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

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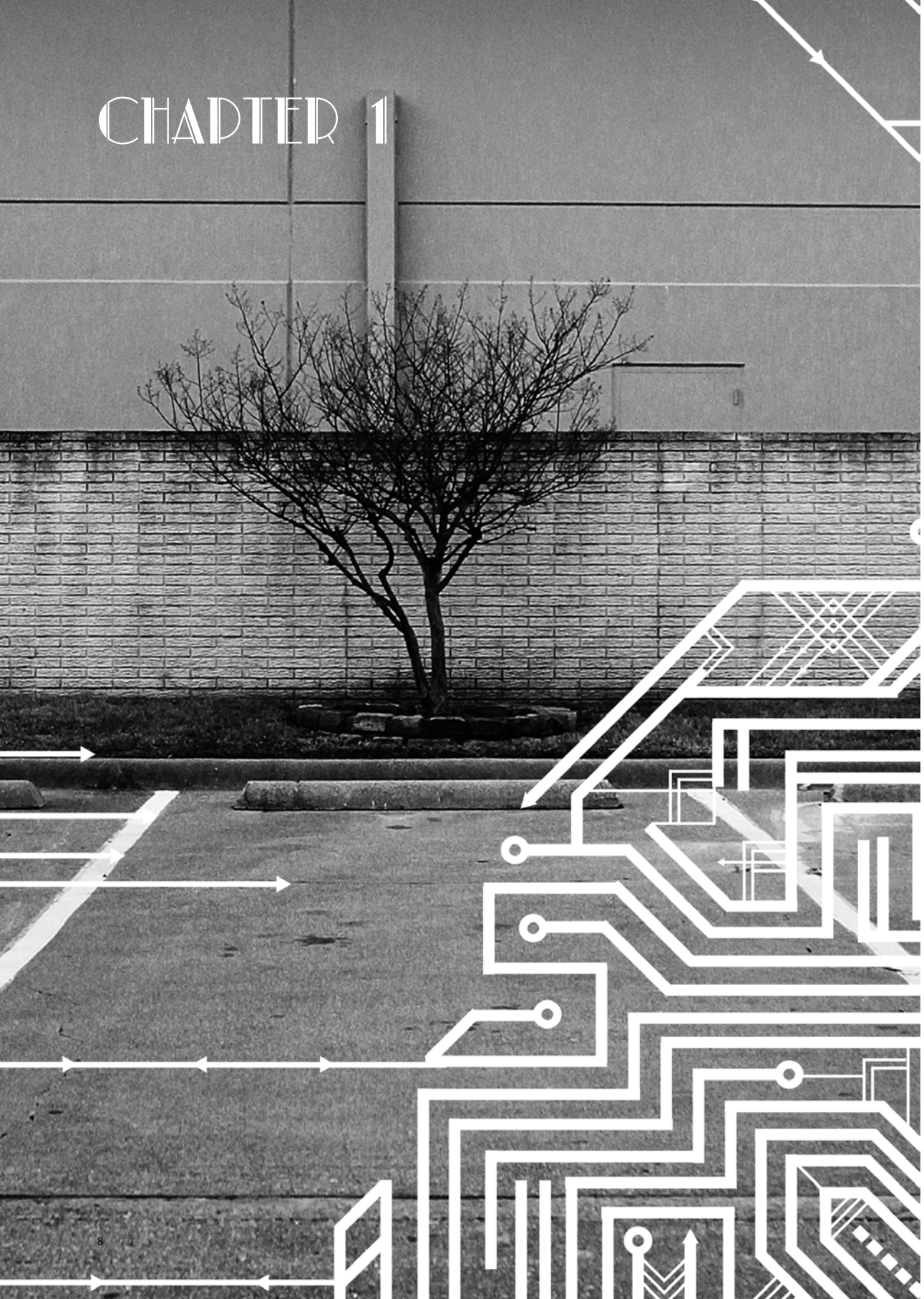




# General introduction

## 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 informaton 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 de 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 (Happe, 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 schizophrenia 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 complex 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.

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