brein, wegens de relatief late en langer durende periode van rijping van de vermeende onderliggende corticale gebieden (Courchesne & Pierce, 2005). De ogenschijnlijke 'daling' in het intelligentieprofiel met de leeftijd van de kinderen met ASD zou mogelijk verband kunnen houden met het achterblijven van deze ontwikkeling van EF.

Bij het onderzoeken van de sterkte-zwakke profielen bij kinderen met ASD op subtestniveau, bleek bij de oudere kinderen dat de prestaties op de subtest Begrijpen relatief zwakker waren dan de prestaties op de andere subtesten van de factor Verbaal Begrip, in vergelijking met de jongere kinderen (zes- en zevenjarigen). Dit betekent dat leeftijd ook hier een rol speelt; specifieke beperkingen met betrekking tot verbaal begrip en sociaal redeneervaardigheden blijken mogelijk ernstiger te zijn bij oudere kinderen in vergelijking met jongere kinderen met ASD. Dit specifieke leeftijdsverschil ten aanzien van de prestaties op Begrijpen suggereert mogelijk EF problematiek bij oudere kinderen met ASD, omdat afwijkingen in de frontale gebieden van het brein mogelijk onderliggend zijn aan moeite om binnen een sociale context te redeneren (Walker & Bollini, 2002). Rond de leeftijd van 7 jaar nemen vaardigheden in het redeneren en probleem oplossen bij normaal ontwikkelende kinderen toe en kinderen ontwikkelen rond deze leeftijd het vermogen

om in verschillende dimensies te denken (Anderson, 2001). Deze EF zijn nodig bij het sociaal redeneren zoals gemeten met de subtest Begrijpen. Problemen met het aanleren van deze vermogens bij kinderen met ASD kunnen resulteren in afwijkingen van verwachte ontwikkelingspatronen. In tegenstelling tot de karakteristieke problemen met verbaal begrip en sociaal redeneren, hebben kinderen met ASD superieure of relatief intacte abstracte visueel-ruimtelijke vaardigheden, zoals blijkt uit goede prestaties op de subtest Blokpatronen (bijvoorbeeld Asarnow et al., 1987; Happé, 1994; Siegel et al., 1996; Shah & Frith, 1993). Dit patroon werd ook gevonden in het huidige onderzoek, maar leeftijd bleek geen rol te spelen met betrekking tot de abstract visueel-ruimtelijke vaardigheden.

### *Het risico op SSD bij ASD*

Het derde doel van dit proefschrift betreft het ontrafelen van de relatie tussen autismespectrum en schizofrene spectrum trekken bij adolescenten die in de kinderleeftijd gediagnosticeerd zijn met ASD. Hoewel ASD en SSD afzonderlijke classificaties zijn volgens de DSM-IV en beide duidelijk van elkaar te onderscheiden ontwikkelingspaden hebben, laat deze studie een treffende overeenkomst zien van hun klinische fenotypes (hoofdstuk 4). Adolescenten met ASD scoorden hoger op alle dimensies van schizotypie in vergelijking met normaal ontwikkelende adolescenten. Naast hoge niveaus van negatieve symptomen (zoals beperkt affect en sociale angst), lieten de adolescenten met ASD tevens hoge niveaus van positieve symptomen (zoals denkstoornissen en buitengewone percepties) en gedesorgeriseerde symptomen (zoals vreemde spraak en opvallend gedrag) zien. De gevonden overlap tussen autistische trekken en schizotypische symptomen toont overeenkomsten met de visie van Bleuler (1911) en komt overeen met bevindingen van studies naar de correspondentie tussen beide spectrum stoornissen (Hurst et al., 2007; Konstantareas & Hewitt, 2001; Sheitman et al., 2004).

De huidige bevindingen suggereren dat de gedragsmatige overeenkomst niet beperkt blijft tot negatieve schizotypische symptomen, maar dat er tevens sprake is van overlap tussen autistische symptomen en gedesorgeriseerd gedrag en positieve symptomen. Deze resultaten zijn consistent met bevindingen van andere studies die deze verhoogde mate van schizotypische symptomen vonden bij individuen met ASD (Blackshaw, 2001; Dykens, 1991; Graig et al., 2004; Rumsey et al., 1986). Er dient te worden opgemerkt dat

vooral problemen met het verdelen van aandacht en communicatieproblemen, behorend bij autistische symptomen, het sterkst geassocieerd waren met de schizotypische symptomen. Ernstige communicatieproblemen waren geassocieerd met een hoger niveau van negatieve en desorganisatie symptomen. De problemen met het verdelen van aandacht bij ASD vallen vooral op omdat deze gerelateerd blijken te zijn met alle dimensies van schizotypie. Dit suggereert dat problemen in de controle van de aandachtfuncties mogelijk ten grondslag liggen aan een breed scala aan schizotypische gedragingen. Nader onderzoek was nodig om de onderliggende cognitieve mechanismen te onderzoeken die bijdragen aan SSD bij ASD.

#### *Onderliggende neurocognitieve mechanismen voor de kwetsbaarheid voor SSD bij ASD*

In verband met het verhoogde risico op SSD bij ASD is het van belang om indicatoren te vinden voor dit risico. Het vierde doel van dit proefschrift was het beantwoorden van de vraag of problemen met cognitieve controle bijdragen aan SSD symptomen bij adolescenten die gediagnosticeerd zijn met ASD op de kindereleeftijd (hoofdstuk 5). Er bleek sprake van veel SSD kenmerken bij de adolescenten met ASD en aanzienlijke problemen met cognitieve controle; er werden problemen gevonden met het inhiberen van een voor de hand liggende, geautomatiseerde, respons (zogenaamde prepotente respons) ten gunste van de gewenste reactie; problemen met mentale flexibiliteit; moeite met visuo-motorische controle waarbij aansturing van hogere cognitieve functies wordt vereist; en van afleidingsgevoeligheid. Alleen problemen met de responsinhibitie bleken geassocieerd met de schizotypische symptomen bij ASD, terwijl er geen verband gevonden werd tussen cognitieve controle en ASD symptomen. De specificiteit van deze uitkomst werd benadrukt door de bevinding dat de adolescenten met ASD niet meer afweken van de normaal ontwikkelende adolescenten met betrekking tot responsinhibitie, na het controleren voor het effect van de schizotypische symptomen. Dit betekent dat problemen met responsinhibitie bij ASD vooral samenhangen met de aanwezigheid van schizotypische symptomen (en niet worden verklaard door de autisme symptomen), hetgeen suggereert dat problemen met responsinhibitie mogelijk een aanwijzing is voor de kwetsbaarheid voor de ontwikkeling van SSD symptomen bij ASD.

Het is belangrijk om co-morbiditeit te onderzoeken bij ASD omdat

de aanwezigheid van inhibitieproblemen samenhangt met de aanwezigheid van schizotypische symptomen binnen ASD. Tegenstrijdige bevindingen in het wetenschappelijk onderzoek met betrekking tot inhibitie bij ASD zijn mogelijk het gevolg van onvoldoende rekening houden met deze co-morbiditeit (Kenworthy et al., 2008). Meta-analysestudies naar onderzoeken rondom inhibitiefuncties rapporteren een gebrekkige responsinhibitie bij ASD (e.g., Hill 2004a), zoals we ook hebben gevonden binnen dit onderzoek. Op basis van de bevindingen van deze thesis willen we benadrukken dat responsinhibitie problemen bij een individu met ASD mogelijk een hoger risico inhouden op het ontwikkelen van SSD symptomen. Overeenkomstig met deze conclusie hebben ook andere onderzoekers inhibitieproblemen gerelateerd aan schizotypische trekken bij andere stoornissen die geassocieerd worden met de kwetsbaarheid voor SSD pathologie (Van Rijn, Aleman, De Sonneville, & Swaab, 2009).

Met betrekking tot de relaties tussen specifieke EF problemen en verschillende dimensies van schizotypie, blijkt dat responsinhibitie problemen verband houden met gedesorganiseerd gedrag en positieve symptomen. Deze resultaten onderschrijven de bevindingen van de meta-analyse van Dibben et al. (2009) waarbij inhibitieproblemen werden geassocieerd met gedesorganiseerd gedrag. De bevindingen van Dibben werden echter gevonden bij volwassenen met schizofrenie, terwijl onze bevindingen aangeven dat problemen met responsinhibitie tijdens de adolescentie verband houden met schizotypische symptomen binnen ASD.

#### **Algemene conclusie, klinische implicaties en aanwijzingen voor toekomstig onderzoek**

Om beter te kunnen begrijpen hoe kinderen met ASD zich ontwikkelen en om meer inzicht te krijgen in de consequenties van problemen met adaptief gedrag in sociale situaties, kenmerkend voor ASD, zijn de lange termijn uitkomsten van ASD geëvalueerd door het onderzoeken van de kwaliteit van leven bij jong volwassenen die op kindereleeftijd zijn gediagnosticeerd met een autismespectrumstoornis (hoofdstuk 2). Hoewel verschillende studies hebben aangetoond dat er sprake is van relatief slechte uitkomsten bij psychopathologie, bleek uit dit onderzoek dat kwaliteit van leven meer bedreigd is bij jong volwassenen die gediagnosticeerd zijn met ASD op de kindereleeftijd, verge-



leken met volwassenen die gediagnosticeerd zijn met andere psychiatrische stoornissen op de kinderleeftijd. Zelfs als alleen de hoogopgeleide volwassenen met ASD werden vergeleken met hoogopgeleide volwassenen met andere kinderpsychiatrische stoornissen, bleek dat de volwassenen met ASD het grootste risico hadden op een beperkte QoL.

Dit was het eerste onderzoek dat de langetermijn effecten (follow-up periode van bijna 14 jaar) van ASD voor de kwaliteit van leven bij volwassenen in kaart bracht, met drie op leeftijd gematchte vergelijkingsgroepen bestaande uit volwassenen met de andere belangrijke kinderpsychiatrische stoornissen. Een belangrijke kracht van dit onderzoek is de exclusie van onderlinge co-morbiditeit van de drie psychiatrische controlegroepen, waardoor er pure vergelijkingsgroepen ontstonden. Naast een onderscheid naar diagnose is er nader onderzoek nodig om de relaties tussen QoL en andere factoren te begrijpen, zoals bijvoorbeeld onderzoek naar de invloed van de ernst van problematiek, naar het vermogen om sociale vaardigheden in te kunnen zetten en naar het al dan niet hebben van sociale netwerken. Dit onderzoek is de eerste stap in het belichten van beperkte kwaliteit van leven binnen ASD, de volgende stap zou het onderzoek kunnen zijn naar de factoren die leiden tot deze uitkomsten.

Vanuit een klinisch oogpunt zijn deze bevindingen zeker relevant. Ouders van kinderen met ASD hebben accurate informatie nodig met betrekking tot de prognose van de problemen waar hun kinderen tegen aanlopen tijdens de ontwikkeling (Kisler & McConachie, 2010). Op basis van onze bevindingen zijn we beter in staat te informeren over de specifieke consequenties van ASD voor het dagelijks functioneren van kinderen met ASD in de volwassenheid. Gedurende de ontwikkeling worden de consequenties voor het functioneren duidelijker en meer voelbaar aangezien de eisen die gesteld worden met betrekking tot onafhankelijk functioneren met de leeftijd toenemen. Een zorgvuldig beeld van de prognose voor een kind heeft verschillende voordelen (Goin-Kochel, Peters & Treadwell-Deering, 2008), zoals het ontwikkelen van realistische verwachtingen over het aangaan van relaties en prestaties van het kind en het stellen van meer haalbare doelen van interventies en therapieën. Kinderen met ASD hebben over het algemeen meer ondersteuning nodig bij het functioneren in het dagelijks leven en ze hebben meer hulp nodig om zich staande te houden in onze samenleving dan anderen in verschillende fasen van hun ontwikkeling. Dit onderstreept het belang van behandeling die

gericht is op de bevordering van de sociale vaardigheden of het aanpassen van de omgeving aan de behoeften van deze kinderen, waarmee hun QoL en beleving van hun levensomstandigheden mogelijk verbeterd worden. Deze behandeling of ondersteuning omvat verschillende vormen van begeleiding, of speciaal gecreëerde omgevingen en sociale regelingen. Het verzorgen van deze vormen van ondersteuning is een belangrijk doel van zorgprogramma's binnen de geestelijke gezondheidszorg. Het concept QoL is in toenemende mate meer centraal komen te staan bij de ontwikkeling van zorgbeleid, waarbij het tevens kan worden gebruikt ter evaluatie van de efficiëntie en effectiviteit van de behandelingen ten aanzien van levensstijl van de patiënten (Schalock, 2004).

Het onderzoek beschreven in hoofdstuk 3 betreft het niveau van de cognitieve ontwikkeling door het vaststellen van intelligentieprofielen bij 6 tot 15 jarige kinderen en adolescenten met ASD, waarbij tevens de rol van leeftijd werd onderzocht. De bevindingen van dit cross-sectionele onderzoek wijzen uit dat oudere kinderen met ASD een ongunstiger profiel hebben dan jongere kinderen. Het is dus van belang om rekening te houden met de leeftijd bij het in kaart brengen van cognitieve vaardigheden. Kinderen met ASD laten verschillende problemen zien op verschillende leeftijden, er dient rekening gehouden te worden met afwijkingen in de hiërarchische ontwikkeling van hun cognitieve vermogens. Longitudinale studies zijn nodig om te onderzoeken of er daadwerkelijk sprake is van progressieve beperkingen bij kinderen met ASD gedurende hun ontwikkeling, zoals naar voren komt in intelligentieprofielen. Voor klinici en ouders betekent dit dat het cognitief functioneren regelmatig geëvalueerd dient te worden tijdens de ontwikkeling, om zo de verwachtingen van en de ondersteuning voor kinderen met ASD op realistische wijze bij te kunnen stellen.

In de zoektocht naar de factoren die bepalend zijn voor de uitkomsten op lange termijn is specifiek aandacht besteed aan de risico's voor SSD bij ASD (hoofdstuk 4). Andere studies verschaften wetenschappelijke onderbouwing voor overeenkomst in diagnostische criteria van de twee spectrumstoornissen. Het huidige onderzoek voegt daaraan toe dat de overlap in gedragskenmerken niet beperkt blijft tot negatieve schizotypische symptomen, maar zich uitstrekt naar positieve schizotypische symptomen en gedesorganiseerd

gedrag. Enigszins speculatief kan geredeneerd worden dat, als hoge niveaus van schizotypie een hoog risico op het ontwikkelen van schizofrenie indiceren (Mata et al., 2000; Miller et al., 2002; Vollema et al., 2002), het significante verband tussen autistische symptomen en positieve symptomen of gedesorganiseerd gedrag bij ASD een verhoogd risico op SSD impliceert bij deze adolescenten. De implicaties die voortkomen uit de prognostische waarde van specifieke autistische trekken voor de ontwikkeling van schizofrenie in de volwassenheid moet verder worden onderzocht in longitudinale studies.

De bevindingen van deze studie passen in de voortdurende discussie over de veronderstelde relatie tussen ASD en SSD. Classificatiesystemen, zoals de DSM-IV, doen geen uitspraken over de onderliggende etiologie van de stoornissen. Het is echter heel waarschijnlijk dat psychiatrische stoornissen zich op verschillende leeftijden klinisch anders presenteren, als manifestaties van dezelfde onderliggende stoornis. Het idee van leeftijdsafhankelijke manifestaties van psychopathologische symptomen zal dan ook meer in ogenschouw genomen moeten worden bij de discussie over de co-morbide ontwikkeling van psychiatrische stoornissen en de mogelijke oorzaken naar de ontstaansgeschiedenis (Hollis, 2001). In aanvulling op het gebruik van een dichotoom categoriaal classificatiesysteem waarin een individu wel of niet voldoet aan de optelsom van criteria, zou het gebruik van een dimensionaal systeem kunnen helpen, waarin een individu op verschillende niveaus op een continue schaal symptomen kan hebben. De mate waarin een kind of adolescent met ASD een verhoogd niveau van autistische trekken, maar ook een verhoogd niveau van schizotypische trekken laat zien, zoals een grote mate van instabiliteit van functioneren, problemen met affect regulatie en hoge niveaus van angst, kan bijdragen aan het herkennen van het risico op schizotypische kenmerken.

In hoofdstuk 5 is het onderzoek beschreven dat als doel had om in beeld te brengen welke problemen met cognitieve controle mogelijk kunnen bijdragen aan het verhoogde risico op SSD symptomen bij ASD. Problemen met responsinhibitie bleken sterk en specifiek samen te hangen met schizotypische symptomen bij adolescenten met ASD, vooral met positieve en gedesorganiseerde symptomen. Problemen met responsinhibitie zijn dus mogelijke aanwijzingen voor de kwetsbaarheid voor de ontwikkeling van SSD symptomen bij ASD tijdens de adolescentie. In hoeverre respons inhibitieproblemen bij

ASD daadwerkelijk voorspellers zijn voor psychotische stoornissen zal moeten blijken uit een follow-up onderzoek. In toekomstig onderzoek zal rekening gehouden moeten worden met ontwikkelingsaspecten omdat de SSD symptomen bij ASD zich op verschillende leeftijden anders kunnen manifesteren door de ontwikkelingsmijlpalen van responsinhibitie.

De bevindingen van dit onderzoek impliceren dat klinici alert moeten zijn op inhibitieproblemen bij adolescenten met ASD, want dit kan samenhangen met het risico op schizofrene pathologie later in hun leven. De inhibitieproblemen zijn mogelijk de onderliggende mechanismen voor problemen met het reguleren van gedachten en gevoelens bij deze adolescenten.

#### *Methodologische aspecten*

Om de bevindingen van dit proefschrift goed op waarde te kunnen schatten moet er rekening gehouden worden met de volgende beperkingen van de studies. Het samenstellen van de ASD steekproef besloeg een lange periode van 1984 tot 2005. Pas in 2003 zijn er in Nederland gestandaardiseerde interview procedures ontwikkeld om ASD vast te stellen (bijvoorbeeld de Autism Diagnostic Interview; ADI). Deze instrumenten werden niet gebruikt in het eerste en tweede onderzoek om de ASD diagnoses te bevestigen. In de laatste twee onderzoeken zijn de ASD diagnoses in de kinderleeftijd wel gevalideerd door de ADI tijdens de adolescentie. Vervolgens beperkt de exclusie van verstandelijk beperkte ASD patiënten in de eerste studie en de inclusie van hoog-functionerende ASD groepen in de drie laatste studies de representativiteit van de steekproeven en daarmee samenhangend, wordt de generaliseerbaarheid van de bevindingen begrensd. Tenslotte wordt de informatie uit de vragenlijsten in de eerste, derde en vierde studie beïnvloedt door beperkingen die inherent zijn aan zelfevaluatie. Dit geldt in het bijzonder voor adolescenten en volwassenen met ASD, die mogelijk moeite hebben om op hun eigen gedrag te reflecteren.

#### **Samenvatting**

Naar aanleiding van de vier onderzoeksvragen van dit proefschrift, kunnen de volgende conclusies worden getrokken:

Opgroeïende kinderen met ASD hebben een specifiek risico op beperkte

kwaliteit van leven op volwassen leeftijd, ook in vergelijking met kinderen met andere psychiatrische stoornissen, zelfs wanneer het intelligentie- en opleidingsniveau relatief hoog ligt. Ten tweede blijkt dat kinderen en adolescenten met ASD verschillend presteren op specifieke domeinen van intelligentie op verschillende leeftijden, hetgeen lijkt te wijzen op een progressieve impact van de stoornis. Daarom wordt herhaalde evaluatie van cognitieve en uitvoerende functies bij kinderen en adolescenten met ASD aanbevolen gedurende hun ontwikkeling. Ten derde, kinderen met ASD hebben een verhoogd risico op SSD symptomen in hun adolescentiefase, o.a. negatieve schizotypische symptomen maar ook gedesororganiseerd gedrag en positieve symptomen, hetgeen mogelijk wijst op een verhoogd risico op problematiek in het spectrum van schizofrene stoornissen. Deze symptomen zijn gerelateerd aan problemen in de cognitieve inhibitie. Ouders, leerkrachten en medici dienen alert te zijn op inhibitieproblemen bij adolescenten met ASD omdat deze problemen mogelijk een verhoogd risico voorspellen met betrekking tot het ontwikkelen van schizofrene spectrum pathologie op latere leeftijd.

## Referenties

- Anderson, P. (2002). Assessment and development of executive function (EF) during childhood. *Child Neuropsychology, 8* (2) 71-82.
- Anderson, V., Northam, E., Hendy, J., & Wrennall, J. (2001). *Developmental neuropsychology, a clinical approach*. Hove: Psychology Press Ltd.
- Asarnow, R.F., Tanguay, P.E., Bott, L., Freeman, B.J. (1987). Patterns of intellectual functioning in non-retarded autistic and schizophrenic children. *Journal of Child Psychology and Psychiatry, 28* (2) 273-280.
- Bastiaansen, D., Koot, H.M., Ferdinand, R.F., Verhulst, F.C. (2004). Quality of life in children with psychiatric disorders: self, parent, and clinician report. *Journal of American Academy Child Adolescent Psychiatry, 43*, 221-30.
- Blackshaw, A.J., Kinderman, P., Hare, D.J., Hatton, C. (2001). Theory of mind, causal attribution and paranoia in asperger syndrome. *Autism 5* (2) 147-163.
- Bleuler, E. (1911). *Dementia Praecox oder Gruppe der Schizophrenien*, in: Van Aschaffenburg, G. (Ed.), *Handbuch der Psychiatrie*. Duticke, Leipzig.
- Courchesne, E. & Pierce, K. (2005). Brain overgrowth in autism during a critical time in development: implications for frontal pyramidal neuron and interneuron development and connectivity. *International Journal of Developmental Neuroscience, 23*, 153-170.
- Craig, J.S., Hatton, G., Craig, F.B., Bentall, R.P. (2004). Persecutory beliefs, attributions and theory of mind: comparison of patients with paranoid delusions, asperger's syndrome and healthy controls. *Schizophrenia Research, 69* (1) 29-33.
- Dibben, C.R.M., Rice, C., Laws, K., & McKenna, P.J. (2009). Is executive impairment associated with schizophrenic syndromes? A meta-analysis. *Psychological Medicine, 39* (3) 381-392.
- Dykens, E., Volkmar, F., Glick, M. (1991). Thought disorder in high-functioning autistic adults. *Journal of Autism and Developmental Disorders, 21* (3) 291-301.
- Goin-Kochel, R.P., Peters, S.U., Treadwell-Deering, D. (2008). Parental reports on the prevalence of co-occurring intellectual disability among children with autism spectrum disorders. *Research in Autism Spectrum Disorders, 2* (3) 546-556.
- Happé, F. G. (1994). Wechsler IQ profile and theory of mind in autism: a research note. *Journal of Child Psychology and Psychiatry, 35*, 1461-1471.
- Hill, E.L. (2004). Executive dysfunction in autism. *Trends in Cognitive Sciences, 8* (1) 26-32.
- Hollis, C. (2001). *Diagnosis and differential diagnosis*. In: Remschmidt, H. (Ed). *Schizophrenia in children and adolescents*. Cambridge: University Press.
- Hurst, R.M., Nelson-Gray, R.O., Mitchell, J.T., Kwapil, T.R. (2007). The relationship of Asperger's characteristics and schizotypal personality traits in a non-clinical adult sample. *Journal of Autism and Developmental Disorders, 37* (9) 1711-1720.
- Kenworthy, L., Yerys, B.E., Anthony, L.G., & Wallace, G.L. (2008). Understanding executive control in autism spectrum disorders in the lab and in the real world. *Neuropsychology Review, 18*, (4) 320-338.
- Kim-Cohen, J., Caspi, A., Moffitt, T.E., Harrington, H., Milne, B.J., Poulton, R. (2003). Prior juvenile diagnoses in adults with mental disorder: developmental follow-up of a prospective-longitudinal cohort. *Archives of General Psychiatry, 60*, 709-717.
- Kisler, J., & McConachie, H. (2010). Parental reaction to disability. *Paediatrics and Child Health, 20* (7) 309-314.
- Konstantareas, M.M., Hewitt, T., 2001. Autistic disorder and schizophrenia: Diagnostic overlaps. *Journal of Autism and Developmental Disorders, 31* (1) 19-28.
- Mata, I., Sham, P.C., Gilvarry, C.M., Jones, P.B., Lewis, S.W., Murray, R.M. (2000). Childhood schizotypy and positive symptoms in schizophrenic patients predict schizotypy in relatives. *Schizophrenia Research, 44* (2) 129-136.
- Miller, P., Byrne, M., Hodges, A., Lawrie, S.M., Owens, D.G., Johnston, E.C. (2002). Schizotypal components in people at high risk of developing schizophrenia: Early findings from the Edinburgh high-risk study. *British Journal of Psychiatry, 180*, 179-184.
- Rumsey, J.M., Andreasen, N.C., Rapoport, J.L. (1986). Thought, language, communication, and affective flattening in autistic adults. *Archives of General Psychiatry, 43* (8) 771-777.
- Sawyer, M.G., Whaites, L., Rey, J.M., Hazell, P.L., Graetz, B.W., Baghurst, P. (2002). Health-related quality of life of children and adolescents with mental disorders. *Journal of Academic of Child Adolescent Psychiatry, 41*, 530-37.
- Schalock, R.L. (2004). The concept of quality of life: what we know and do not know. *Journal of Intellectual Disability Research, 48* (3) 203-216.
- Shah, A., Frith, U. (1993). Why do autistic individuals show superior performance on the block design task? *Journal of Child Psychology and Psychiatry, 34* (8) 1351-1364.
- Siegel, D. J., Minshew, N. J., & Goldstein, G. (1996). Wechsler IQ profiles in diagnosis of high-functioning autism. *Journal of Autism and Developmental Disorders, 26*, 389-406.
- Sheitman, B.B., Bodfish, J.W., Carmel, H. (2004). Are the negative symptoms of schizophrenia consistent with an autistic spectrum illness? *Schizophrenia Research, 69* (1) 119-120.
- 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*, 1474-1484.
- Swaab, H. (2013). *Pervasieve ontwikkelingsstoornissen [pervasive developmental disorders]*. In: Basisboek Psychopathologie, I. Franken, P. Muris, & D. Denys (ed). Chapter 4, pag. 62-74. Utrecht: De tijdstroom.

Van der Gaag, R.J., Caplan, R., Van Engeland, H., Loman, F., Buitelaar, J.K. (2005). A controlled study of formal thought disorder in children with autism and multiple complex developmental disorders. *Journal of Child Adolescent Psychopharmacology*, 15(3) 465-476.

Van Rijn, S. (2011). *Emotie en sociale cognitie [emotion and social cognition]*. In: klinische kinderneuropsychologie, H. Swaab, A. Bouma, J. Hendriksen, C. Konig (ed). Chapter 8, pag. 189-211.

Van Rijn, S., Aleman, A., De Sonneville, L., & Swaab, H. (2009). Cognitive mechanisms underlying disorganization of thought in a genetic syndrome (47,XXY). *Schizophrenia Research*, 112, 91-98.

Vollema, M.G., Sitskoorn, M.M., Appels, M.C., Kahn, R.S. (2002). Does the schizotypal personality questionnaire reflect the biological-genetic vulnerability to schizophrenia? *Schizophrenia Research*, 54 (1-2) 39-45.

Walker, E., & Bollini, A.M. (2002). Pubertal neurodevelopment and the emergence of psychotic symptoms. *Schizophrenia Research*, 54 (1) 17-23

## Curriculum Vitae

Petra Suzanne Barneveld werd geboren op 30 september 1980 te Oud Zuilen. Na het behalen van haar HAVO diploma op het Niftarlake College te Maarssen in 1997, heeft zij in 2001 de opleiding 'Personeel en Arbeid' aan de Hogeschool van Utrecht afgerond. In 2004 begon zij aan de studie Psychologie aan de Universiteit Leiden. Sinds 2004 is ze werkzaam bij Psychologie Praktijk Oud Zuilen, de zelfstandig gevestigde praktijk van prof. dr. Hanna Swaab. Petra is daar actief in de patiëntzorg aan kinderen, adolescenten en hun ouders waarbij zorgen bestaan over de cognitieve ontwikkeling, het didactisch functioneren en de sociaal-emotionele ontwikkeling. De relaties tussen emotionele en gedragsmatige problemen en neurocognitieve disfuncties die het gevolg zijn van verstoringen in de ontwikkeling van het brein, staan daarbij centraal. Petra Barneveld studeerde in 2008 Cum Laude af in de Klinische Neuropsychologie aan de Universiteit Leiden. Zij schreef de masterscriptie getiteld 'Executive functioning in 6-to-10-year-old children with Intrauterine Growth Restriction (IUGR) and influence of COMT-gen polymorphism'. Voor deze scriptie heeft de Nederlandse Vereniging voor Neuropsychologie de prestigieuze scriptieprijs 2007/2008 aan haar toegekend. Deze prijs wordt jaarlijks uitgereikt ter stimulering en als blijk van waardering voor jonge onderzoekers op het gebied van de neuropsychologie. In 2009 begon zij aan haar promotieonderzoek aan de Universiteit Leiden, afdeling Orthopedagogiek, onder begeleiding van prof. dr. Hanna Swaab, prof. dr. Herman van Engeland en dr. Leo de Sonneville. De resultaten van dit onderzoek zijn beschreven in dit proefschrift. Sinds 2012 volgt Petra Barneveld naast haar traject als promovendus, de opleiding tot GZ-psycholoog en orthopedagoog-generalist en is ze werkzaam op het Ambulatorium, onderdeel van de Faculteit der Sociale Wetenschappen van de Universiteit Leiden. De klinische activiteiten bestaan uit diagnostiek en behandeling van kinderen en jongeren met vragen omtrent de ontwikkeling of in de opvoeding.

Petra Suzanne Barneveld was born on September 30 of 1980 in Oud Zuilen, The Netherlands. After completing her secondary education in 1997 at the Niftarlake College in Maarssen, The Netherlands, she graduated from Human Resources Management in 2001. In 2004 she started her Bachelor in psychology at Leiden University and, in addition, she started working at Psychological Practice Oud Zuilen (Psychologie Praktijk Oud Zuilen) under the supervision of prof. dr. Hanna Swaab. Petra Barneveld's work for PPOZ is aimed at helping parents who have concerns about their children. These concerns can be about their cognitive development, their functioning at school, and their social and emotional development. Her work is focused on dysfunctional brain-behaviour interactions that may lead to developmental psychopathology and result in social dysfunctioning and cognitive and emotional problems. Petra Barneveld obtained her master's degree in Clinical Neuropsychology Cum Laude in 2008 for which she wrote the master's thesis 'Executive functioning in 6-to-10-year-old children with Intrauterine Growth Restriction (IUGR) and influence of COMT-gen polymorphism'. For this thesis she received the NVN Thesis Award 2007/2008 from the Netherlands Society for Neuropsychology. This prestigious award is given annually to a young researcher as a token of appreciation and stimulation. In 2009 she started her PhD project at the department of Clinical Child and Adolescent Studies at Leiden University. This project, supervised by prof. dr. Hanna Swaab, prof. dr. Herman van Engeland, and dr. Leo de Sonnevile, resulted in the present dissertation. During her work as a PhD candidate, she also has been working as a psychologist in training to become a registered Healthcare Psychologist (GZ-Psycholoog) at the University Outpatient Department (Ambulatorium), which is part of the Faculty of Social and Behavioural Sciences at Leiden University.

## Dankwoord

Dit promotieavontuur zit er bijna op. Omdat dit onderzoek een follow-up studie betreft heb ik kunnen werken met onderzoeksdata die ver teruggaan in de tijd. Achter het grote databestand gaat veel zorg schuil van klinici en wetenschappers voor alle deelnemers aan dit onderzoek. Daarom wil ik graag mijn dank uitspreken voor de medewerking en ondersteuning die ik gekregen heb bij de totstandkoming van dit proefschrift.

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## List of publications

Barneveld, P.S., Pieterse, J., De Sonnevile, L., Van Rijn, S., Lahuis, B., Van Engeland, H., & Swaab, H. (2011). Overlap of autistic and schizotypal traits in adolescents with Autism Spectrum Disorders. *Schizophrenia Research*, 126 (1-3) 231-236

Barneveld, P.S., De Sonnevile, L., Van Rijn, S., Van Engeland, H., & Swaab, H. (2013). Impaired response inhibition in autism spectrum disorders, a marker of vulnerability to schizophrenia spectrum disorders? *Journal of International Neuropsychological Society*, 19, 1-10

Barneveld, P.S., Swaab, H., Fagel, S., Van Engeland, H., & De Sonnevile, L.M.J. (in press). Quality of Life: a case-controlled long-term follow-up study, comparing young high-functioning adults with autism spectrum disorders with adults with other psychiatric disorders diagnosed in childhood. *Comprehensive Psychiatry*.

## Abstracts

Barneveld, P.S., De Sonnevle, L., Van Rijn, S., Lahuis, B., Van Engeland, H., & Swaab, H. (2013). Deficits in Executive functioning in adolescents with Autism Spectrum Disorders: markers of vulnerability to develop Schizotypal symptomatology? International Neuropsychological Society (INS), Amsterdam, The Netherlands.

Swaab, H., Barneveld, P.S., Fagel, S., Van Engeland, H., & De Sonnevle, L.M.J. (2013). Compromised Quality of Life in Autism Spectrum Disorders. A case-controlled long-term follow-up study, comparing young high-functioning adults with autism spectrum disorders with adults with other psychiatric disorders diagnosed in childhood. International Society for Autism Research (INSAR), San Sebastian, Spain

Barneveld, P.S., De Sonnevle, L., Pieterse, J., van Rijn, S., Lahuis, B., Van Engeland, H., & Swaab, H. (2011). Deficits in executive functioning in adolescents with autism spectrum disorder: predicting psychosis? European Society of Child & Adolescent Psychiatry (ESCAP), Helsinki, Finland

Barneveld, P.S., De Sonnevle, L., Pieterse, J., Van Rijn, S., Lahuis, B., Van Engeland, H., & Swaab, H. (2010). Deficits in executive functioning and schizotypal traits in adolescents with autism spectrum disorder, predicting psychosis? Federation of the European Societies of Neuropsychology (ENS), Amsterdam, The Netherlands





