# Childhood psychopathology and development of adult schizotypal symptoms

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# Chapter 1

# General introduction

It goes without saying that the identification of early mechanisms of developmental risk for serious psychopathology in adulthood is important. This follow-up study from childhood into adulthood focuses on the relation of behavioral and emotional problems and its underlying mechanisms in childhood and adolescence and the development of adult schizotypal symptomatology.

The idea to study developmental indicators of milder forms of schizophrenia spectrum pathology, i.e., schizotypal symptomatology, follows from the legacy of two important psychiatrists, i.e., Karl Ludwig Kahlbaum (1828-1899) and Emil Kraepelin (1856-1926). Kahlbaum stated a century ago that 'snapshot' observations of patients' symptoms could be misleading because the presentation of an illness may vary in time (Hoenig, 1995). A few decades later, Kraepelin argued that 'symptoms change with time and patients should therefore be observed throughout their lifetimes' (Hoenig, 1995) to further understand mechanisms of developmental psychopathology. In addition, the majority of individuals with classifications within the schizophrenia spectrum does not show a disorder at the extreme end of the schizophrenia spectrum but manifests a host of schizophrenia-like, but non-psychotic, abnormalities (Raine, 1991; Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Tsuang, Stone, Tarbox, & Faraone, 2002), i.e., schizotypal symptoms. This makes the investigation of juvenile indicators of adult schizotypal symptoms a valid and noteworthy area of exploration with strong implications for clinical practice and research. However, the population presenting with schizotypal symptoms is clearly understudied. Studies so far have only intensively investigated developmental origins of disorders at the extreme end of the schizophrenia spectrum, i.e., schizophrenia and psychosis. Further, schizophrenia spectrum pathology is a very heterogeneous condition with a variety of diagnostic criteria and definitions (Kendell, 1987; Pfol & Andreasen, 1986). It is therefore difficult to ascertain how precursors that have been associated with the development of schizophrenia spectrum disorders relate

to different symptoms within the schizophrenia spectrum. One approach that might advance insight into the mechanisms that facilitate the development of schizophrenia spectrum pathology is to focus on more homogeneous symptoms within the spectrum. The aim of the present thesis is therefore to investigate how developmental precursors in childhood and adolescence, with specific focus on behavioral and cognitive precursors, relate to (dimensions of) schizotypal symptomatology in adult life.

## Schizophrenia spectrum pathology

The concept of the schizophrenia spectrum can be traced back to Bleuler and his book 'Dementia Praecox or the Group of Schizophrenias' (Bleuler, 1911). With 'Group of Schizophrenias' he refers to the notion that schizophrenia spectrum pathology might well be heterogeneous and composed of multiple disorders with different signs and symptoms, disease course, and outcome. The definition of schizophrenia spectrum pathology has since been refined and is now known as a syndrome characterized by (1) distortions of cognitive and perceptual reality, collectively known as positive symptoms, (2) interpersonal withdrawal (negative symptoms), and (3) disorganized speech and behavior (disorganized symptoms), that might share a similar disease mechanism and aetiology (Matheson & Langdon, 2008). However, what distinguishes the conditions within the schizophrenia spectrum is the gradient of dysfunction, ranging from a milder (non-clinical) form of schizotypy to conditions at the extreme end of the spectrum, such as schizophrenia and psychosis.

Due to this variety in expression and dependent on how schizophrenia spectrum pathology is defined by different studies, prevalence rates vary between .5% (Jablensky & Kalaydjieva, 2003) for schizophrenia and about 2% for milder forms within the spectrum and related impairments such as schizophrenia personality disorder (Raine, 2006). Disorders within the schizophrenia spectrum are a major problem for subjects, their families, and society. These disorders are a lifelong serious condition that strikes individuals early in life (late teens to early 20s; Kessler et al., 2007) and have a very serious impact on many aspects of life. It can lead to a life with frequent hospitalization (i.e., more than 50% of all schizophrenic patients needs to be hospitalized during their first psychotic episode and 17% needs hospitalization during the first year of treatment; Whitehorn, Richard, & Kopala, 2004), suicide attempts (approximately 5% of schizophrenic patients will die of suicide; Inskip, Harris, & Barraclough, 1998; Palmer, Pankratz, & Bostwick, 2005), self harm (estimates ranging between 30% and 50%; Breier

et al., 1991; Harkavy-Friedman et al., 1999), aggression to others (14%; Foley et al., 2005; Proctor, Mitford, & Paxton, 2004), and to severe functional impairments across a broad range of domains in daily life, such as persistent social disability (Wiersma et al., 2000). Schizotypal symptoms are considered to be milder than symptoms in schizophrenia. Nevertheless, they can have a very profound effect on a subject's Quality of Life, with a high risk for substantial impairments across a broad range of domains, such as academic and social functioning, and with impact on occupational functioning (Cohen & Davis, 2009; Chapman et al., 1994; Gooding, Tallent, & Matts, 2005; Kwapil, 1998). Moreover, schizotypal symptoms might disguise a risk to develop schizophrenia (Vollema, Sitskoorn, Appels, & Kahn, 2002).

## Neurodevelopmental framework

Since the median age of expression of symptoms within the schizophrenia spectrum lies in early adulthood (Kessler et al., 2007), for decades literature has been dominated by the idea of schizophrenia spectrum pathology being a disorder of adulthood. In addition, from a historical context of clinical specialization, the focus of clinicians devoting their practice and research to disorders of childhood was separated from the focus of clinicians treating disorders of adulthood (Frances, First, & Pincus, 1995). This arbitrary bifurcation in conceptualization and classification of mental disorders across developmental stages has hampered the study of the longitudinal course of psychopathology and also schizophrenia spectrum disorders for a long time (Pine et al., 2002).

However, inspired by the observations of Kahlbaum and Kraepelin that some children who will develop disorders within the schizophrenia spectrum later in life have a markedly abnormal development during childhood or adolescence, longitudinal studies were set up and showed that, in at least a subgroup of subjects, the disorder doesn't emerge fully-formed at once (e.g., Fuller Torrey, Bowler, Taylor, & Gottesman, 1994; Murray, O'Callaghan, Castle, & Lewis, 1992; Neumann, Grimes, Walker, & Baum, 1995; Offord & Cross, 1969; Rossi, Pollice, Daneluzzo, Marinangeli, & Stratta, 2000). Instead, the pathology seems to have its roots much earlier in life and is probably the resultant of a disturbance in developmental processes. This idea finally converged into the neurodevelopmental hypothesis of schizophrenia, which was proposed in two pioneering papers of Weinberger (1987) and Murray and Lewis (1987). This hypothesis posits that a psychotic episode seems to be the resultant of pathological processes originating from either a genetic predisposition or a spontaneous genetic mutation in early life, which by

interplay with environmental factors during the prenatal period, e.g. viral infections (Anderson & Maes, 2012), vitamin deficiencies (Bao et al., 2012; McGrath, Brown, & St Clair, 2011), perinatal factors like obstetric complications (Suvisaari et al., 2012) or factors in postnatal life, e.g., childhood trauma (Larsson et al., 2012) or cannabis use (Husted, Ahmed, Chow, Brzustowicz, & Bassett, 2012), will affect plastic neural systems during development. The progressive loss of neuroregulatory control, possibly associated with a disruption in the programming of normal neurodevelopment (Keshavan, 1999) is supposed to consequently lead to impairments in anatomical and functional maturation of certain highly evolved and complex brain regions that reach functional maturity in early adulthood. During the adult phase of life, a person enters a stage of development that is characterized by ongoing exposure to the complexities of life and demands of society necessitating optimal functionality of these complex brain regions like the pre-frontal cortex and the communication between different brain areas (Friston, 1999). So, if a person at high risk enters the adult phase of life, this person might be impaired in making necessary cognitive and behavioral adaptations. In the most severe cases, a psychotic decompensation might follow, characterized by several symptoms: behavior that seems inappropriate, thinking that is confused, and by delusions and social withdrawal. Because of further disturbances in modulating feedback processes in the brain, the high risk individual cannot control this activity which might finally cascade into aberrant behavior and cognition such as agitation, fearfulness, or even hallucinations (Weinberger, 1987).

The impact of the neurodevelopmental hypothesis of schizophrenia has been enormous and as a result strong evidence for the developmental origins of schizophrenia has gradually accumulated. This is best illustrated by the increasing amount of studies that have been published about this subject from 1989 until now. A quick search through Pub Med with key terms as ‘neurodevelopment AND schizophrenia’ shows only 20 studies being published from 1989 up to 1994, an increasing number of 52 studies being published from 1995 up to 2000, 113 studies being published from 2001 up to 2005 and even more than 300 studies being published from 2006 up to 2013. In the next section we will give a summary of the findings of these studies and discuss the assets of the present study.

## Research strategies to identify juvenile behavioral and cognitive features that are associated with the development of schizophrenia spectrum pathology

Several research strategies have been applied throughout the years to investigate behavioral and cognitive functioning in childhood or adolescence and its association with future schizophrenia spectrum pathology. These research strategies apply one of the following designs: (1) inspection of earlier records reporting on childhood or adolescent behavior of adult subjects showing disorders within the schizophrenia spectrum, (2) genetic high-risk (HR) studies, (3) birth cohort studies, and (4) clinical HR studies. The next paragraphs will provide an overview of the arguments for and against these different study designs.

The retrospective design is one of the research designs that was first applied to reveal insight into developmental cues of schizophrenia spectrum pathology. The retrospective examination of subjects with schizophrenia spectrum pathology was a particularly practical approach because of a prevalence rate varying between .5% (Jablensky & Kalaydjieva, 2003) and 2% (Raine, 2006), schizophrenia is not a common disorder in the general population. However, since the questions being asked are often about behaviors of many years (sometimes several decades) ago, an important drawback of this research design is that the outcome largely depends on the memory of the person being questioned. As memory can also be influenced by the present state of a person, the reliability of data obtained from retrospective studies is obviously hampered by recall bias (Van Engeland, 1990). To avoid this recall bias, prospective longitudinal research designs were set up.

The genetic HR design is one of the prospective longitudinal research designs that was initiated during the 1960s and is still often used. This design typically incorporates individuals in whom the risk for schizophrenia spectrum pathology is supposed to be enhanced and involves the follow-up of offspring of schizophrenic parents, younger siblings of schizophrenic patients, and discordant monozygotic (MZ) twins, with one of the twinpair having a diagnosis within the schizophrenia spectrum and the other twin not. This idea of examining young relatives at risk for schizophrenia pathology goes back to Emil Kraepelin who stated that 'In children . . . one might think of . . .prophylaxis especially if the malady had already been observed in the parents or brothers or sisters' (Kraepelin, 1919). Since the lifetime risk for schizophrenia spectrum disorders in a general population approximates 1.5% (Hanssen, Bijl, Vollebergh, & Van Os, 2003). Furthermore, children with a schizophrenic parent appear to have a lifetime risk of 10

to 15 % (Mednick & Schulsinger, 1968). This clearly indicates a genetic high risk, with the prospective identification of precursors of schizophrenia spectrum pathology in HR populations being a highly efficient and cost-effective research strategy. However, despite the obvious evidence of a high genetic predisposition for schizophrenia for spectrum pathology in family members of schizophrenic patients, the majority of subjects with schizophrenia does not have an affected parent (89%) or a first or second degree affected relative (63%; Gottesman, 1991). Even in identical twins the concordance rate for schizophrenia does not exceed 50% (Kendler, 1983; Gottesman & Erlingmeyer, 2001). So, genetic HR studies may thus be appropriate to address questions of genetic origin. However, the results cannot be generalized to the full syndrome of schizophrenia spectrum pathology. This limited generalizability can be avoided by using other prospective research strategies such as birth cohort studies and clinical HR studies.

Birth cohort studies with patients from a stratified sample of the general population are not troubled by a selection bias. Its findings are therefore more suitable to generalize to genetically as well as non-genetically determined variants of symptoms within the schizophrenia spectrum. Although this research strategy is very time consuming and thus very expensive, several birth cohort studies have been set up throughout the last decades. However, with the majority of studies focusing on disorders within the schizophrenia spectrum, it took a few decades before the first subjects reached the age on which a psychotic breakdown became apparent. Therefore, it was not until the 1990s that the first results were published. These studies have revealed many interesting findings and have brought forward the identification of many different candidate precursors of schizophrenia spectrum pathology. The results of these birth cohort studies will be outlined in the following section, not before noting the finding by Kim-Cohen et al. (2003) that strikes out in its relevance for our study. Kim-Cohen and colleagues found that 75% of their adult psychiatric cases had received a psychiatric diagnosis before the age of eighteen years. In our view, this underscores the developmental course of schizophrenia spectrum disorders and is suggestive for the idea that the majority of adult individuals with schizophrenia spectrum pathology could have been identified long before the clinical onset of symptoms within the schizophrenia spectrum, i.e., by seeking psychiatric care during childhood or adolescence for a spectrum of psychopathology. This knowledge has led to the introduction of clinical HR studies following juvenile psychiatric patients into adulthood.

It is important to note that the reported behavioral and cognitive deficits in childhood and adolescence that were found to be associated with adult schizotypal symptoms might also be indicative for the development of many other psychiatric

disorders. This makes the interpretation of these findings difficult in terms of specificity for schizophrenia spectrum pathology. Only a few clinical HR studies so far have used psychiatric controls for comparison. Although the results of these studies are very promising with respect to the question of specificity of the identified behavioral and cognitive precursors of schizophrenia spectrum pathology, these studies have used specific psychiatric subgroups such as PDD or ADHD for comparison. Therefore, a follow-up study covering all major child psychiatric categories, with subjects not being selected based on genetic risk may help to disentangle possible developmental cues that are specifically related to schizophrenia spectrum pathology.

## Heterogeneity of schizophrenia spectrum pathology

The study of precursors of schizophrenia spectrum pathology has led to the identification of juvenile behavioral and cognitive abnormalities that might be indicative for the development of schizophrenia spectrum pathology. However, the etiology of this devastating disorder remains shrouded in mystery (Cornblatt, Obuchowski, Roberts, Pollack, & Erlenmeyer-Kimling, 1999). Presently, there are still no effective treatments for most aspects of schizophrenia spectrum pathology and its functional impairments. One explanation might be found in the substantial variability within each diagnostic group of schizophrenia spectrum patients studied so far. For example, some of the patients with disorders within the schizophrenia spectrum respond poorly to all available treatments and have a poor outcome, while others respond well to a treatment, and sometimes even have full remission of all symptoms and full recovery even to the premorbid level of functioning (McGrath, 2008). One approach that might advance insight into the mechanisms that facilitate development of schizophrenia spectrum pathology is to focus on more homogeneous symptom clusters within the spectrum.

Factor analytic studies have shown that along the schizophrenia spectrum of symptoms, it typically evolves into separate clusters like positive symptoms (hallucinations and delusions), negative symptoms (emotional and behavioral disturbances), and disorganized symptoms (difficulty in pursuing a logical train of thought and understanding and utilizing information; Kaplan, Sadock, & Grebb, 1994). This makes the investigation of different symptom clusters within the schizophrenia spectrum highly relevant. Focusing on the development of symptom clusters rather than on profiles of symptoms, as can be found in schizophrenia disorder, might help in unraveling the mechanisms of schizophrenia spectrum disorders. More so, since it is found that the majority of indi-

viduals at risk to develop schizophrenia spectrum pathology will not show manifest illness (Meehl, 1990; Gottesman & Shields, 1982; Raine, 1991; Chapman et al., 1994; Tsuang et al., 2002), but rather presents with milder schizotypal symptoms, it would be relevant, apart from focusing on candidate precursors of schizophrenia, to examine precursors of milder features of schizophrenia spectrum pathology along its dimensions. Especially within recent years, this strategy has been regarded a way that can provide important insights into the origins and mechanisms of schizophrenia (Raine, 2006).

## Schizotypal symptomatology

The existence of schizophrenia-like, but non-psychotic, characteristics in relatives of schizophrenia patients was already reported by Kraepelin and Bleuler and, later, by many clinicians in office practice who described patients who seemed to have subtle thought disorders and interpersonal oddities that suggested a relation to schizophrenia (Lenzenweger, 2006). This schizotypal symptomatology is nowadays identified as representing a phenotypic, attenuated expression of a genetic predisposition for schizophrenia (Battaglia, Cavallini, Macciardi, & Bellodi, 1997; Nelson et al., 2011) lying on a continuum of schizophrenia spectrum pathology. The association of this symptomatology with schizophrenia has been verified in a variety of studies (Torgersen, 1985; Baron, Gruen, Asnis, & Lord, 1985; Chapin, Wightman, Lycaki, Joset, & Rosenbaum, 1987; Siever, 1985; McGGlashan, 1986; Silverman et al., 1987). The three-factor model of schizotypal symptoms is modeled on the Diagnostic and Statistical Manual of Mental disorders (APA, 1987) criteria for schizotypal personality disorder (Raine, 1991). Factor analytical studies have revealed three schizotypal dimensions, i.e., positive, negative, and disorganized symptoms (Raine et al., 1994; Vollema & Hoijtink, 2000). This factor structure parallels the factor structure obtained in schizophrenia patients (Raine, 2006) and has been found to be invariant to gender, ethnicity, religion, and social background (Reynolds, Raine, Mellingen, Venables, & Mednick, 2000). Vollema, Sitskoorn, Appels, and Kahn (2002) suggested that the Schizotypal Personality Questionnaire (SPQ; Raine, 1991), the questionnaire to assess these dimensions, may be regarded as an indicator of the (genetic) vulnerability for schizophrenia, because it is sensitive to gradient levels of schizophrenia, proportional to the risk for schizophrenia associated with the degree of kinship with schizophrenic family members.

In line with the aforementioned desire to better understand mechanisms underlying the development of schizotypal symptoms, the next section will present an overview of the research findings that inspired the studies reported in the current thesis.

## How adult schizotypal symptomatology affects a person´s objective and subjective Quality of Life

Several studies, probing into how impoverished QoL relates to the heterogeneous manifestations of schizophrenia spectrum pathology, have reported that especially negative symptoms seem to have a profound influence on QoL in comparison to positive or disorganized symptoms (Browne et al.,1996; Meltzer, Burnett, Bastani, & Ramirez, 1990; Wilson & Cleary, 1995; Xiang, Weng, Leung, Tang, & Ungvari, 2007; Law et al., 2005; Orsel, Akdemir, & Dag, 2004; Malla & Payne, 2005; Fitzgerald et al., 2001; Corrigan & Buican, 1995). In addition to studies focusing on QoL as a unitary concept, some studies have discriminated between Objective QoL (OQoL), i.e., evaluating the patients´ living conditions (Corrigan & Buican, 1995), and Subjective Quality of Life (SQoL), i.e., evaluating the patient's appraisal of these conditions (Corrigan & Buican, 1995). The results of these studies are suggestive for each of the symptom domains being associated with reduced OQoL and SQoL (Fitzgerald et al., 2001; Cohen & Davis, 2009; Narvaez, Twamley, McKibbin, Heaton, & Patterson, 2008; Fitzgerald et al., 2003), and negative symptoms in particular (Cohen & Davis, 2009).

There is, however, a caveat. Previous studies only included typically developing controls for comparison. Since psychiatric disorders such as depression (Ishak et al., 2011), ADHD (Danckaerts et al., 2010), and psychopathology in general (Lehman, 1983) have commonly been found to unfavorably affect OQoL and SQoL, the question thus remains unanswered in what way the presence of schizophrenia spectrum symptomatology in psychiatric patients specifically relates to QoL. To our knowledge no study has yet investigated this issue. The answer to this question would carry relevant information for treatment protocols aimed to improve QoL in patients with schizophrenia spectrum symptomatology. This issue will be addressed in Chapter 2.

## Juvenile behavioral indicators of adult schizotypal symtomatology

Without taking into account the underlying three-factor structure of schizophrenia spectrum pathology, retrospective and prospective longitudinal studies have identified a wide range of juvenile psychiatric disorders and behavioral abnormalities preceding adult disorders within the schizophrenia spectrum. The results of the birth cohort study of Kim-Cohen et al. (2003) showed that 75% of the schizophrenic adult cases had received a juvenile psychiatric diagnosis before the age of 18. More specifically, diagnostic

shifts towards schizophrenia later in life were found in juvenile psychiatric disorders such as pervasive developmental disorders (Van Engeland & Van der Gaag 1994; Mouridsen, Rich, & Isager, 2008; Larsen & Mouridsen 1997; Stahlberg et al., 2004; Rubino et al., 2009), Attention Deficit Disorders, Disruptive disorders (Rubino et al., 2009; Keshavan et al., 2002; Menkes, Rowe, & Menkes, 1967; De la Serna et al., 2010), and Anxiety and Depressive disorders (Kim-Cohen et al., 2003; Ambelas, 1992; Meyer et al., 2005).

In addition to this categorical all or none approach of juvenile problem behavior, dimensional juvenile behavioral indicators of schizophrenia spectrum pathology have been studied throughout the years. This has led to the identification of a very broad range of juvenile candidate behavioral anomalies that have been associated with disorders within the schizophrenia spectrum. Retrospective studies, for example, found social impairments to be especially present in pre-schizophrenic subjects (Watt & Lubensky, 1976; Zigler, Levine, & Zigler, 1977; Foerster, Lawis, Owen & Murray, 1991; Rossi et al., 2000). Genetic HR studies reported that at a very young age, HR babies already showed lower communicative competence (Goodman, 1987), and appeared to be more quiet (Fish, 1987). HR adolescents showed more anxious and hostile behavior (Goodman, 1987), more disruptive behavior and aggression at school (Mednick & Schulsinger, 1968; Weintraub, Prinz, & Neale, 1978), poor peer relations (Ayalon & Merom, 1985), poor affective control (Fish, 1987; Nagler & Glueck, 1985), more situational anxiety, more nervous tension and depression (Cunningham, Miller, Lawrie, & Johnstone, 2005) compared to children and adolescents without genetic risk for disorders within the schizophrenia spectrum. In addition, birth cohort studies have found evidence for behavioral indicators of schizophrenia spectrum pathology in four behavioral domains: delay in neuromotor development (Jones, Rodgers, Murray, & Marmot, 1994; Crow, Done, & Sacker, 1995; Rosso et al., 2000; Fish, Marcus, Hans, Auerbach, & Perdue, 1992; Walker, Lewis, Loewy, & Palyo, 1999; Cannon et al., 1999), delays in aspects of language development (Jones et al., 1994; DeLisi et al., 1991; Bearden et al., 2000), problems in the area of social functioning (Crow et al.,1995; Bearden et al., 2000; Malmberg, Lewis, David, & Allebeck, 1998; Davidson et al., 1999), and high levels of aggressive behavior (Miller, Byrne, Hodges, Lawrie, & Johnstone, 2002).

So far, several clinical HR studies focusing on specific subgroups of subjects seeking psychiatric help in childhood or adolescence have revealed specific risk for the development of disorders within the schizophrenia spectrum, especially in children with neurodevelopmental disorders such as PDD, ADHD, and Disruptive Behavior Disorders (Van Engeland & Van der Gaag, 1994; Mouridsen et al., 2008; Larsen & Mouridsen, 1997; Stahlberg et al., 2004; Rubino et al., 2009; Keshavan et al., 2002; Menkes et al., 1967; De

la Serna et al., 2010). In addition, only three longitudinal studies have studied juvenile behavioral indicators for adult disorders within the schizophrenia spectrum in comparison with patients diagnosed with affective disorders (Dworkin, Lewis, Cornblatt, & Erlenmeyer-Kimling, 1994), anorexia (Muratori, Salvadori, D'Arcangelo, Viglione, & Picchi, 2005), or non-psychotic HR subjects (Velthorst et al., 2009), respectively. As a result, these studies have identified specific juvenile behavioral problems in more restricted behavioral domains: i.e., the social domain (Dworkin et al., 1994; Muratori et al., 2005; Velthorst et al., 2009), the regulation of thought (Muratori et al., 2005; Velthorst et al., 2009), and attention (Muratori et al., 2005).

The question, however, remains unanswered in what way these aforementioned behavioral abnormalities of childhood and adolescence may be associated with the development of distinctive adult schizotypal symptoms in a cohort of subjects presenting with juvenile psychopathology. This issue will be the subject of Chapter 3 and Chapter 4.

## Juvenile cognitive precursors of adult schizotypal symptomatology

The association of cognitive impairments and especially intellectual impairments with development of schizophrenia or psychosis has been extensively studied throughout the years.

Longitudinal studies have well-established that intellectual functioning in childhood or adolescence is lower in adult patients who develop disorders within the schizophrenia spectrum, such as schizophrenia (Cannon, Bearden, Hollister, Rosso, Sanchez, & Hadley, 2000; Mortensen, Sorensen, Jensen, Reinisch, & Mednick, 2005; Ott, Spinelli, Rock, Roberts, & Amminger, 1998; Seidman, Buka, Goldstein, & Tsuang, 2006), and (non-affective) psychotic disorders (Mortensen et al., 2005; Urfer-Parnas, Mortensen, Saebye, & Parnas, 2010; Zammit et al., 2004).

However, studies are less consistent when it comes to deciding whether specific domains of intellectual functioning relate to this general impairment. While some studies have found that deficits in verbal intelligence in childhood or adolescence are especially indicative for the development of future schizophrenia or psychosis (Aylward, Walker, & Bettes, 1984; Cannon et al., 2000; David, Malmberg, Brandt, Allebeck, & Lewis, 1997; Ott et al., 1998; Seidman et al., 2006), other studies have pinpointed deficits in nonverbal intelligence in childhood or adolescence as precursors (Amminger et al., 2000; Cannon et al., 2000; Jones et al., 1994). Then again, the results of Sørensen, Mortensen,

Parnas, & Mednick (2006) and the meta-analysis of Khandaker, Barnett, White & Jones (2011) are suggestive for verbal and nonverbal capacities in childhood or adolescence being equally affected in these patients.

Similar inconsistencies in results are found when looking at subdomains of intellectual functioning. While some studies have found that lower scores on subtests pertaining to juvenile verbal intelligence, such as Information (Seidman et al., 2006), Similarities (Sørensen et al., 2010), and Digit span (Seidman et al., 2006), are indicative for the development of clinical abnormalities within the schizophrenia spectrum, other studies have shown that failures in non-verbal components of intelligence in childhood or adolescence, such as Coding (Kendler et al., 1993; Niendam, Bearden, Rosso, Sanchez, & Hadley, 2003; Seidman et al., 2006; Sørensen et al., 2006), Mazes (Sørensen et al., 2010), and Object assembly (Sørensen et al., 2010) are especially indicative for the development of schizophrenia or psychosis.

What might explain inconsistency of results is that aformentioned studies have exclusively relied on disorders at the extreme end of the spectrum. In addition, studies that have focused on intellectual functioning and distinctive symptoms of schizophrenia spectrum pathology have only cross-sectionally investigated this association in adult patients. These studies have reported inverse associations of general intellectual functioning with negative (Tandon, Nasrallah, & Keshavan, 2009; Barrantes-Vidalatal et al., 2002) and positive schizotypal symptoms (Barrantes-Vidalatal et al., 2002; Matheson & Langdon, 2008). With regard to specific subdomains of intellectual functioning, Noguchi, Hori, & Kunugi (2008) showed that lower verbal intelligence was associated with higher levels of positive symptoms. To our knowledge, no study as yet has investigated how intellectual functioning in childhood and adolescence is associated with the development of distinctive adult symptoms of schizophrenia spectrum pathology. This issue will therefore be the subject of Chapter 5.

## Gender differences and development of schizophrenia spectrum pathology

Differences between boys and girls during normal maturation are well-established. For example, during late childhood boys exhibit more expansive behavior and show a slightly higher frequency of attention deficits, whereas girls are found to present with more anxiety (Anderson, Williams, McGee, & Silva, 1987; Campball, 1990; Cohen et al., 1993; Gomez, Harvey, Quick, Scharer, & Harris, 1999). From puberty on, males are found to

show a greater frequency of hyperactivity, attention deficit disorder, aggressiveness and antisocial personality disorders whereas females are found to have a greater frequency of anxiety and affective disorders (Hafner, 2003; Rosenfield, 2000). Because of these gender differences in development during normal maturation, gender specific precursors are very likely present in the course of schizophrenia spectrum pathology. Indeed, studies have identified gender specific factors within the course of disorders at the extreme end of the schizophrenia spectrum, i.e., schizophrenia or psychosis, such as age of onset, with earlier onset (Angermeyer & Kuhn, 1988), higher risk (Aleman, Kahn, & Selten, 2003), poorer premorbid functioning, treatment response, course and outcome in men than in women (Castle, Wessely, & Murray, 1993; Goldstein & Lewine, 2000; Häfner et al., 1994; Leung & Chue, 2000). However, the very few studies investigating gender differences in clinical presentation during childhood and adolescence have reported mixed results. For example, some studies report that the development of schizophrenia spectrum pathology is more often associated with externalizing problems, such as aggressive (Welham et al., 2009), delinquent behavior (Welham et al., 2009), hostile behavior (Crow et al., 1995), and social maladjustment (Done, Crow, Johnstone, & Sacker, 1994) in boys. However, this externalizing behavior is also reported in a study who noted 'premorbid asociality' in the primary school records of girls, but not boys, who later developed schizophrenia (Watt, 1978; Watt & Lubensky, 1976). With regard to internalizing problems, both girls and boys are found to show internalizing problems prior to the development of schizophrenia spectrum pathology, i.e., depressive and withdrawn behavior in girls (Crow et al., 1995) and anxious and depressed behavior in boys (Crow et al., 1995). Also with regard to cognition, the results of comparative studies are inconsistent. While some studies have shown that premorbid cognitive performance is poorer in females, as compared to males (Weiser et al., 2000; Jones & Done, 1997), other studies have reported exact opposite results (Offord, 1974; Watt & Lubensky, 1976). The reasons for this inconsistency might be due to the methodologies of these studies (Goldstein, 1993; 1995a,b; Lauriello et al., 1997; Goldstein & Lewine, 2000), and with the small sample sizes of these studies in particular (Moldin, 2000). The sample size of the present follow-up study allowed us to investigate gender specific behavioral and cognitive factors in the development of schizophrenia spectrum pathology.

## Participants and procedure of the current follow-up study

The follow-up study presented in this thesis was initiated in 1984 to evaluate both global

as well as clinical outcome of referred patients. It was started by two board members of the Department of Child and Adolescent Psychiatry of the University Medical Centre of Utrecht (UMCU), the Netherlands, i.e., Prof. dr. Herman van Engeland and Prof. dr. Hanna Swaab. At T1, baseline juvenile Axis I psychiatric diagnosis was obtained at the time of referral by consensus between at least two board certified psychiatrists on the basis of a complete child psychiatric examination, consisting of observation, a semi-structured clinical diagnostic interview according to the current DSM criteria at the time of the original assessment (American Psychiatric Association, 1980; American Psychiatric Association, 1987; 1994), the subjects' developmental history and a review of medical records. Based on the nature of the diagnostic question, additional behavioral and neuropsychological assessment was done.

In 2006, when the majority of patients had reached adult age, i.e., the age of onset of possible classifications within the schizophrenia spectrum, the follow-up of the patients was initiated at Leiden University, at the Department of Clinical Child and Adolescent studies, in cooperation with the University Medical Centre Utrecht, at the Department of Child and Adolescent Psychiatry. Patients meeting the following criteria were approached for participation in this follow-up study during 2006 to 2010 (T2): (1) aged 18 years or younger at T1, (2) aged 18 years or older at T2, (3) no DSM-diagnosis of mental retardation (IQ<70) at T1, and (4) no axis I DSM diagnosis before or at time of original assessment (T1) of child psychotic disorder, schizophrenia or any other psychotic disorder, bipolar disorder or dissociative disorder. Dependent on the specific research question, additional selection criteria were applied. As a result, a different number of patients was therefore eligible for follow-up as described in the chapters of this thesis. The patients eligible for follow-up were sent a letter informing them about the aims of the follow up study and asking them to participate. If possible, patients were contacted by phone to encourage participation. If included in the study, patients were asked to complete a questionnaire about their QoL and were asked about schizotypal symptomatology using the Schizotypal Personality Questionnaire (SPQ; Raine, 1991). The ethical principles of the Helsinki Declaration (Schuklenk, 2001) were followed and ethical approval was obtained from the Medical Ethical Committee of the University Medical Centre of Utrecht (number 05-319/K).

## *Instruments*

### Objective and Subjective Quality of Life

QoL was evaluated using a questionnaire concerning global and clinical outcome in adult life. This questionnaire was developed at the Department of Child and Adolescent Studies of Leiden University. Based on the publication of Corrigan and Buican (1995) QoL was discriminated between OQoL, i.e., evaluating the patients' living conditions, and SQoL, i.e. evaluating the patients' appraisal of these conditions. The first section examined self-reported Objective measures of QoL (OQoL): educational level, marital status, living arrangement, mental health care, medication use, and employment. Educational level was defined as the highest level of education attained by the patient, with scores ranging from 2 ((pre)primary education) to 7 (second stage of tertiary education). The level of education of the patients was reported on the basis of the Standaard Onderwijs Indeling (SOI-2006), which is based on the International Standard Classification of Education (ISCED; International Standard Classification of Education, 1997). The second section examined self-reported Subjective measures of QoL (SQoL), that is the respondents' satisfaction with life in seven areas that are generally considered as basic to QoL, i.e., living arrangement, employment or education, physical health, partner-relationship, social contacts, mood, and future perspective. These domains were scored on a six-item scale, ranging from very dissatisfied to very satisfied. Higher scores are indicative for higher levels of SQoL and OQoL. Since patients have been shown to assess their OQoL accurately and consistently (Vorunganti, Heslegrave, Awad, & Seeman, 1998; Becchi, Rucci, Placentino, Neri, & De Girolamo, 2004), and self-reported measures of OQoL have been found to be more valid than clinician-reported OQoL measures (Narvaez et al., 2008), self-reported measures were used to assess OQoL.

## Adult schizotypal symptoms

Adult schizotypal symptoms were measured using the Schizotypal Personality Questionnaire-Revised (SPQ-R; Vollema & Hoijtink, 2000; Raine, 1991). The SPQ-R is a self-report measure of schizotypal symptoms, modeled on the Diagnostic and Statistical Manual of Mental Disorders (APA, 1994) conceptualization of schizotypy (Raine, 2006). Factor analytical studies have revealed three schizotypal dimensions, i.e., positive, negative, and disorganized symptoms (Vollema & Hoijtink, 2000; Raine, 1994). This factor structure has been found to be invariant to gender, ethnicity, religion, and social background (Reynolds et al., 2000), and it parallels the factor structure obtained in schizophrenia patients (Raine, 2006). Vollema, Sitskoorn, Appels, and Kahn (2002) suggested that the SPQ may be regarded as an indicator of the (genetic) vulnerability for schizophrenia, because it is

sensitive to gradient levels of schizophrenia, proportional to the risk for schizophrenia associated with the degree of kinship with schizophrenic family members. Higher scores on the SPQ-R indicate higher levels of schizotypal symptoms.

## Objectives and outline of the present thesis

First, we studied how Quality of Life (QoL) in adulthood is affected by distinctive schizotypal symptoms. Then, it was studied how juvenile behavioral and intellectual (dys)functioning was associated with distinctive adult schizotypal symptoms. This was studied in a sample of patients who all sought psychiatric care during child age.

Contrasting earlier studies that have mainly evaluated QoL in psychiatric patients in comparison to typically developing controls, the first step in this thesis was to identify whether and how the presence of schizotypal symptoms influences the level of objective and subjective QoL in a sample of patients representing a wide spectrum of psychiatric disorders (chapter two). 690 patients of the Department of Child and Adolescent Psychiatry of the University Medical Centre Utrecht, the Netherlands, were prospectively reassessed on OQoL and SQoL after a mean period of 15.0 (*SD*=5.3) years for adult schizotypal symptoms using the Schizotypal Personality Questionnaire-Revised (SPQ-R; Vollema & Hoijtink, 2000). Since severity of adult schizotypal symptoms in general (Chan, 2002; Awad, 1992; Awad, Hogan, Voruganti, & Heslegrave, 1995), and negative symptoms in particular are frequently found to be associated with worse objective (Fitzgerald et al., 2001; Cohen & Davis, 2009; Narvaez et al., 2008; Fitzgerald, 2003), and subjective quality of life (Cohen & Davis, 2009), we expected to find that elevated levels of schizotypal symptoms, in particular negative symptoms, are associated with less favorable objective and subjective QoL.

The complex dynamics of psychopathology in childhood or adolescence and the development of symptoms within the schizophrenia spectrum were studied by investigating the association between psychiatric disorders in childhood and adolescence and adult schizotypal symptoms (chapter three). 731 patients of the Department of Child and Adolescent Psychiatry of the University Medical Centre Utrecht, the Netherlands, were prospectively reassessed after a mean period of 15.3 (*SD*=5.1) years for adult schizotypal symptoms using the Schizotypal Personality Questionnaire-Revised (SPQ-R; Vollema & Hoijtink, 2000). Covering thirteen categories of DSM psychiatric disorders in childhood or adolescence in which at least twenty subjects were present, differences between juvenile psychiatric patients and normal controls on adult schizotypal total and factor scores

were analyzed. In line with the results of earlier studies focusing on disorders within the schizophrenia spectrum (Kim-Cohen et al., 2003; De la Serna et al., 2010; Keshavan et al., 2002; Rubino et al., 2009; Meyer et al., 2005; Larsen & Mouridsen, 1997; Mouridsen, Rich, & Isager, 2008), it was hypothesized that psychiatric disorders in childhood and adolescence such as PDD, ADHD, ODD, anxiety disorders, and depressive disorders were associated with higher levels of adult schizotypal symptoms. Using a three-factor model of schizotypal symptoms, discriminating between positive, negative, and disorganized symptoms (Vollema & Hoijtink, 2000), it was further explored whether juvenile psychopathology was specifically associated with one or more of the three main schizotypal symptom domains.

In chapter four it is investigated how specific juvenile behavioral problems or symptom dimensions are associated with distinctive adult schizotypal symptom dimensions. 159 patients of the Department of Child and Adolescent Psychiatry of the University Medical Centre Utrecht, the Netherlands, were prospectively reassessed after a mean period of 11.6 (*SD*=3.1) years for adult schizotypal symptoms using the Schizotypal Personality Questionnaire-Revised (SPQ-R; Vollema & Hoijtink, 2000). By using teacher reports of behavior at school in childhood and adolescence, we aimed to examine how juvenile behavioral problems precede distinctive schizotypal symptoms in a clinical cohort of subjects presenting with behavioral and emotional disturbances. In line with the results of other studies (Miller, Byrne, Hodges, Lawrie, & Johnstone, 2002; Muratori et al., 2005; Johnstone, Ebmeier, Miller, Owens, & Lawrie, 2005; Scott et al., 2009; Amminger et al., 1999), we hypothesized that severity of behavioral problems would be associated with higher levels of adult schizotypal symptoms. These studies also suggest that childhood problems in the social domain (Dworkin et al., 1994; Muratori et al., 2005; Velthorst et al., 2009), in regulation of thought (Muratori et al., 2005; Velthorst et al., 2009), and in attention regulation (Muratori et al., 2005) are particularly associated with the risk for higher levels of adult schizotypal symptoms. How different domains of juvenile behavior were related to the three schizotypal symptom domains was therefore assessed. Finally, the role of gender was explored.

We finish by investigating the association between intellectual (dys)functioning in childhood and adolescence and adult schizotypal symptoms (chapter five). 317 patients of the Department of Child and Adolescent Psychiatry of the University Medical Centre Utrecht, the Netherlands, were prospectively reassessed after a mean period of 13.2 (*SD*=5.2) years for adult schizotypal symptoms using the Schizotypal Personality Questionnaire-Revised (SPQ-R; Vollema & Hoijtink, 2000). We aimed to examine how intellectual (dys)functioning in childhood and adolescence was associated with the

development of adult distinctive schizotypal symptoms. In line with the results of earlier studies investigating intellectual functioning and its relation with distinctive schizotypal symptoms (Niendam et al., 2003; Noguchi et al., 2008), it was hypothesized that lower levels of general intellectual functioning in childhood and adolescence, in specific verbal intelligence, would be most strongly linked to adult schizotypal symptoms and especially positive and negative symptoms. Whether this relation was valid for specific intellectual subdomains was further investigated. In addition, the role of gender was explored.

In Chapter Six a summary and discussion of the presented findings will be provided.

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