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.

References

Aleman, A., Kahn, R.S., Selten, J.P. (2003). Sex differences in the risk of schizophrenia. Evidence from meta-analysis. *Arch Gen Psychiatry,* 60, 565– 571.

Ambelas, A. (1992). Preschizophrenics: Adding to the evidence, sharpening the focus. *Br J Psychiatry*, 160(3), 401-404.

American Psychiatric Association. (1980). *Diagnostic and Statistical Manual of Mental Disorders* (*3th ed.)*. Washington, DC: American Psychiatric Association Press.

American Psychiatric Association. (1987). *Diagnostic and Statistical Manual of Mental Disorders* (*3th revised ed.)*. Washington, DC: American Psychiatric Association Press.

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders (4th ed.).* Washington, DC: American Psychiatric Association Press.

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders (4th revised ed.).* Washington, DC: American Psychiatric Association Press.

Amminger, G.P., Pape, S., Rock, D., Roberts, S., Ott, S., Squires-Wheeler, E., Kestenbaum, C., & Erlenmeyer-Kimling, L. (1999). Relationship between childhood behavioral disturbance and later schizophrenia in the New York High-Risk project. *Am J Psychiatry,* 156, 525-530.

Amminger, G.P., Schlogelhofer, M., Lehner, T., Ott, S., Friedrich, M., & Aschauer, H. (2000). Premorbid performance IQ deficit in schizophrenia. *Acta Psych Scand,* 102, 414–422.

Anderson, J.C., Williams, S., McGee, R., & Silva, P.A. (1987). DSM-III disorders in preadolescent children: prevalence in a large community sample. *Arch Gen Psychiatry,* 44, 69–76.

Anderson, G., & Maes, M. (2013). Schizophrenia: Linking prenatal infection to cytokines, the tryptophan catabolite (TRYCAT) pathway, NMDA receptor hypofunction, neurodevelopment and neuroprogression. *Prog Neuropsychopharmacol Biol Psychiatry,* 42, 5-19.

Angermeyer, M.C., & Kühn, L. (1988). Gender differences in age at onset of schizophrenia. *Eur Arch Psychiatry Neurol Sci,* 237, 351–364.

Ayalon, M., & Merom, H. (1985). The teacher interview. *Schizophr Bull,* 11, 117-120.

Aylward, E., Walker, E., & Bettes, B. (1984). Intelligence in Schizophrenia: Meta-analysis of the research. *Schizophr Bull,* 10(3), 430-459.

Awad, A.G. (1992). Quality of life of schizophrenic patients on medications and implications for new drug trials. *Hosp Community Psychiatry,* 43(3), 262-265.

Awad, A.G., Hogan, T.P., Voruganti, L.N., & Heslegrave, R.J. (1995). Patients' subjective experiences on antipsychotic medications: implications for outcome and quality of life. *Int Clin Psychopharmacol,* 10(3), 123-32.

Bao, Y., Ibram, G., Blaner, W.S., Quesenberry, C.P., Shen, L., McKeague, I.W., Schaefer, C.A., Susser, E.S., & Brown, A.S. (2012). Low maternal retinol as a risk factor for schizophrenia in adult offspring. *Schizophr Res,* 137(1-3), 159-65.

Baron, M., Gruen, R., Asnis, L., & Lord, S. (1985). Familial transmission of schizotypal and borderline personality disorders. *Am J Psychiatry,* 142, 927-934.

Barrantes-Vidal, N., Fananas, L., Rosa, A., Caparros, B., Riba, M.D., & Obiols, J.E. (2002). Neurocognitive, behavioural and neurodevelopmental correlates of schizotypy clusters in adolescents from the general population. *Schizophr Res*, 61, 293–302.

Battaglia, M., Cavallini, M.C., Macciardi, R., & Bellodi, L. (1997). The structure of DSM-III-R schizotypal personality disorder diagnosed by direct interviews. *Schizophr Bull,* 23, 83-92.

Bearden, C., Rosso, I., Hollister, J., Sanchez, L., Hadley, T., & Cannon, T. (2000). A prospective cohort study of childhood behavioral deviance and language abnormalities as predictors of adult schizophrenia. *Schizophr Bull,* 26, 395-410.

Becchi, A., Rucci, P. Placentino, A. Neri G., & De Girolamo, G. (2004). Quality of life in patients with schizophrenia: Comparison of self-report and proxy assessments. *Soc Psychiatry Psychiatr Epidemiol,* 39, 397–401.

Bleuler E. (1911). *Dementia Praecox or the Group of Schizophrenias.* New York: International Universities Press.

Breier, A., Schreiber, J. L., Dyer, J., & Pickar, D. (1991). National Institute of Mental Health longitudinal study of chronic schizophrenia. Prognosis and predictors of outcome. *Arch Gen Psychiatry,* 48(3), 239–246.

Browne, S., Roe, M., Lane, A., Gervin, M., Morris, M., Kinsella, A., Larkin, C., & O'Callaghan, E. (1996). Quality of life in schizophrenia: relationship to sociodemographic factors, symptomatology and tardive dyskinesia. *Acta Psychiatr Scand,* 94(2), 118-124.

Campball, S.B. (1990). *Behavior Problems in Preschool Children.* New York: Guildford.

Cannon, M., Jones, P., Huttunen, M., Tanskanen, A., Rabe-Hesketh, S., & Murray, R. (1999). School performance in Finnish children and later development of schizophrenia: a population-based longitudinal study. *Arch Gen Psychiatry*, 56, 457-463.

Cannon, T.D., Bearden, C., Hollister, J.M., Rosso, I.M., Sanchez, L.E., & Hadley, T. (2000). Childhood cognitive functioning in schizophrenia patients and their unaffected siblings. *Schizophr Bull,* 26(2), 379–393.

Castle, D., Wessely, S., & Murray, R.M. (1993). Sex and schizophrenia: effects of diagnostic stringency, and associations with premorbid variables. *Br J Psychiatry,* 162, 658–664.

Chan, S., & Yu, I.W. (2002). Quality of life of clients with schizophrenia. *J Adv Nurs,* 45(1), 72–83.

Chapin, K., Wightman, L., Lycaki, H., Joset, N., & Rosenbaum, G. (1987). Difference in reaction time between subjects with schizotypal and borderline personality disorders. *Am J Psychiatry,* 144, 948-950.

Chapman, L.J., Chapman, J.P., Kwapil, T.R., Eckblad, M., & Zinser, M.C. (1994). Putatively psychosis-prone subjects 10 years later. *J Abnormal Psychol,* 103(2), 171-183.

Cohen, A.S., & Davis, T.E. (2009). Quality of life across the schizotypy spectrum: findings from a large nonclinical adult sample. *Compr Psychiatry,* 50(5), 408–414.

Cohen, P., Cohen, J., Kasen, S., Velez, C.N., Hartmark, D., Johnson, J., et al. (1993). An epidemiological study of disorders in late childhood and adolescence, I: age and gender specific prevalence. *J Child Psychol Psychiatry,* 34, 851–867.

Cornblatt, B., Obuchowski, M., Roberts, S., Pollack, S., & Erlenmeyer-Kimling, L. (1999). Cognitive and behavioral precursors of schizophrenia. *Dev Psychopathol,* 11, 487–508.

Corrigan, P.W. & Buican, B. (1995). The construct validity of subjective quality of life for the severely mentally ill. *J Nerv Ment Dis,* 183, 281-285.

Crow, T.J., Done, D.J., & Sacker, A. (1995). Childhood precursors of psychosis as clues to its evolutionary origin. *Eur Arch of Psychiatry and Clinical Neuroscience,* 245, 61-69.

Cunningham, D., Miller, O., Lawrie, S., & Johnstone, E. (2005). Pathogenesis of schizophrenia: a psychopathological perspective. *Br J Psychiatry,* 186, 386-393.

Danckaerts, M., Sonuga-Barke, E.J., Banaschewski, T., Buitelaar, J., Dopfner, M., Hollis, C., Santosh, P., Rothenberger, A., Sergeant, J., Steinhausen, H.C., Taylor, E., Zuddas, A., & Coghill, D. (2010). The quality of life of children with attention deficit/hyperactivity disorder: a systematic review. *Eur Child Adolesc Psychiatry,* 19(2), 83–10.

David, A.S., Malmberg, A., Brandt, L., Allebeck, P., & Lewis, G. (1997). IQ and risk for schizophrenia: a population-based cohort study. *Psychol Med*, 27, 1311–1323.

Davidson, M., Reichenberg, A., Rabinowitz, J., Weiser, M., Kaplan, Z., & Mark, M. (1999). Behavioral and intellectual markers for schizophrenia in apparently healthy male adolescents. *Am J Psychiatry,* 156, 1328-1335.

De la Serna, E., Baeza, I., Toro, J., Andrés, S., Puig, O., Sánchez-Guistau, V., Romero, S., Bernardo, M., & Castro-Fornieles, J. (2010). Relationship between clinical and neuropsychological characteristics in child and adolescent first degree relatives of subjects with schizophrenia. *Schizophr Res,* 116(2-3), 159-167.

DeLisi, L., Boccio, A., Rliordan, H., Hoff, A., Dorfman, A., McClelland, J., Kushner, M., Van Eyl, O., & Oden, N. (1991). Familial thyroid disease and delayed language development in first admission patients with schizophrenia. *Psychiatry Res*, 38, 39-50.

Done, D.J., Crow, T.J., Johnstone, E.C., & Sacker, A. (1994). Childhood antecedents of schizophrenia and affective illness: social adjustment at ages 7 and 11. *Br Med Journal,* 309, 699-703.

Dworkin, R., Lewis, J., Cornblatt, B., & Erlenmeyer-Kimling, L. (1994). Social competence deficits in adolescents at risk for schizophrenia. *J Nerv Ment Dis,* 182, 103-108.

Fish, B. (1987). Infant predictors of the longitudinal course of schizophrenic development. *Schizophr Bull,* 13, 395-409.

Fish, B., Marcus, J., Hans, S., Auerbach, J.G., & Perdue, S. (1992). Infants at risk for schizophrenia: sequelae of a genetic neurointegrative defect. *Arch Gen Psychiatry,* 49, 221-35.

Fitzgerald, P.B., Williams, C.L., Corteling, N., Filia, S.L., Brewer, K., Adams, A., De Castella, A.R., Rolfe, T., Davey, P., & Kulkarni, J. (2001). Subject and observer-rated quality of life in schizophrenia. *Acta Psychiatr Scand*, 103(5), 387-92.

Fitzgerald, P.B., De Castella, A.R.A., Filia, K., Collins, J., Brewer, K., Williams CL, Davey P, & Kulkarni, J. (2003). A longitudinal study of patient- and observerrated quality of life in schizophrenia. *Psychiatry Res*, 119(1), 55-62.

Foerster, A., Lawis, S., Owen, M., & Murray, R. (1991). Pre-morbid adjustment and personality in psychosis. *Br J Psychiatry,* 158, 171-176.

Foley, S.R., Kelly, B.D., Clarke, M., McTigue, O., Gervin, M., Kamali, M., Larkin, C., O'Callaghan, E., & Browne, S. (2005). Incidence and clinical correlates of aggression and violence at presentation in patients with first episode psychosis. *Schizophr Res,* 72(2-3), 161-8.

Frances, A. J., First, M. B., & Pincus, H.A. (1995). *DSM-IV guidebook.* Washington DC: American Psychiatric Press.

Friston, K.J. (1999). Schizophrenia and the disconnection hypothesis. *Acta Psychiatr Scand,* Suppl. 395, 68–79.

Fuller Torrey, E., Bowler, A.E., Taylor, EH., & Gottesman, I.I. (1994). *Schizophrenia and manic-depressive disorder. The biological roots of mental illness as revealed by the landmark study of identical twins.* New York: BasicBooks.

Goldstein, J.M. (1993). Impact of sampling biases in explaining discrepancies in studies on gender and schizophrenia: a reply. *Schizophr Bull,* 19, 9–14.

Goldstein, J.M. (1995a). *The impact of gender on understanding the epidemiology of schizophrenia.* In: Seeman, M.V. (Ed.), Gender and Psychopathology (pp. 159–199). Washington DC: American Psychiatric Press.

Goldstein, J.M. (1995b). *Gender and the famial transmission of schizophrenia.* In: Seeman, M.V. (Ed.). Gender and Psychopathology. Washington DC: American Psychiatric Press.

Goldstein, J.M., & Lewine, R.R.J. (2000). *Overview of sex differences in schizophrenia: where have we been and where do we go from here?* In: Castle, D.J., McGrath, J., Kulkarni, J. (Eds.). Women and Schizophrenia. Cambridge: Cambridge University Press.

Gomez, R., Harvey, J., Quick, C., Scharer, I., & Harris, G. (1999). DSM-IV AD/HD: confirmatory factor models, prevalence and gender and age differences based on parent and teacher ratings of Australian primary school children. *J Child Psychol Psychiatry*, 40, 265–274.

Goodman, S. (1987). Emory university project on children of disturbed parents. *Schizophr Bull,* 13, 411-423.

Gooding, D.C., Tallent, K.A., & Matts, C.W. (2005). Clinical status of at-risk individuals 5 years later: further validation of the psychometric highrisk strategy. *J Abnorm Psychol,* 114(1), 170-5.

Gottesman, I.I., & Shields, J.A. (1982). *Schizophrenia, the epigenetic puzzle.* Cambridge: Cambridge University Press.

Gottesman, I.I. (1991). *Schizophrenia Genesis: the origins of madness* (pag. 96).New York, USA: WH Freeman & Co.

Gottesman, I.I., & Erlenmeyer-Kimling, L. (2001). Family twin studies as a head start in defining prodromes and endophenotypes for hypothetical early-interventions in schizophrenia. *Schizophr Res,* 51, 93-102.

Häfner, H., Maurer, K., Löffler, W., Fätkenheuer, B., Heiden an der, W., Riecher-Rössler, A., Behrens, S., & Gattaz, W. (1994). The epidemiology of early schizophrenia. Influence of age and gender on onset and early course. *Br J Psychiatry,* 164 (Suppl 23), 29– 38.

Häfner, H. (2003). Gender differences in schizophrenia. *Psychoneuroendocrinology*, 28, 17–54.

Hanssen, M.S., Bijl, R.V., Vollebergh, W., & Van Os, J. (2003). Self-reported psychotic experiences in the general population : a valid screening tool for DSM-III-R psychotic disorders? *Acta Psychiatr Scand*, 107, 369-377.

Harkavy-Friedman, J.M., Restifo, K., Malaspina, D., Kaufmann, C. A., Anadmo, X. F., Yale, S. A., & Gorman, J. M. (1999). Suicidal behavior in schizophrenia: Characteristics of individuals who had and had not attempted suicide. *Am J Psychiatry,* 156(8), 1276–1278.

Hoenig, J. (1995). Schizophrenia. In: G.E. Berrios and R. Porter (Eds). *A history of clinical psychiatry: the origin and history of psychiatric disorders.* New York: New York University Press.

Husted, J.A., Ahmed, R., Chow, E.W., Brzustowicz, L.M., & Bassett, A.S. (2012). Early environmental exposures influence schizophrenia expression even in the presence of strong genetic predisposition. *Schizophr Res,* 137(1-3), 166-8.

Inskip, H. M., Harris, E. C., & Barraclough, B. (1998). Lifetime risk of suicide for affective disorder,alcoholism and schizophrenia. *Br J Psychiatry,* 172, 35–37.

ISCED (International Standard Classification of Education) see United Nations Educational, Scientific and Cultural Organization. (1997).

Ishak, W.W., Greenberg, J.M., Balayan, K., Kapitanski, N., Jeffrey, J., Fathy, H., Fakhry, H., & Rapaport, M.H. (2011). Quality of life: the ultimate outcome measure of interventions in major depressive disorder. *Harv Rev Psychiatry,* 19(5), 229-239.

Jablensky, A.V., & Kalaydjieva, L.V. (2003). Genetic epidemiology of schizophrenia: phenotypes, risk factors, and reproductive behavior. *Am J Psychiatry,* 160(3), 425-9.

Johnstone, E., Ebmeier, K., Miller, P., Owens, D., & Lawrie, S. (2005). Predicting schizophrenia: findings from the Edinburgh High-Risk Study. *Br J Psychiatry,* 186, 18-25.

Jones, P., & Done, D.J. (1997). In: Keshavan, M.S., Murray, R.M. (Eds.), *From Birth to Onset: a Developmental Perspective of Schizophrenia in Two National Birth Cohorts* (pp. 119–136). Cambridge: Cambridge University Press.

Jones, P., Rodgers, B., Murray, R., & Marmot, M. (1994). Child development risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet,* 344, 1398–1402.

Kaplan, H.I., Sadock, B.J., & Grebb, J.A. (1994). *Kaplan and Sadock's synopsis of psychiatry,* 7th ed. In: Kaplan HI, Sadock BJ, (eds). Baltimore, MD: Williams & Wilkins.

Khandaker, G.M., Barnett, J.H., White, I.R., & Jones, P.B. (2011). A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. *Schizophr Res.* 132(2-3), 220-7.

Kendell, R.E. (1987). *Schizophrenia: clinical features.* In: Michels, R., & Cavenar, J. (Eds.), Psychiatry, Vol 1. Philadelphia: JB Lippincott.

Kendler, K. (1983). Overview: a current perspective on twin studies of schizophrenia. *Am J Psychiatry*, 140, 1413-1425.

Kendler, K., McGuire, M., Gruenberg, A.M., O'Hare, A., Spellman, M., & Walsh, D. (1993). The Roscommon family study: I. methods, diagnosis of probands, and risk of schizophrenia in relatives. *Arch Gen Psychiatry,* 50, 527–540.

Keshavan, M.S. (1999). Development, disease and degeneration in schizophrenia: a unitary pathophysiological model. *J Psychiatr Res*, 33(6), 513–521.

Keshavan, M.S., Sujata, M., Mehra, A., Montrose, D.M., & Sweeney, J.A. (2002). Psychosis proneness and ADHD in young relatives of schizophrenia patients. *Schizophr Res,* 9(1), 85-92.

Kessler, R.C., Amminger, G.P. Aguilar-Gaxiola, S. Alonso, J., Lee, S., & Ustün, T.B. (2007). Age of onset of mental disorders: a review of recent literature. *Curr Opin Psychiatry*, 20, 359-364.

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-back of a prospective-longitudinal cohort. *Arch Gen Psychiatry,* 60(7), 709-17.

Koenen, K.C., Moffitt, T.E., Roberts, A.L., Martin, L.T., Kubzansky, L., Harrington, H., Poulton, R, & Caspi, A. (2009). Childhood IQ and adult mental disorders: a test of the cognitive reserve hypothesis. *Am J Psychiatry*, 166, 50–57.

Kraepelin, E. (1919). *Dementia praecox and paraphrenia,* Barclay R (trans). Chicago: Chicago Medical Book.

Kwapil, T.R. (1998). Social anhedonia as a predictor of the development of schizophrenia spectrum disorders. *J Abnorm Psychol*, 107(4), 558-65.

Larsen, F.W., & Mouridsen, S.E. (1997). The outcome in children with childhood autism and Asperger syndrome originally diagnosed as psychotic. A 30-year follow-up study of subjects hospitalized as children. *Eur Child Adolesc Psychiatry,* 6(4), 181-190.

Lauriello, J., Hoff, A., Wieneke, M.H., Blankfeld, H., Faustman, W.O., Rosenbloom, M., DeMent, S., Sullivan, E.V., Lim, K.O., & Pfefferbaum, A. (1997). Similar extent of brain dysmorphology in serverely ill women and men with schizophrenia. *Am J Psychiatry,* 154, 819–825.

Law, C.W., Chen, E.Y., Cheung, E.F., Chan, R.C., Wong, J.G., Lam, C.L., Leung, K.F., & Lo, M.S. (2005). Impact of untreated psychosis on quality of life in patients with first-episode schizophrenia. *Qual Life Res,* 14(8), 1803-1811.

Larsen, F.W., & Mouridsen, S.E. (1997). The outcome in children with childhood autism and Asperger syndrome originally diagnosed as psychotic. A 30-year follow-up study of subjects hospitalized as children. *Eur Child Adolesc Psychiatry,* 6(4), 181-190.

Larsson, S., Andreassen, O.A., Aas, M., Røssberg, J.I., Mork, E., Steen, N.E., Barrett, E.A., Lagerberg, T.V., Peleikis, D., Agartz. I., Melle, I., & Lorentzen, S. (2013). High prevalence of childhood trauma in patients with schizophrenia spectrum and affective disorder. *Compr Psychiatry*, 54(2), 123-7.

Lehman, A.F. (1983). The well-being of chronic mental patients: assessing their quality of life. *Arch Gen Psych,* 40(4), 369-373.

Lenzenweger, M.F. (2006). Schizotaxia, schizotypy, and schizophrenia: Paul E. Meehl's blueprint for the experimental psychopathology and genetics of schizophrenia. *J AbnormPsychol.* 115(2), 195–200.

Leung, A., & Chue, P. (2000). Sex differences in schizophrenia, a review of the literature. *Acta Psychiatr Scand* (Suppl.), 101, 3 –38.

Malla, A., & Payne, J. (2005). First-episode psychosis: psychopathology, quality of life, and functional outcome. *Schizophr Bull,* 31(3), 650-71.

Malmberg, A., Lewis, G., David, A., & Allebeck, P. (1998). Premorbid adjustment and personality in people with schizophrenia. *Br J Psychiatry*, 172, 308-313; discussion 314-315.

McGlashan, T.H. (1986). Schizotypal personality disorder. Chesnut Lodge follow up study: IV. Long term follow- up perspectives. *Arch Gen Psychiatry,* 43, 329-334.

Matheson, S., & Langdon, R. (2008). Schizotypal traits impact upon executive working memory and aspects of IQ. *Psychiatry Res*, 159, 207-214.

McGrath, J. (2008). Dissecting the heterogeneity of schizophrenia outcomes. *Schizophr Bull*, 34, 247-8.

McGrath, J., Brown, A., & St Clair, D. (2011). Prevention and schizophrenia: the role of dietary factors. *Schizophr Bull*, 37(2), 272-83.

Mednick, S., & Schulsinger, F. (1968). Some premorbid characteristics related to breakdown in children with schizophrenic mothers. *Psychiatry Res*, 6, 267-291.

Meehl, P.E. (1990). Toward an integrated theory of schizotaxia, schizotypy, and schizophrenia. *J Pers Disord*, 4, 1-99.

Meltzer, H.Y., Burnett, S., Bastani, B., & Ramirez, L.F. (1990). Effects of six months of clozapine treatment on the quality of life of chronic schizophrenic patients. *Hosp Commun Psych,* 41(8), 892-897.

Menkes, M., Rowe, J., Menkes, J. (1967). A 25 year follow-up study on the hyperkinetic child with minimal brain dysfunction. *Pediatrics,* 39(3), 393-399.

Meyer, S.E., Bearden, C.E., Lux, S.R,, Gordon, J.L., Johnson, J.K., O'Brien, M.P., Niendam, T.A., Loewy, R.L., Ventura, J., & Cannon, T.D. (2005). The psychosis prodrome in adolescent patients viewed through the lens of DSM-IV. *J Child Adolesc Psychopharmacol*, 15(3), 434-51.

Miller, P.M., Byrne, M., Hodges, A., Lawrie, S.M., & Johnstone, E.C. (2002). Childhood behaviour, psychotic symptoms and psychosis onset in young people at high risk of schizophrenia: early findings from the Edinburgh high risk study. *Psychol Med*, 32, 173-179.

Moldin, S.O. (2000). *Gender and schizophrenia: an overview*. In: Frank, E. (Ed.). Gender and its effects on psychopathology (pp. 169–186). Washington DC: American Psychiatric Press.

Mortensen, E.L., Sorensen, H.J., Jensen, H.H., Reinisch, J.M., & Mednick, S.A. (2005). IQ and mental disorder in young men. *Br J Psychiatry,* 187, 407–415.

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.

Murray, R.M., & Lewis, S.W. (1987). Is schizophrenia a neurodevelopmental disorder? *Br Med Journal*, 295, 681-82.

Murray, R.M., O'Callaghan, E., Castle, D.J., & Lewis, S.W. (1992). A neurodevelopmental approach to the classification of schizophrenia. *Schizophr Bull*, 18(2), 319-332.

Muratori, F., Salvadori, F., D'Arcangelo, G., Viglione, V., & Picchi, L. (2005). Childhood psychopathological antecedents in early onset schizophrenia. *Eur Psychiatry,* 20, 309–314.

Nagler, S., & Glueck, Z. (1985). The Clinical Interview. *Schizophr Bull*, 11, 38-47.

Narvaez, J.M., Twamley, E.W., McKibbin, C.L., Heaton, R.K., & Patterson, T.L. (2008). Subjective and objective quality of life in schizophrenia. *Schizophr Res,* 98(1-3), 201–208.

Nelson, M., Seal, M., Phillips, L., Merritt, A.H., Wilson, R., & Pantelis, C. (2011). An investigation of the relationship between cortical connectivity and schizotypy in the general population. *J Nerv Ment Dis*, 199, 348-353.

Neumann, C.S., Grimes, K., Walker, E.F., & Baum, K. (1995). Developmental pathways to schizophrenia: behavioral subtypes. *J Abnorm Psychol,* 104(4), 558-566.

Niendam, T.A., Bearden, C.E., Rosso, I.M., Sanchez, L.E., & Hadley, T. (2003). A Prospective Study of Childhood Neurocognitive Functioning in Schizophrenic Patients and their Siblings. *Am J Psychiatry*, 160, 2060–2062.

Noguchi, H., Hori, H., & Kunugi, H. (2008). Schizotypal traits and cognitive function in healthy adults. *Psychiatry Res,* 161(2), 162–169.

Offord, D.R., & Cross, L.A. (1969). Behavioral antecedents of adult schizophrenia: a review. *Arch Gen Psychiatry, 2*1(3), 267-83.

Offord, D.R. (1974). School performance of adult schizophrenics their siblings and age mates. *Br J Psychiatry*, 125, 12–19.

Orsel, S., Akdemir, A., & Dag, I. (2004). The sensitivity of quality-of-life scale WHOQOL-100 to psychopathological measures in schizophrenia. *Compr Psychiatry,* 45(1), 57-61.

Ott, S.L., Spinelli, S., Rock, D., Roberts, S., Amminger, G.P., & Erlenmeyer-Kimling, L. (1998). The New York High-Risk Project: social and general intelligence in children at risk for schizophrenia. *Schizophr Res,* 31, 1–11.

Palmer, B. A., Pankratz, V. S., & Bostwick, J. M. (2005). The lifetime risk of suicide in schizophrenia: a reexamination. *Arch Gen Psychiatry*, 62, 247–253.

Pfohl, B., & Andreasen, N. (1986). *Schizophrenia: diagnosis and classification.* In: Hales, F.A. (Ed.). Psychiatry update, vol. 5 (pp. 38–51). Washington DC: American Psychiatric Press.

Pine, D.S., Alegria, M., Cook, E.H., Costello, E.J., Dahl, R.E., Koretz, D., Merikangas, K.R., Reiss, A.L., & Vitiello, B. (2002). *Advances in developmental science and DSM-V.* In: Kupfer, D.J., First, M.B., & Regier, D.E. (Eds.). A research agenda for DSM-V (pp. 85–122). Washington, DC: American Psychiatric Association.

Proctor, S.E., Mitford, E., & Paxton, R. (2004). First episode psychosis: a novel methodology reveals higher than expected incidence; a reality-based population profile in Northumberland, UK. *J Eval Clin Pract*, 10(4), 539-47.

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

Raine, A., Reynolds, C., Lencz, T., Scerbo, A., Triphon, N., & Kim, D. (1994). Cognitive-perceptual, interpersonal, and disorganized features of schizotypal personality. *Schizophr Bull*, 20, 191-201.

Raine, A. (2006). Schizotypal personality: neurodevelopmental and psychosocial trajectories. *Annu Rev Clin Psychol,* 2, 291–326.

Reynolds, C., Raine, A., Mellingen, K., Venables, P., & Mednick, S. (2000). Three-factor model of schizotypal personality: invariance across culture, gender, religious affiliation, family adversity, and psychopathology. *Schizophr Bull*, 26, 603–618.

Rosenfield, S. (2000). Gender and dimensions of the self: implications for internalizing and externalizing behavior. In: Frank, E. (Ed.), *Gender and its effects on psychopathology.* American Psychopathological Association Series (pp. 23–36). Washington, DC, American Psychiatric Press.

Rossi, A., Pollice, R., Daneluzzo, E., Marinangeli, M., & Stratta, P. (2000). Behavioral neurodevelopment abnormalities and schizophrenic disorder: a retrospective evaluation with the Childhood Behavior Checklist (CBCL). *Schizophr Res*, 44, 121–128.

Rosso, I., Bearden, C., Hollister, J., Gasperoni, T., Sanchez, L., Hadley, T., & Cannon, T. (2000). Childhood neuromotor dysfunction in schizophrenia patients and their unaffected siblings: a prospective cohort study. *Schizophr Bull,* 26, 367-378.

Rubino, I.A., Frank, E., Croce Nanni, R., Pozzi, D., Lanze di Scalea, T., & Siracusano, A. (2009). A comparative study of Axis I antecedents before age 18 of unipolar depression, bipolar disorder and schizophrenia. *Psychopathology*, 42, 325-332.

Schuklenk, U. (2001). Helsinki Declaration revisions. *Issues Med Ethics*, 9, 29.

Scott, J., Martin, G., Welham, J., Bor, W., Najman, J., O'Callaghan, M., Williams, G., Aird, R., & McGrath, J. (2009). Psychopathology during childhood and adolescence predicts delusional-like experiences in adults: a 21-year birth cohort study. *Am J Psychiatry*, 166, 567–574.

Seidman, L.J., Buka, S.L., Goldstein, J.L., & Tsuang, M.T. (2006). Intellectual decline in schizophrenia: evidence from a prospective birth cohort 28 year follow-up study. *J Clin Exp Neuropsychol*, 28, 225–242.

Siever, L.J. (1985). Biological markers in schizotypal personality disorder. *Schizophr Bull*, 11, 564-575.

Silverman, J.M., Mohs, R.C., Davidson, M., Losonczy, M.F., Keefe, R.S.E., Breitner, J.C.S., Sorokin, J.E., & Davis, K.L. (1987). Familial schizophrenia and treatment response. *Am J Psychiatry,* 144, 1271-1276.

Sørensen, H.J., Mortensen, E.L., Parnas, J., & Mednick, S.A. (2006). Premorbid neurocognitive functioning in schizophrenia spectrum disorder. *Schizophr Bull*, 32, 578–583.

Sørensen, H.J., Mortensen, E.L., Schiffman, J., Ekstrøm, M., Denenney, D., & Mednick, S.A. (2010). Premorbid IQ and adult schizophrenia spectrum disorder: Verbal performance subtests. *Psych Research,* 178, 23–26.

Stahlberg, O., Soderstrom, H., Rastam, M.,& Gilberg, 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.

SOI-2006 (Standaard Onderwijs Indeling; Standard Classification of Education); see Central Bureau for Statistics, 2006.

Suvisaari, J.M., Taxell-Lassas, V., Pankakoski, M., Haukka, J.K., Lönnqvist, J.K., & Häkkinen, L.T. (2012). Obstetric complications as risk factors for schizophrenia spectrum psychoses in offspring of mothers with psychotic disorder. *Schizophr Bull,* 39(5), 1056-1066.

Tandon, R. Nasrallah, H.A., & Keshavan, M.S. (2009). Schizophrenia, "just the facts" 4. Clinical features and conceptualization. *Schizophr Res*, 110, 1–23.

Torgersen, S. (1985). Relationship of schizotypal personality disorder to schizophrenia: genetics. *Schizophr Bull*, 11(4), 554-563.

Tsuang, M., Stone, W., Tarbox, S., & Faraone, S. (2002). An integration of schizophrenia with schizotypy: identification of schizotaxia and implications for research on treatment and prevention. *Schizophr Res,* 54, 169-175.

Urfer-Parnas, A., Mortensen, E.L., Saebye, D., & Parnas, J. (2010). Premorbid IQ in mental disorders: a Danish draft-board study of 7486 psychiatric patients. *Psychol Med,* 40, 547–556.

Van Engeland, H. (1990). Some premorbid characteristics related to breakdown in children with schizophrenic mothers. In: Rothenberger, A. (Ed). *Brain and Behavior in Child Psychiatry.* Elmsford, New York: Pergamon Press.

Van Engeland, H., & Van der Gaag, J. (1994). MCDD in childhood: a precursor of schizophrenic spectrum disorders. *Schizophr Res*, 11(2), 197-201.

Vollema, M., & Hoijtink, H. (2000). The multidimensionality of self-report schizotypy in a psychiatric population: an analysis using multidimensional rasch models. *Schizophr Bull*, 26, 565-575.

Vollema, M.G., Sitskoorn, M.M., Appels, M.C.M., & Kahn, R. (2002). Does the schizotypal personality questionnaire reflect the biological-genetic vulnerability to schizophrenia? *Schizophr Res,* 54, 39-45.

Vorunganti, L., Heslegrave, R., Awad, A.G., & Seeman, M.V. (1998). Quality of life measurement in schizophrenia: reconciling the quest for subjectivity with the question of reliability. *Psychol Med,* 28(1), 165-172.

Velthorst, E., Nieman, D., Becker, H., Van de Fliert, R., Dingemans, P., Klaassen, R., De Haan, L., Van Amelsvoort, T., & Linszen, D. (2009). Baseline differences in clinical symptomatology between ultra high risk subjects with and without a transition to psychosis. *Schizophr Res*, 109, 60–65.

Walker, E., Lewis, N., Loewy, R., & Palyo, S. (1999). Motor dysfunction and risk for schizophrenia. *Devel Psychopathol,* 11, 509–523.

Watt, N., & Lubensky, A. (1976). Childhood roots of schizophrenia. *J Consult Clin Psychol*, 44, 363-375.

Watt, N. (1978). Patterns of Childhood Social Development in Adult Schizophrenics. *Arch Gen Psychiatry*, 35(2), 160-165.

Welham, J., Scott, J., Williams, G., Najman, J., Bor, W., O'Callaghan, M., & McGrath, J. (2009). Emotional and behavioural antecedents of young adults who screen positive for non-affective psychosis: a 21- year birth cohort study. *Psychol Med*, 39, 625-634.

Weinberger, D.R. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry*, 44(7), 660-669.

Weintraub, S., Prinz, R., & Neale, J. (1978). Peer evaluations of the competence of children vulnerable to psychopathology. *J Abnorm Child Psychol*, 6, 461-473.

Wiersma, D., Wanderling, J., Dragomirecka, E., Ganev, K., Harrison, G., An Der Heiden, W., Nienhuis, F.J., & Walsh, D. (2000). Social disability in schizophrenia: its development and prediction over 15 years in incidence cohorts in six European centres. *Psychol Med,* 30(5), 1155-67.

Weiser, M., Reichenberg, A., Rabinowitz, J., Kaplan, Z., Mordechai, M., Nahon, D., & Davidson, M. (2000). Gender differences in premorbid cognitive performance in a national cohort of schizophrenic patients. *Schizophr Res,* 45, 185–190.

Wilson, I.B., & Cleary, P.D. (1995). Linking clinical variables with health related quality of life: a conceptual model of patient outcomes. *JAMA*, 273(1), 59-65.

Whitehorn, D., Richard, J.C., & Kopala, L.C. (2004). Hospitalization in the first year of treatment for schizophrenia. *Can J Psychiatry* 49(9), 635-8.

Xiang, Y., Weng, Y., Leung, C., Tang ,W., & Ungvari, G.S. (2007). Quality of life of Chinese schizophrenia outpatients in Hong Kong: relationship to sociodemographic factors and symptomatology. *Aust N Z J Psychiatry*, 41(5), 442-449.

Zammit, S., Allebeck, P., David, A.S., Dalman, C., Hemmingsson, T., Lundberg, I., & Lewis, G. (2004). A longitudinal study of premorbid IQ score and risk of developing schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses. *Arch Gen Psychiatry*, 61, 354–360.

Zigler, E., Levine, J., & Zigler, B. (1977). Pre-morbid social competence and paranoid-non paranoid status in female schizophrenic patients. *J Nerv Ment Dis*, 164, 333-339.

Chapter 2

How schizotypal symptoms affect objective and subjective quality of life in a clinical cohort

Fagel, S.S.A.A., Swaab, H., Van Engeland, H., & De Sonneville, L.M.J. How the presence of schizotypal symptoms affects objective and subjective quality of life: A follow-up of child and adolescent psychiatric patients into adulthood. *Revised manuscript under review.*

Abstract

It is unclear how subclinical symptoms of schizophrenia spectrum pathology impact on Quality of Life in psychiatric patients. It is examined how adult schizotypal symptoms affect objective QoL and subjective QoL (OQoL;SQoL) in a clinical cohort. 690 patients of the Department of Child and Adolescent Psychiatry of the University Medical Centre Utrecht, the Netherlands, were reassessed after 15.0 years (*SD*=5.3) for adult schizotypal symptoms using Schizotypal Personality Questionnaire-Revised. Associations between schizotypal symptoms, distinctive schizotypal symptoms and OQoL were analyzed using (M)ANOVA. The strength of the relation between schizotypal symptoms and seven domains of SQoL were examined by computing Pearson's bivariate correlations. Partial correlations were computed between each symptom dimension and domain of SQoL while statistically controlling for the other two symptom dimensions. Each schizotypal dimension unfavorably affected each domain of OQoL. Negative schizotypal symptoms had the largest effect on OQoL. Impoverished SQoL, in particular dissatisfaction with social contacts, was predominantly influenced by negative schizotypal symptoms. The findings show that the extent of schizotypal symptomatology in psychiatric patients already characterized by a decreased level of QoL even further modifies QoL in an unfavorable way. Negative schizotypal symptoms most strongly affected OQoL and SQoL.

Introduction

Literature so far has extensively reported about the very unfavorable impact of schizophrenia spectrum pathology on the patients' Quality of Life (QoL). Schizophrenia spectrum pathology is composed of multiple conditions that are characterized by distortions of cognitive and perceptual reality, collectively known as positive symptoms, interpersonal withdrawal (negative symptoms), and disorganized speech and behavior (disorganized symptoms) (Liddle, 1987; Suhr & Spitznagel, 2001). Several studies, probing into how impoverished QoL relates to these heterogeneous manifestations of schizophrenia spectrum pathology, reported consistent results, in that general schizophrenia spectrum pathology (Awad, 1992; Awad, Hogan, Vorungati, & Heslegrave, 1995) and negative symptoms in particular seem to have a more profound influence on QoL than positive or disorganized symptoms (Browne et al., 1996; Corrigan & Buican, 1995; Fitzgerald et al., 2001; Law et al., 2005, Malla & Payne, 2005, Meltzer, Burnett, Bastani, & Ramirez, 1990; Orsel, Akdemir, & Dag, 2004; Wilson & Cleary, 1995; Xiang, Weng, Lueng, Tang, & Ungvari, 2007). By discriminating 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), studies have reported that each of the symptom domains is associated with reduced OQoL and SQoL (Cohen & Davis, 2009), but again negative symptoms are specifically associated with worse OQoL (Cohen & Davis, 2009; Fitzgerald et al., 2001; Fitzgerald et al., 2003; Narvaez, Twamley, McKibbin, Heaton, & Patterson, 2008) and SQoL (Cohen & Davis, 2009).

There is, however, a caveat. Since previous studies have only included typically developing controls for comparison and 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 remains unanswered in what way the presence of schizophrenia spectrum symptomatology in psychiatric patients specifically relates to QoL. The answer to this question would carry relevant information for treatment protocols aimed to improve QoL in patients with schizophrenia spectrum symptomatology.

Moreover, as only a minority of individuals at risk to develop schizophrenia spectrum pathology will show manifest illness (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Meehl, 1962; Tsuang, Stone, Tarbox, & Faraone, 2002), it is considered more clinically relevant to investigate how subclinical schizophrenia-like abnormalities, i.e., schizotypal symptoms, affect OQoL and SQoL in a cohort of patients who all sought

psychiatric help during child age.

The aim of this study was to examine how adult schizotypal symptoms affect OQoL and SQoL in psychiatric patients. It is hypothesized that elevated schizotypal symptoms, in particular negative symptoms, are associated with worse OQoL and SQoL.

Method

Participants and procedure

This study is part of a longitudinally prospective study designed to evaluate both global and clinical outcomes in adulthood of patients, referred during 1984 to 2004 (T1), to the Department of Child and Adolescent Psychiatry at the University Medical Centre of Utrecht (UMCU), the Netherlands. Patients meeting the following criteria were approached for participation during 2006 to 2010 (T2): (1) aged 18 years or younger at T1, (2) aged 18 years or older at T2, (3) presence of axis I diagnosis based on Diagnostic Statistical Manual (DSM) criteria of the American Psychiatric Association (1980, 1987, 1994), (4) no axis II DSM diagnosis (1980, 1987, 1994) of mental retardation (IQ<70) at T1, and (5) no axis I DSM diagnosis before or at T1 with child psychotic disorder, schizophrenia or any other psychotic disorder, bipolar disorder or dissociative disorder. There were 2690 non-retarded patients who were suitable candidates for follow-up. They were sent a letter informing them about the aims of the study, asking them to participate in the study. The patients who did not respond were contacted by phone when they could be traced in the public phone registry, to explain the aim of the study and to encourage participation. A total of 2000 patients declined participation, resulting in a final sample consisting of 690 (306 male and 384 female) adult patients with age 12.2 years (*SD*=3.9) at T1, and reassessed at the age of 27.2 years (*SD*=5.6) at T2. The intelligence profile of the group was within the normal range with a total IQ of 103.4 (*SD*=14.2), a performance IQ of 104.5 (*SD*=15.6), and a verbal IQ of 103.1 (*SD*=14.2). The ethical principles of the Helsinki Declaration (Schluklenk, 2001) were followed and ethical approval was obtained from the Medical Ethical Committee of the University Medical Centre of Utrecht (number 05-319/K). Table 1 describes the juvenile DSM diagnostic categories of participants.

Table 1. Juvenile DSM diagnostic categories of participants

Juvenile DSM diagnostic category	***n***
Affective disorders	151
Attention-deficit and disruptive behavior disorders	147
Eating disorders	138
Pervasive Developmental Disorders	62
Other conditions that may be a focus of clinical attention	39
Deferred diagnoses axis I or II	25
Other disorders of infancy, childhood, or adolescence	23
Somatoform disorders	22
Sexual and gender identity disorders	20
Tic disorders	18
Adjustment disorders	18
Elimination disorder	10
Communication disorder	8
Learning disorders	7
Substance related disorders	1
Sleeping disorders	1

Non-participants

Participants and non-participants were compared on age, gender distribution and IQ. Proportionally more participants appeared to be females (55.7 % female participants versus 38.5% female dropouts; $\chi^2(1,2690)=61.986$, $p<0.001$). The participants were slightly older at T1 (M=12.1; *SD*=3.9) than the dropouts (M=11.6; *SD*=4.0; $F(1,2669)=11.695$, $p=0.001$, $\eta_p^2=.004$), but did not differ on age at T2 (M=27.2; *SD*=5.6 vs. M=27.0; *SD*=5.6). Participants had a higher intelligence than dropouts, but differences were small for total IQ (M=104.2; *SD*=14.3 vs. M=100.3; *SD*=14.0; $F(1,995)=15.157$, $p<0.001$, $\eta_p^2=.015$), verbal IQ (M=103.2; *SD*=14.1 vs. M=99.2; *SD*=14.2; $F(1,995)=16.048$, $p<0.001$, $\eta_p^2=.016$), and performance IQ (M=104.5; *SD*=15.7 vs. M=101.6; *SD*=14.2; $F(1,995)=7.247$, $p=0.007$, $\eta_p^2=.007$).

Measurement instruments

Adult schizotypal symptoms

Adult schizotypal symptoms were measured using the revised 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 (American Psychiatric Association, 1987) criteria for schizotypal personality disorder (Raine, 1991). In the study of Raine (1991) 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 ($\chi^2=7.3$, $p=0.007$). 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. Factor analytical studies have revealed three schizotypal dimensions, i.e., positive, negative, and disorganized symptoms (Raine, 1994, Vollema & Hoijtink, 2000). This factor structure has been found to be invariant to gender, ethnicity, religion, and social background (Reynolds, Raine, Mellingen, Vanables, & Mednick, 2000), and it parallels the factor structure obtained in schizophrenia patients (Raine, 2006). Vollema, Sitskoorn, Appels & 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. The SPQ has high internal reliability (0.91), test-retest reliability (0.82), convergent validity (0.59 to 0.81), discriminant validity (0.63), and criterion validity, 0.68; Raine, 1991). All items endorsed "yes" are scored 1. Higher scores on the SPQ-R indicate higher levels of schizotypal symptoms, with a range of 0 to 100 for the SPQ total

score, 0 to 38 for the SPQ positive factor, 0 to 43 for the SPQ negative factor, and 0 to 19 for the SPQ disorganized factor.

Objective and Subjective Quality of Life

Objective and Subjective quality of life were evaluated using a questionnaire concerning global and clinical outcome in adult life which was developed at the Department of Child and Adolescent Studies of Leiden University and consisted of two sections. 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 two((pre)primary education) to seven (second stage of tertiary education). The level of education of the patients was reported on the basis of the Standaard Onderwijs Indeling (SOI-2006; Central Bureau for Statistics, 2006), which is based on the International Standard Classification of Education (ISCED; 1997). The second section examined self-reported Subjective measures of QoL (SQoL), i.e., 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. Self-reported measures of OQoL and SQoL were used since patients have been shown to assess their QoL accurately and consistently (Becchi, Rucci, Placentino, Neri, & De Girolamo, 2004; Reynolds, et al. 2000), and self-reported measures of QoL have been found to be more valid than clinician-reported QoL measures (Narvaez, et al., 2008).

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences 21.0 (SPSS Inc, Chicago, Il, USA). To examine how adult schizotypal symptoms affect different categories of OQoL,univariate and multivariate analysis of variances ((M)ANOVA) were performed with total schizotypal symptoms and factor scores as dependent variables respectively, and each OQoL domain as between subjects factor. For specific within-domain group by group comparisons on total schizotypal symptoms, post-hoc

analyses were performed using Bonferroni correction for multiple testing. Partial eta squared (η_p^2) was used to estimate effect sizes, with η_p^2~0.03 representing a weak effect, η_p^2~0.06 representing a moderate effect and η_p^2≥0.14 representing a significantly large effect (Stevens, 2002). The strength of the relation of total schizotypal symptoms with all seven domains of SQoL were examined by computing Pearson's bivariate correlations (rs) (small effect size: r_s=0.1−0.23; medium: r_s=0.24−0.36; large: r_s≥0.37) (Cohen, 1992). In addition, to determine the unique contribution of each schizotypal symptom scale to each SQoL domain, partial correlations were computed between each symptom dimension and each of the seven domains of SQoL while statistically controlling for the other two symptom dimensions. Alpha was set at .01.

Results

Adult schizotypal symptoms and OQoL

Higher levels of adult schizotypal symptoms were significantly associated with lower levels on each of the six OQoL domains. i.e., Employment (F(3,686)=15.473, p<0.001, η_p^2=.063), Marital status (F(1,688)=22.220, p<0.001, η_p^2=.031), Living arrangement (F(2,687)=14.805, p<0.001, η_p^2=.041), Mental health care (F(1,688)=68.702, p<0.001, η_p^2=.091), Medication use (F(2,687)=34.472, p<0.001, η_p^2=.091), and Educational level (F(5,684)=9.986, p<0.001, η_p^2=.068). Post-hoc univariate analyses revealed significant higher levels of schizotypal symptoms for the following groups: social security recipients in comparison with employed patients (p<0.001) and patients who were in training (p<0.001), single patients in comparison with patients who were married or living together with their partner (p<0.001), institutionalized patients in comparison with patients who lived together with their parents or other family members (p<0.001) or who were self-reliant (p<0.001), patients who were currently receiving mental health care in contrast to patients who did not (p<0.001), patients who were currently using medication compared to patients who did not (p<0.001) or in the past (p<0.001), patients who only received (pre) primary or secondary education in comparison with patients who fulfilled first stage tertiary education (p<0.001), and second stage tertiary education (p<0.001), and patients who only received upper secondary education in comparison with second stage of tertiary eduation. (See Table 2).

Table 3. Schizotypal symptomatology and Subjective QoL (*n*=690)

	Total schizotypal symptoms		Positive schizotypal symptoms		Negative schizotypal symptoms		Disorganized schizotypal symptoms	
Subjective QoL domain	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Living arrangement	-.222	<.001	-.012	.752	-.175	<.001	.040	.296
Employment or education	-.338	<.001	-.062	.104	-.157	<.001	-.045	.237
Physical health	-.305	<.001	-.123	.001	-.083	.029	-.038	.326
Partner-relationship	-.332	<.001	.087	.022	-.222	<.001	-.124	.001
Social contacts	-.394	<.001	.138	<.001	-.402	<.001	.009	.820
Mood	-.434	<.001	-.028	.457	-.305	<.001	.011	.772
Future perspective	-.418	<.001	.038	.318	-.283	<.001	-.080	.037

Table 4. Negative schizotypal traits and Subjective QoL domains (*n*=690)

	Ideas of reference	Excessive social anxety	No close friends	Constricted affect	Suspiciousness
Subjective Qol domains	*r*	*r*	*r*	*r*	*r*
Living arrangement	-.197*	-.203*	-.187*	-.178*	-.320*
Employment or education	-.192*	-.314*	-.252*	-.248*	-.308*
Physical health	-.215*	-.261*	-.155*	-.187*	-.312*
Partner-relationship	-.241*	-.299*	-.291*	-.284*	-.288*
Social contacts	-.239*	-.427*	-.446*	-.364*	-.341*
Mood	-.338*	-.412*	-.366*	-.321*	-.393*
Future perspective	-.264*	-.404*	-.356*	-.369*	-.360*

*p<.001

Total schizotypal symptoms and SQoL

Pearson bivariate correlations between Total schizotypal symptoms and each of the seven SQoL domains separately revealed that Total schizotypal symptoms negatively affected SQoL in each of the seven domains (see Table 3).

Schizotypal symptom dimensions and OQoL

The MANOVAs of the three schizotypal symptom dimensions for each of the OQoL domain separately, revealed that higher levels of schizotypal symptoms were significantly associated with lower OQoL, i.e., Employment, (F(3,686)=5.392, p<0.001, η_p^2=.023), Marital status, (F(3,686)=12.994, p<0.001, η_p^2=.054), Living arrangement (F(3,685)=7.594, p<0.001, η_p^2=.032), Mental health care (F(3,686)=22.957, p<0.001, η_p^2=.091), Medication use (F(6,686)=11.670, p<0.001, η_p^2=.049), and Educational level (F(15,684)=5.726, p<0.001, η_p^2=.040). In general, effect sizes were highest for negative schizotypal symptoms and lowest for positive schizotypal symptoms. The univariate analyses revealed that higher levels of positive, negative and disorganized schizotypal symptoms corresponded with worse outcome on each OQoL domain, i.e., patients showing highest levels of schizotypal symptoms were the ones who were social security recipients, were single, institutionalized, who currently used medication or received mental health care, or who had a lower Educational level. (See Table 2).

Schizotypal symptomatology and SQoL

Partial correlations between each schizotypal symptom dimension and each SQoL domain revealed that negative schizotypal symptoms were significantly correlated with all SQoL domains, except physical health, indicating that level of negative symptoms were inversely related to SQoL (see Table 3). These associations were particularly substantial for dissatisfaction with social contacts, mood, and patient's future perspective. Positive symptoms showed significant but opposite relations with SQoL domains, i.e., satisfaction with social contacts being positively associated and satisfaction with physical health being negatively associated. Disorganized schizotypal symptoms were only significantly correlated with dissatisfaction with partner-relationship. (See Table 3).

Table 2. Schizotypal symptomatology and Objective QoL

	Total schizotypal symptoms					Positive schizotypal symptoms			
	n	M	*SD*	*p*	η_p^2	M	*SD*	*p*	
Employment									
In training	76	24.2	15.9			8.4	6.4		
Employed	482	22.4	17.5			7.5	6.2		
Sheltered employed	14	30.4	23.0			11.4	10.4		
Social security recipient	118	34.9	21.3	<.001	.063	11.3	8.7	<.001	
Marital Status									
Single	371	28.0	18.7			8.9	7.0		
Married or living together	319	21.3	18.1	<.001	.031	7.7	6.9	.027	
Living Arrangement									
Self-reliant	495	23.3	19.0			8.1	7.1		
With parents or other family members	154	26.3	16.7			8.3	6.2		
Institutionalized	41	39.2	16.1	<.001	.041	12.3	7.0	.001	
Mental health care									
Yes	150	35.6	20.6			11.9	7.9		
No	540	21.9	17.1	<.001	.091	7.4	6.4	<.001	
Medication use									
At this moment	130	36.1	20.2			11.8	8.1		
None, but medication use in the past	106	26.2	17.5			8.9	6.5		
None	454	21.4	17.2	<.001	.091	7.2	6.4	<.001	
Educational level (SOI)									
SOI 1+2: (Pre) primary education	46	33.3	18.5			9.5	6.3		
SOI 3 : Lower secondary education	119	31.1	19.1			10.3	7.4		
SOI 4 : Upper secondary education	322	25.2	19.6			8.6	7.2		
SOI 5 : Post-secondary non-tertiary education	6	32.7	14.4			15.3	7.4		
SOI 6 : First stage of tertiary education	128	19.6	15.9			7.0	6.4		
SOI 7 : Second stage of tertiary education	69	16.7	11.9	<.001	.068	5.3	4.2	<.001	

		Negative schizotypal symptoms				Disorganized schizotypal symptoms			
	η_p^2	M	*SD*	*p*	η_p^2	M	*SD*	*p*	η_p^2
		11.1	8.0			4.5	4.1		
		10.6	9.1			4.3	4.5		
		13.6	9.2			5.5	5.5		
	.045	16.7	10.0	<.001	.059	6.9	5.3	<.001	.042
		13.4	9.5			5.6	4.9		
	.007	9.8	9.0	<.001	.037	3.8	4.3	<.001	.037
		10.9	9.4			4.4	4.6		
		12.9	9.2			5.21	4.6		
	.020	18.0	8.1	<.001	.036	9.0	4.4	<.001	.053
		16.9	10.2			6.9	5.1		
	.071	10.3	8.7	<.001	.082	4.2	4.5	<..001	.054
		17.0	9.8			7.3	5.2		
		12.7	9.3			4.6	4.4		
	.065	10.0	8.8	<.001	.082	4.1	4.4	<.001	.064
		16.1	9.4			7.7	5.3		
		14.6	9.5			6.2	5.0		
		12.0	9.9			4.6	4.7		
		15.0	9.2			2.3	2.1		
		8.8	7.8			3.8	4.2		
	.051	8.1	7.0	<.001	.063	3.3	3.5	<.001	.063

Negative schizotypal traits and SQoL

Further exploration of the different negative schizotypal traits, i.e., ideas of reference, social anxiety, no close friends, constricted affect, and suspiciousness (together representing the negative schizotypal symptom dimension), and SQoL showed that all of the traits were negatively associated with all SQoL domains (p<0.001). Highest correlations were found for satisfaction with social contacts, future perspective, and mood (.264<r<.446). (See Table 4).

Discussion

In contrast to earlier studies that have mainly evaluated QoL in psychiatric patients in comparison to typically developing controls, the present follow-up study focused on the question whether and how the presence of schizotypal symptoms influences the level of OQoL and SQoL in a sample of patients representing a wide spectrum of psychiatric disorders. It was found that each schizotypal dimension, i.e., positive, negative and disorganized schizotypal symptoms, unfavorably affected each domain of OQoL. Impoverished QoL, and in particular dissatisfaction with social contacts, was predominantly influenced by negative schizotypal symptoms.

Objective QoL

Elevated levels of positive, negative and disorganized schizotypal symptomatology corresponded with less favorable outcomes across all OQoL domains: i.e., increased dependency on institutionalized residence, unemployment or institutionalized employment, lower education, more need for mental health care and more use of medication. In addition to findings of earlier studies that have reported about the very profound impact of schizotypal symptomatology on OQoL, referenced against the QoL of normal controls only (Cohen & Davis, 2009), the present results add to these findings, by showing that the extent of schizotypal symptomatology in a sample of psychiatric patients already characterized by a decreased level of QoL, even further modifies the QoL in an unfavorable way. It was also shown that the extent of negative schizotypal symptoms had the largest effect on OQoL. This is consistent with reports about negative schizotypal symptoma-

tology being associated with lower OQoL (Fitzgerald et al., 2001; Fitzgerald et al., 2003; Narvaez et al, 2008).

Subjective QoL

Interestingly, impoverished SQoL was almost exclusively accounted for by negative, and not positive or disorganized schizotypal symptoms, and this unfavorable influence extended to all domains of SQoL. The finding that in psychiatric patients, SQoL is inversely related to the severity of negative symptomatology, supports the findings of earlier studies that focused on individuals with schizophrenia or schizoaffective disorder (Browne et al., 1996; Huppert et al., 2001) or first episode psychosis (Law et al., 2005; Wegener et al., 2005) and typically developing controls (Cohen & Davis, 2009), and again emphasizes the effect that negative symptoms have on a person´s SQoL.

The unfavorable impact of negative schizotypal symptoms is further illustrated by the post-hoc evaluation of the association between total schizotypal symptoms and SQoL, after adjusting for the influence of negative schizotypal symptomatology. In that case, Total schizotypal symptoms remain only negatively associated with satisfaction with physical health ($r(687)=-.136$, $p<0.001$), and with social contacts in the opposite direction ($r(687)=.129$, $p<0.001$).

One explanation for the unfavorable effect of negative schizotypal symptomatology on SQoL might be found in Calman's gap (Calman, 1984), i.e., that a person's SQoL can be equivalent to the narrowness of the gap between a person's expectations and achievements and how this gap is influenced by a person's affective state, i.e., the affective fallacy (Schwarz & Clore, 1983). There are two ways of keeping Calman´s gap narrow: being successful in arriving at one's aims on the one hand, and lowering one's level of aspiration on the other hand (Katschnig, 2000). As a consequence of a person's affective state, it has been found that depressed patients experience their own well-being, social functioning and living conditions more worse than they appear to be for an independent observer (Kay, Roth, & Beamish, 1964), while, for example, manic patients rate their SQoL as very good (Katschnig, 1997). In accordance to Calman's gap, patients scoring high on negative symptoms might therefore have higher personal expectations rather than being less successful. Since this is especially relevant to target specific interventions, this issue needs further investigation.

Social contacts

Dissatisfaction with social contacts showed strongest associations with schizotypal symptomatology and particularly pertained to patients scoring high on negative schizotypal symptoms. This result is in accordance with the finding of Cohen & Davis (2009) who reported that negative symptoms showed the most striking unique contributions to QoL and in particularly to those domains associated with social relationships. Surprisingly, severity of positive schizotypal symptoms was associated with more satisfaction with social contacts. The nature of this distinctive association between schizotypal symptoms and dissatisfaction with social contacts is unclear. Although suggestive, this might be a consequence of a reduced need of social contacts. In accordance with Malmbergs suggestion (Malmberg, Lewis, David, & Allebeck, 1998), patients scoring high on negative schizotypal symptomatology might experience problems in approaching and initiating contact rather than having a lack of interest in relationships. More in-depth investigation of adult negative schizotypal traits indeed showed that (in order of the magnitude of the effect) excessive social anxiety, more constricted affect and higher levels of suspiciousness were especially associated with more dissatisfaction with social contacts. Whether patients scoring high on positive schizotypal symptomatology either experience less difficulty in approaching and initiating contact or have a lack of interest in relationships is unclear and needs further investigation.

Strengths and limitations

The number of 690 subjects in the final sample is considered to be substantial. Nevertheless, inherent to this long follow-up period, this study suffered from attrition as this number constitutes nearly 30% of the original sample. However, the background variables of the participants were in majority quiet similar to that of the non-participants, except for their slightly higher intelligence. Further, since the mean age of participants was 27.2 (*SD*=5.6) years, not all subjects may have passed the (full) period of risk for schizophrenia spectrum pathology, the level of schizotypal symptoms might therefore be underestimated. In addition, the screening by self-report does carry some limitations, as compared with interviews or observations. Self-report questionnaires might not ensure sufficient sensitivity and specificity for specific schizotypal signs such as an odd

or guarded appearance, an expression of aloofness, or poor eye contact, and restricted affect (Kendler, 1988). In future studies, direct observation of these specific symptoms might be a way to address these additional questions. Besides these limitations, the current study suited the purpose to illustrate how the presence of schizotypal symptoms affects OQoL and SQoL in a sample consisting of only subjects who sought psychiatric help at child age.

Conclusion

The present findings show that the extent of schizotypal symptomatology in psychiatric patients, who are already characterized by a decreased level of QoL, even further modifies QoL in an unfavorable way. Negative schizotypal symptoms most strongly affected OQoL and SQoL.

References

American Psychiatric Association. (1980). *Diagnostic and Statistical Manual of Mental Disorders (3rd ed.*). Washington DC: American Psychiatric Association Press.

American Psychiatric Association. (1987). *Diagnostic and Statistical Manual of Mental Disorders (3rd revised ed.).* Washington DC: American Psychiatric Association Press.

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders (4th ed.).* Washington DC: American Psychiatric Association Press.

Awad, A.G. (1992). Quality of life of schizophrenic patients on medications and Implications for new drug trials. *Hosp Community Psychiatry.* 43, 262-265.

Awad, A.G., Hogan, T.P., Voruganti, L.N., & Heslegrave, R.J. (1995). Patients' subjective experiences on antipsychotic medications: implications for outcome and quality of life. *Int Clin Psychopharmacol*, 10, 123-32.

Becchi, A., Rucci, P., Placentino, A., Neri, G., & De Girolamo, G. (2004). Quality of life in patients with schizophrenia: comparison of self-report and proxy assessments. *Soc Psychiatry Psychiatr Epidemiol*, 39, 397–401.

Browne, S., Roe, M., Lane, A., Gervin, M., Morris, M., Kinsella, A., Larkin, C., O'Callaghan, E. (1996). Quality of life in schizophrenia: relationship to sociodemographic factors, symptomatology and tardive dyskinesia. *Acta Psychiatr Scand,* 94, 118-124.

Calman, K.C. (1984). Quality of life in cancer patients: a hypothesis. *J Med Ethics,* 10, 124-127.

Chan, S., & Yu, I.W. (2002) Quality of life of clients with schizophrenia. *J Adv Nurs,* 45, 72–83.

Chapman, L.J., Chapman, J.P., Kwapil, T.R., Eckblad, M., & Zinser, M.C. (1994). Putatively psychosis-prone subjects 10 years later. *J Abnormal Psychol,* 103, 171-183.

Cohen, J. (1992). A power primer. *Psychol Bull,* 112, 155–15.

Cohen, A.S., & Davis, T.E. (2009). Quality of life across the schizotypy spectrum: findings from a large nonclinical adult sample. *Compr Psychiatry*, 50, 408–414.

Corrigan, P.W., & Buican, B. (1995). The construct validity of subjective quality of life for the severely mentally ill. *J Nerv Ment Dis*, 183, 281-285.

Danckaerts, M., Sonuga-Barke, E.J., Banaschewski, T., Buitelaar, J., Döpfner, M., Hollis, C., Santosh, P., Rothenberger, A., Sergeant, J., Steinhausen, H.C., Taylor, E., Zuddas, A., & Coghill, D. (2010). The quality of life of children with attention deficit/hyperactivity disorder: a systematic review. *Eur Child Adolesc Psychiatry,* 19, 83–10.

Fitzgerald, P.B., Williams, C.L., Corteling, N., Filia, S.L., Brewer, K., Adams, A., de Castella, A.R., Rolfe, T., Davey, P., & Kulkarni, J. (2001). Subject and observer-rated quality of life in schizophrenia. *Acta Psychiatr Scand*, 103, 387-92.

Fitzgerald, P.B., de Castella, A.R., Filia, K., Collins, J., Brewer, K., Williams, C.L., Davey, P., & Kulkarni, J. (2003). A longitudinal study of patient- and observerrated quality of life in schizophrenia. *Psychiatry Res*, 119, 55-62.

Huppert, J.D., Weiss, K.A., Lim, R., Pratt, S., & Smith, T.E. (2001). Quality of life in schizophrenia: contributions of anxiety and depression. *Schizophr Res*, 51, 171-180.

ISCED (International Standard Classification of Education; see United Nations Educational, Scientific and Cultural Organization) 1997.

Ishak, W.W., Greenberg, J.M., Balayan, K., Kapitanski, N., Jeffrey, J., Fathy, H., Fakhry, H., & Rapaport, M.H. (2011). Quality of Life: the ultimate outcome measure of interventions in major depresive disorder. *Harv Rev Psychiatry,* 19, 229-239.

Katschnig, H. (1997). How useful is the concept of quality of life in psychiatry? *Curr Opin Psychiatry,* 10, 337-345.

Katschnig, H. (2000). Schizophrenia and quality of life. *Acta Psychiatr Scand,* 102, 33-37.

Kay, D.W., Roth, M., & Beamish, P. (1964). Old age mental disorders in Newcastle-upon-Tyne, II. A study of possible social and medical causes. *Br J Psychiatry,* 110, 668-682.

Kendler, K.S. (1988). Familial aggregation of schizophrenia and schizophrenia spectrum disorders. Evaluation of conflicting results. *Arch Gen Psychiatry*, 45, 377-383.

Law, C.W., Chen, E.Y., Cheung, E.F., Chan, R.C., Wong, J.G., Lam, C.L., Leung, K.F., & Lo, M.S. (2005). Impact of untreated psychosis on quality of life in patients with first-episode schizophrenia. *Qual Life Res*, 14, 1803-1811.

Lehman, A.F. (1983). The well-being of chronic mental patients: assessing their quality of life. *Arch Gen Psych*, 40, 369-373.

Liddle, P.F. (1987). The symptoms of chronic schizophrenia: a reexamination of the positive and negative dichotomy. *Br J Psychiatry*, 151, 145.

Malmberg, A., Lewis, G., David, A., & Allebeck, A. (1998). Premorbid adjustment and personality in people with schizophrenia. *Br J Psychiatry,* 171, 308-313.

Malla, A., & Payne, J. (2005). First-episode psychosis: psychopathology, quality of life, and functional outcome. *Schizophr Bull*, 31, 650-71.

Meehl, P.E. (1962). Schizotaxia, schizotypy, schizophrenia. *Am Psychol*, 17, 827–838.

Meltzer, H.Y., Burnett, S., Bastani, B.,& Ramirez, L.F. (1990). Effects of six months of clozapine treatment on the quality of life of chronic schizophrenic patients. *Hosp Commun Psych,* 41, 892-897.

Narvaez, J.M., Twamley, E.W., Mckibbin, C.L. Heaton, R.K., & Patterson, T.L. (2008). Subjective and objective quality of life in schizophrenia. *Schizophr Res*, 98, 201–208.

Orsel, S., Akdemir, A., & Dag, I. (2004). The sensitivity of quality-of-life scale WHOQOL-100 to psychopathological measures in schizophrenia. *Compr Psychiatry*, 45, 57-61.

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

Raine, A., Reynolds, C., Lencz, T., Scerbo, A., Triphon, N., & Kim, D. (1994). Cognitive-perceptual, interpersonal, and disorganized features of schizotypal personality. *Schizophr Bull*, 20, 191-201.

Raine A. (2006). Schizotypal personality: neurodevelopmental and psychosocial trajectories. *Annu Rev Clin Psychol,* 2, 291–326.

Reynolds, C.A., Raine, A., Mellingen, K., Venables, P.H., & Mednick, S.A. (2000). Three-factor model of schizotypal personality: invariance across culture, gender, religious affiliation, family adversity, and psychopathology. *Schizophr Bull,* 26, 603–18.

Schuklenk, U. (2001). Helsinki Declaration revisions. *Issues Med Ethics*, 9, 29.

Schwarz, N., & Clore, G.L. (1983). Mood, misattribution, and judgments of well-being: Informative and directive functions of affective states. *J Personality Soc Psychol,* 45, 513-523.

SOI-2006 (Standaard Onderwijs Indeling [Standard Classification of Education]; see Central Bureau for Statistics) 2006.

Stevens, J. (2002). Two-group multivariate analysis of variances. In: Stevens, J. (Ed.). *Applied multivariate statistics for the social sciences, 4th edition* (pag 197). New Jersey: Lawrence Erlbaum Associates.

Suhr, J.A., & Spitznagel, M.B. (2001). Factor versus cluster models of schizotypal traits. I: a comparison of unselected and highly schizotypal samples. *Schizophr Res*, 52, 231–239.

Tsuang, M., Stone, W., Tarbox, S., & Faraone, S. (2002). An integration of schizophrenia with schizotypy: identification of schizotaxia and implications for research on treatment and prevention. *Schizophr Res*, 54, 169-175.

Vollema, M.Q., & Hoijtink, H. (2000). The multidimensionality of self-report schizotypy in a psychiatric population: an analysis using multidimensional rasch models. *Schizophr Bull*, 26, 565-575.

Vollema, M.G., & Sitskoorn, M.M., Appels, M.C.M., & Kahn, R. (2002). Does the schizotypal personality questionnaire reflect the biological-genetic vulnerability to schizophrenia? *Schizophr Res,* , 54, 39-45.

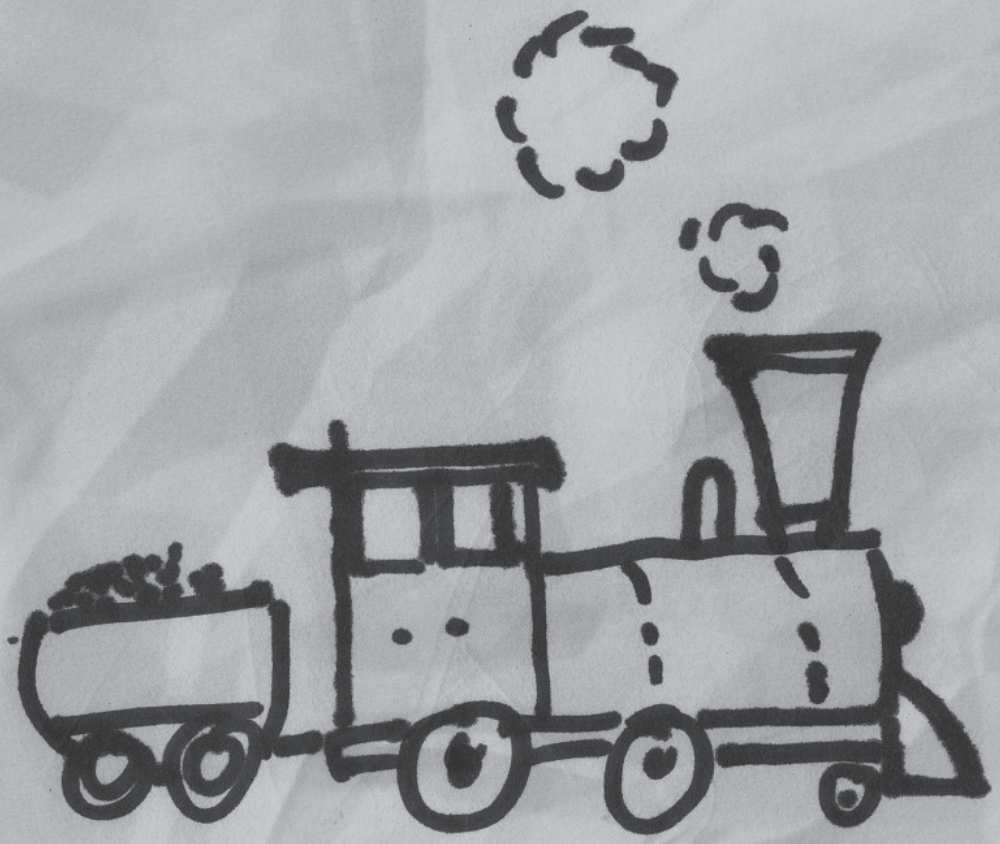
Vorunganti, L., Heslegrave, R., Awad, A.G., & Seeman, M.V. (1998). Quality of life measurement in schizophrenia: reconciling the quest for subjectivity with the question of reliability. *Psychol Med,* 28, 165-172.

Wegener, S., Redoblado-Hodge, M.A., Lucas, S., Fitzgerald, D., Harris, A., & Brennan, J. (2005). Relative contributions of psychiatric symptoms and neuropsychological functioning to quality of life in first-episode psychosis. *Aust N Z J Psychiatry,* 39, 487-492.

Wilson, I.B., & Cleary, P.D. (1995). Linking clinical variables with health related quality of life: a conceptual model of patient outcomes. *JAMA*, 273, 59-65.

Xiang, Y., Weng, Y., Leung, C., Tang, W., & Ungvari, G.S. (2007). Quality of life of Chinese schizophrenia outpatients in Hong Kong: relationship to sociodemographic factors and symptomatology. *Aust N Z J Psychiatry*, 41, 442-449.

Chapter 3



Development of schizotypal symptoms following psychiatric disorders in childhood or adolescence

Fagel, S.S.A.A., Swaab, H., De Sonneville, L.M.J., Van Rijn, S., Pieterse, J.K., Scheepers, F., & Van Engeland, H. (2013). Development of schizotypal symptoms following psychiatric disorders in childhood or adolescence. *European Child and Adolescent Psychiatry. In press*.
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Abstract

It was examined how juvenile psychiatric disorders and adult schizotypal symptoms are associated. 731 patients of the Department of Child and Adolescent Psychiatry of the University Medical Centre Utrecht, the Netherlands, with mean age of 12.1 years (*SD*=4.0) were reassessed at the mean age of 27.9 years (*SD*=5.7) for adult schizotypal symptoms using the Schizotypal Personality Questionnaire-Revised (SPQ-R; Vollema & Hoijtink, 2000). Differences between thirteen juvenile DSM categories and normal controls (*n*=80) on adult schizotypal total and factor scores were analyzed, using (M)ANCOVA. Pervasive developmental disorders (PDD), attention deficit hyperactivity disorders (ADHD), deferred diagnosis, sexual and gender identity disorders and depressive disorders had higher SPQ total scores when compared to normal controls ($p<0.001$). Higher levels of disorganized schizotypal symptoms were found for PDD, ADHD, and deferred diagnosis ($p<0.001$). The same diagnostic groups showed higher level of negative schizotypal.

Introduction

Schizophrenia spectrum pathology is composed of multiple conditions that are characterized by distortions of cognitive and perceptual reality, collectively known as positive symptoms, interpersonal withdrawal (negative symptoms), and disorganized speech and behavior (disorganized symptoms; Liddle, 1987; Suhr & Spitznagel, 2001). These conditions have different 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 (Meehl, 1989), and are considered to be persistent and lifelong and are supposed to present themselves differently at different ages. Consequently, developmental origins of schizophrenia spectrum pathology have been intensively studied throughout the years.

Longitudinal studies have demonstrated that the majority of adults with schizophrenia or psychosis could have been identified as clinically at high risk long before the onset of these disorders. For example, the results of the birth cohort study of Kim-Cohen et al. (2003) showed that 75 % of adults who were diagnosed with schizophrenia did receive a psychiatric diagnosis in childhood or adolescence before the age of eighteen, representing a broad array of juvenile disorders, such as juvenile anxiety, depression, attention deficit hyperactivity disorder (ADHD), and conduct and/or oppositional defiant disorder (ODD). The finding of a broad spectrum of disorders in childhood or adolescence preceding the development of schizophrenia and psychosis in adulthood has been confirmed by other studies that have reported diagnostic shifts towards schizophrenia and psychosis in childhood psychiatric disorders such as attention deficit disorders, disruptive disorders (De la Serna et al., 2010; Keshavan, Sujata, Mehra, Montrose, & Sweeney, 2002; Menkes, Rowe, & Menkes, 1967; Rubino et al., 2009), anxiety and depressive disorders (Kim-Cohen et al., 2003; Ambelas, 1992; Meyer et al., 2005), and pervasive developmental disorders (PDD; Rubino et al., 2009; Larsen & Mouridsen, 1997; Mouridsen, Rich, & Isager, 2008; Stahlberg, Soderstrom, Rastam, & Gillberg, 2004; Van Engeland & Van der Gaag, 1994).

These studies provide important information on how disorders of childhood and adolescence are associated with the development of psychopathology at the extreme end of the schizophrenia spectrum, i.e., meeting the Diagnostic Statistical Manual (DSM) criteria of schizophrenia or psychosis. However, since the majority of at-risk individuals do not meet these criteria at follow-up, but rather tend to manifest subclinical schizophrenia-like abnormalities (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Raine, 1991; Tsuang, Stone, Tarbox, & Faraone, 2002), i.e., schizotypal symptoms, these individuals are absent

in these studies' samples. As a result, literature so far precludes deciding how disorders in childhood or adolescence may develop into these milder symptoms of schizophrenia spectrum pathology in adulthood. This makes the investigation of disorders in childhood or adolescence and its association with adult schizotypal symptoms a valid and noteworthy, yet relatively understudied, area of exploration with strong implications for clinical practice and research.

The present follow-up study therefore aims to investigate the development of adult-specific schizotypal symptoms in relation to psychopathology in childhood and adolescence. 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 and Mouridsen, 1997; Mouridsen, Rich, & Isager, 2008), it is hypothesized that psychiatric disorders in childhood and adolescence such as PDD, ADHD, ODD, anxiety disorders, and depressive disorders are 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 is further explored whether juvenile psychopathology is specifically associated with one or more of the three main schizotypal symptom domains.

Methods

Procedure and participants

This study is part of a longitudinally prospective study designed to evaluate both global and clinical outcomes in adulthood of patients, referred during 1984–2004 (T1), to the Department of Child and Adolescent Psychiatry at the University Medical Centre of Utrecht (UMCU), the Netherlands. Patients meeting the following criteria were approached for participation in a follow-up study during 2006–2010 (T2): (1) a diagnosis based on DSM criteria of the American Psychiatric Association (1980; 1987; 1994) at T1, (2) aged 18 years or younger at T1, (3) no axis II DSM diagnosis of mental retardation (IQ<70) at T1, (4) no axis I DSM diagnosis before or at T1 with child psychotic disorder, schizophrenia or any other psychotic disorder, bipolar disorder or dissociative disorder, and (5) aged 18 years or older at T2. The 2083 patients who were eligible for follow-up were sent a letter with information about the aims of the study, asking them to participate. Whenever possible, the patients were contacted by phone to encourage participation. A total of 1315 patients declined participation, leaving 768 patients in the study. Because there were too few (<20)

Table 1. The number of participants by juvenile DSM diagnostic category.

Juvenile DSM diagnostic categories of the participants	***n***
Eating disorders	153
Pervasive Developmental Disorders	100
Disruptive disorders	89
Depressive disorders	82
Attention Hyperactivity Disorders	78
Other conditions that may be a focus of clinical attention	44
Anxiety disorders	43
Somatoform disorders	28
Deferred diagnosis	27
Other disorders of infancy, childhood, or adolescence	26
Adjustment disorders	21
Tic-disorders	20
Sexual and Gender Identity disorders	20

cases of learning disorders (*n*=6), communication disorders (*n*=9), elimination disorders (*n*=11), sleep disorders *(n*=1), impulse-control disorders not elsewhere classified (*n*=2), unspecified mental disorder (non-psychotic) (*n*=6), delirium, dementia, amnestic and other cognitive disorders (*n*=1), and substance-related disorders (*n*=1) to provide adequate power to test group differences, these subjects (*n*=37) were not evaluated. The final sample consisted of 731 (327 males and 404 females; 35.1%) patients, distributed across thirteen DSM diagnostic categories, with mean age of 12.1 years (*SD*=4.0) at T1, and reassessed at the mean age of 27.9 years (*SD*=5.7) at T2. The intelligence of the patient group was within the normal range with a total IQ of 103.3 (*SD*=14.7), a performance IQ of 103.8 (*SD*=15.7), and a verbal IQ of 103.1 (*SD*=14.5).

Eighty male normal controls were recruited from the general population using recruitment advertisements. Mean age of this group was 29.9 years (*SD*=7.2). None of the controls met the criteria for an axis I psychiatric disorder in adulthood, as shown by screening with the mini-international neuropsychiatric interview plus (MINI-plus; Sheehan et al., 1998). All subjects voluntarily agreed to participate in this study and signed informed consent. The ethical principles of the Helsinki Declaration (Schuklenk, 2001) were followed and approval was obtained from the Medical Ethical Committee of the University Medical Centre of Utrecht (number 05-319/K).

Representativeness

To check the representativeness of the sample, age and gender distributions as well as the distribution of the juvenile DSM classifications of participants and non-participants were compared. Proportionally more participants appeared to be female (55.3% female participants vs. 37.8% female non-responders; $F(1,2083)=58.796$, $p<0.001$). The participants were slightly older at time of childhood assessment (M=12.1 year; *SD*=4.0) than the non-responders (M=11.3 year; *SD*=4.0) at T1, ($F(1,2057)=21.403$, $p<0.001$, $\eta_p^2=0.01$), although this was a very small effect. Participants had a slightly higher intelligence than non-responders, i.e., total IQ (M=103.3; *SD*=14.7 vs. M=99.7; *SD*=14.2), ($F(1,858)=12.259$, $p<0.001$, $\eta_p^2=0.014$), verbal IQ (M=103.1; *SD*=14.5 vs. M=98.8; *SD*=14.4), ($F(1,811)=16.400$, $p<0.001$, $\eta_p^2=0.020$). No differences were found in performance IQ ($p=0.074$). The participants did not differ from the nonparticipants on age at T2 ($p=0.758$). Although the distribution of juvenile DSM classifications within the non-participants and participants was similar for most diagnostic categories, an relative overrepresentation of participants was found in eating disorders (20.9 vs. 9.9%), and a relative underrepresentation of participants was found in ADHD (10.7 vs. 16.4%), ($F(21,2083)=143.763$, $p<0.001$).

Measures

Psychiatric disorders in childhood

Psychiatric diagnosis at time of referral resulted from consensus between at least two board certified psychiatrists on the basis of a complete child psychiatric examination, consisting of a semi-structured clinical diagnostic interview focused on the presence of DSM criteria, the subjects' developmental history, a review of medical records and observation of the child. All diagnoses were converted to DSM-IV-TR (APA, 2000) classifications based on DSM-IV-TR conversion guidelines. DSM-IV-TR preference rules were handled: PDD diagnosis was preferred above comorbid ADHD diagnosis. The juvenile psychiatric records of thirteen subjects in which axis II was used to indicate prominent maladaptive personality features, indicating a personality disorder in development, were reexamined by a senior psychiatrist. This resulted in all of these thirteen subjects being assigned to the category of 'deferred diagnosis'. Juvenile disorders were grouped into the following thirteen broad diagnostic categories: (1) PDD (299.0; 299.80), (2) Tic disorders (307.23; 307.22; 307.21; 307.20), (3) anxiety disorders (300.0; 300.01; 300.02; 300.21; 300.23; 300.29; 300.3; 309.81), (4) somatoform disorders (300.11; 300.7; 300.82; 307.80), (5) sexual and gender identity disorders (302.2;302.3; 302.6; 302.81; 306.85; 302.89; 302.9), (6) Eating disorders (307.1; 307.51; 307.50), (7) adjustment disorders (309.0; 309.24; 309.28; 309.3; 309.4; 309.9), (8) other conditions that may be a focus of clinical attention (V61.10; V61.20; V61.80; V61.90; V62.3; V62.81; V62.82; V62.89; 313,82; V15.81; V61.21), (9) ADHD (314.00; 314.01; 314.9), (10) disruptive disorders (312.9; 313.81; 312.89), (11) depressive disorders (296.2; 296.3;300.4; 311.0), (12) deferred diagnosis (301.0; 301.2; 301.22; 301.4;301.81; 301.9; 301.83; 301.7; 301.5; 799.9), and (13) other disorders of infancy, childhood, or adolescence (307.3; 313.23; 313.89; 313.9; 309.21).

Adult schizotypal symptoms

Adult schizotypal symptoms were measured, using the Schizotypal Personality Questionnaire-Revised (SPQ-R; Raine, 1991; Vollema & Hoijtink, 2000). The SPQ-R is a self-report measure of schizotypal traits, modeled on the diagnostic and statistical manual of mental disorders (American Psychiatric Association, 1994) conceptualization of schizotypy (Raine, 2006). Factor analytical studies have revealed three dimensions of schizotypy, i.e., positive, negative, and disorganized schizotypy (Vollema & Hoijtink,

2000; Raine et al., 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 (Vollema et al., 2002). Higher scores on the SPQ-R indicate higher levels of schizotypal symptoms.

Statistical analysis

Statistical analyses were performed using the statistical package for the social sciences 18.0 (SPSS Inc, Chicago, Il, USA). All variables were screened for normality and outliers, defined as more than 2.5 standard deviations away from the mean of each group. Outlier scores were replaced with scores 2.5 standard deviations away from the group mean accordingly. Sixty-nine scores were replaced: fifteen high total SPQ scores, twenty-six high positive SPQ scores, fifteen high negative SPQ scores, and thirteen high disorganized SPQ scores. We examined age at T2 and gender as potential confounding variables. As only age at T2 was associated with adult schizotypal symptoms, this variable was included in our statistical model as covariate. After square root transformation, univariate and multivariate analyses of covariances ((M)ANCOVA) were performed, using simple contrasts with the normal controls as reference category, with SPQ-R total score and its three-factor scores as dependent variables, respectively, contrasting each DSM category with the normal controls. When the MANCOVA resulted in a significant multivariate effect, the univariate group effects on specific subscales were examined. Partial eta squared (η_p^2) was calculated to estimate effect sizes, with η_p^2~0.03 representing a weak, η_p^2~0.06 a moderate effect and $\eta_p^2 \geq 0.14$ a large effect (Stevens, 2002). Conservative $p<0.01$ by two-tailed test was considered as statistically significant.

Results

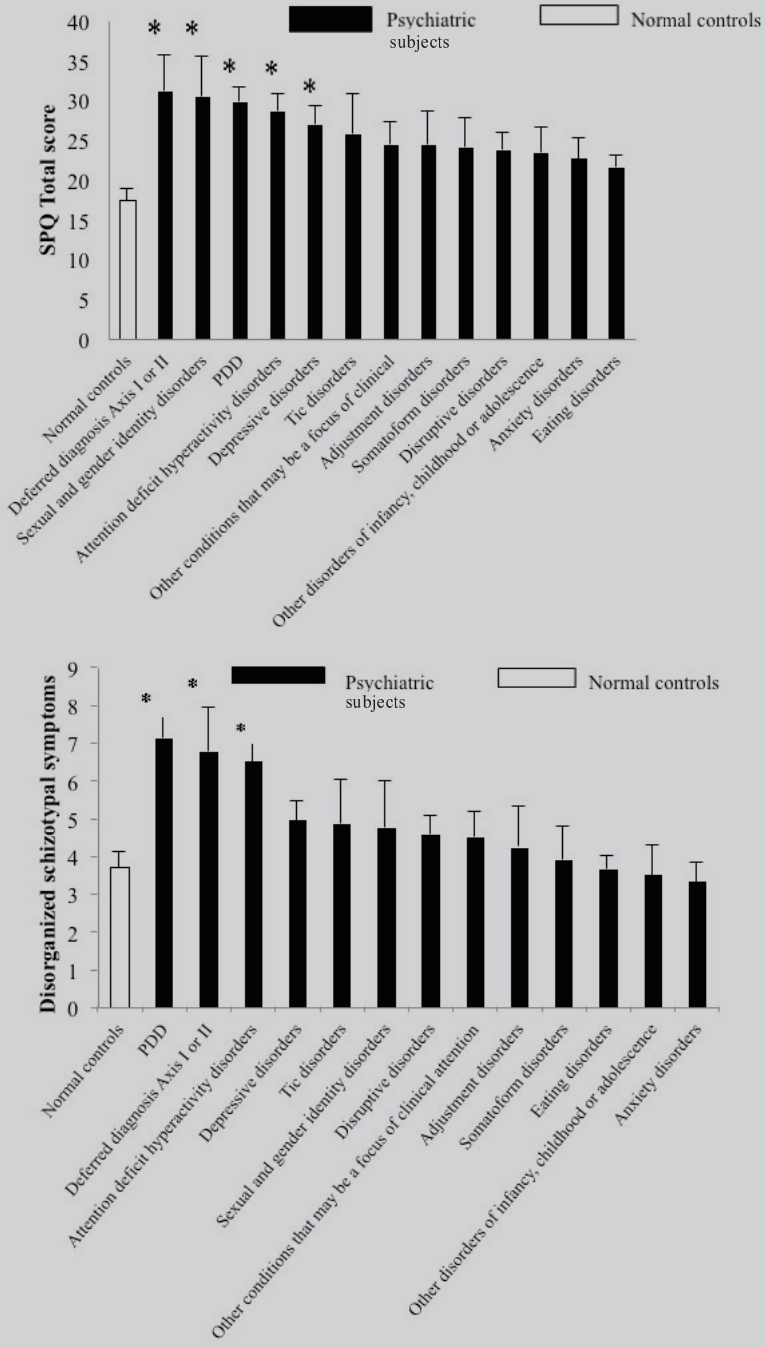
Psychiatric disorders in childhood and adolescence and adult schizotypal symptoms

The ANCOVA of the SPQ-R total score revealed a significant weak effect for group (F(13,796)=2.629, p=0.001, η_p^2=0.041), with no effect of age at T2 (p=0.239). Although all adults with a juvenile psychiatric diagnosis had higher SPQ total scores in comparison with normal controls, the simple contrast with normal controls revealed that differences were significant for five diagnostic groups, i.e., deferred diagnosis, sexual and gender identity disorders, PDD, ADHD, and depressive disorders (0.001<p<0.007), and not for the other categories (0.05<p<0.222). (See Fig. 1).

Psychiatric diagnoses during childhood and adolescence and adult-specific schizotypal symptoms

The MANCOVA of the three schizotypal factors revealed a significant weak multivariate effect of group (F(39,2388)=2.631, p<0.001, η_p^2=0.041), but not of age at T2 (p=0.308). The univariate simple contrast analysis, with normal controls as reference, revealed a significant weak effect of group on negative schizotypal symptoms (F(13,796)=4.631, p=0.001, η_p^2=0.042) for seven juvenile diagnostic groups, i.e., PDD, ADHD, deferred diagnosis, sexual and gender identity disorders, depressive disorders, disruptive disorders, and other conditions that may be a focus of clinical attention (0.001<p<0.01). A significant moderate effect was found for group on disorganized schizotypal symptoms (F(13,796)=3.510, p<0.001, η_p^2=0.063) for three juvenile diagnostic groups, i.e., PDD, ADHD, and deferred diagnosis (0.001<p<0.009; see Figs. 2 and 3). No significant differences between normal controls and juvenile DSM diagnostic groups were found for positive schizotypal symptoms (p=0.110).

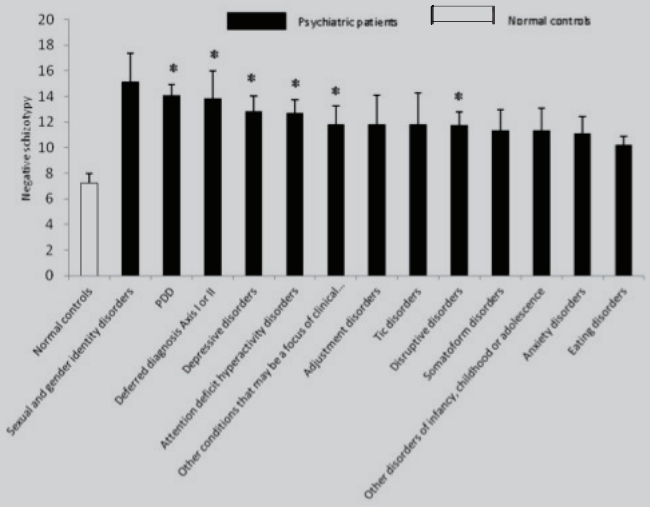
Figure 1. Adult schizotypal symptoms in juvenile psychiatric subjects and normal controls



Values are means, with standard error of the mean represented by vertical bars. * = $p<.01$.

Figure 3.

Level of adult negative schizotypal symptoms in juvenile psychiatric subjects and normal controls



Values are means, with standard error of the mean represented by vertical bars. * = $p<.01$.

Discussion

The present follow-up study explored how and to what extent children and adolescents with a broad range of psychiatric disorders presented with general as well as specific schizotypal symptoms in adulthood. All psychiatric diagnostic categories scored higher on general schizotypal symptoms when they were adults in comparison with normal controls. This suggests a certain generality for the psychopathological domains. A caveat is in place, however. It was found that only children and adolescents diagnosed with PDD, ADHD, deferred diagnosis, sexual and gender identity disorders or depressive disorders scored significantly higher on general schizotypal symptoms than normal controls when they were adults. Also, for three psychiatric disorders, i.e., PDD, ADHD, and Deferred diagnosis, the levels of both disorganized and negative symptoms in adulthood were higher. Four other groups of children with psychiatric disorders showed higher scores on negative schizotypal symptoms in adulthood, i.e., sexual and gender identity disorders, depressive disorders, disruptive disorders, and 'other conditions that may be a focus of clinical attention'. No significant higher levels were found for positive schizotypal symptoms in adulthood. It is concluded that childhood diagnoses are differentially associated with future development of general and specific schizotypal symptoms. This underscores in our view that, apart from a general association between childhood pathology and future symptomatology, certain childhood pathologies are more liable than others to future unfavorable psychopathological development.

The elevated levels of general schizotypal symptoms in the respective DSM categories add to the outcome of previous studies on the association between a variety of juvenile psychiatric disorders and the development of adult disorders within the extreme end of the schizophrenia spectrum. This is further remarkably in line with the legacy of both Kraepelin and Kahlbaum (Hoenig, 1995). Kahlbaum noted that 'snapshot' observations of patients' symptoms could be misleading because how an illness manifests itself may vary over time. Kraepelin noted that symptoms change with time and patients should therefore be observed throughout their life. However, from a historical context of clinical specialization, the focus of clinicians devoting their practice and research to disorders of childhood was separated from clinicians with focus on disorders of adulthood (Frances, First, & Pincus, 1995). This has led to an arbitrary bifurcation in conceptualization and classification of mental disorders across developmental stages (Pine et al., 2002). The current result thus stresses the importance for clinicians to acknowledge the developmental and heterogenetic course of juvenile psychiatric disorders.

The higher levels of schizotypal symptomatology reported for the five DSM

diagnostic categories might be suggestive for the idea that psychiatric disorders in childhood or adolescence are a more general expression of a liability to schizophrenia spectrum pathology in future life. This finding is in line with the neurodevelopmental hypothesis of schizophrenia spectrum pathology (Weinberger, 1987; Murray & Lewis, 1987). This hypothesis states that, in at least a subgroup of subjects, schizotypal symptomatology might be due to pathological processes originating from either a genetic predisposition or a spontaneous genetic mutation in early life, which by interplay with environmental factors during prenatal, perinatal or postnatal life, will affect plastic neural systems during development (Weinberger, 1987; Murray & Lewis, 1987).

PDD and ADHD were the two neurodevelopmental disorders that were significantly associated with the development of higher levels of adult disorganized as well as negative schizotypal symptoms. The existing literature has so far mainly reported about ADHD (De la Serna et al., 2010; Keshavan et al., 2002; Menkes et al., 1967; Rubino et al., 2009) and PDD (Rubino et al., 2009; Van Engeland and Van der Gaag, 1994) being associated with the risk for development of psychopathology at the extreme end of the schizophrenia spectrum, i.e. schizophrenia and psychosis. The current results suggest that a disorder within the ADHD and PDD spectrum might be associated with higher risk for development of schizotypal symptomatology, especially with respect to negative symptoms and disorganized behavior. Previous studies did not focus on disorganized and negative symptoms in adulthood in subjects who were diagnosed with ADHD at childhood or adolescence.

The current finding of higher levels of negative symptoms and disorganized behavior in adults who were diagnosed with PDD in childhood is in line with the outcome of studies that reported illogical thinking and loose associations in children with PDD (Solomon, Ozonoff, Carter, & Caplan, 2008; Van der Gaag, Caplan, Van Engeland, Loman, & Buitelaar, 2005), and about the presence of disorganized (Dykens, Volkmar, & Glick, 1991; Konstantareas & Hewitt, 2001) and negative symptoms (Konstantareas & Hewitt, 2001; Rumsey, Andreasen, & Rapoport, 1986) in adolescents and adults with PDD.

Surprisingly, there is no evidence for any of the evaluated diagnostic groups of an increased level of positive schizotypal symptoms. Since insight is more or less inversely proportional to the level of positive symptoms (Trevisi et al., 2012), one might argue that the use of a self-report questionnaire might have consequently led to an underestimation of the reported positive symptoms. This certainly being probable, one may also wonder whether this issue poses a threat to the validity of the Schizotypal Personality Questionnaire to assess schizotypal positive symptoms. The SPQ, however, has good convergent validity and evidence exists that the SPQ constitutes a valid way to

assess positive schizotypal symptoms. For example, Raine (1991) showed high correlations with the two SPQ subscales that together cover the positive symptoms (r=0.58 with odd beliefs/magical thinking and r=0.65 with odd speech) with dimensional scores for schizotypal personality disorder from SCID Interview.

Children with a 'non-descriptive' diagnosis, i.e., 'deferred diagnosis on axis I or II' represent a diagnostic group showing the highest level of overall schizotypal symptomatology, the second highest level of disorganized schizotypal symptoms, and the third highest level of negative schizotypal symptoms in adult life. This subgroup of children with atypical behavior that does not fit any DSM category has not been associated with the development of schizophrenia spectrum pathology in the literature before. This juvenile behavior that is best described as 'odd' or 'incongruent' (Ambelas, 1992; Hollis, 1995; Zeitlin, 1986) is probably labeled by clinicians as 'deferred diagnosis' to stress the severity of these developmental problems, but yet find no category that fits their behavior in childhood or adolescence. It might be speculated that the nature of these associations possibly relates to a disruption of communication processes, where the problem of communication lies in the appropriate expression and understanding of meaning in a social context. Hollis (1995) proposed that as a result of this failure to utilize socially agreed rules of communication, social isolation might follow. This might explain the present association of this juvenile diagnosis being associated with higher levels of negative schizotypal symptoms in adulthood. The association with higher levels of adult disorganized behavior might be the result of a developmental progression from a long-standing communication disorder to the onset of thought disorder and disorganized behavior (Hollis, 1995). Future research should clarify these issues.

Four juvenile psychiatric groups, i.e., sexual and gender identity disorders, depressive disorders, disruptive disorders, and 'other conditions that may be a focus of clinical attention', showed higher levels on negative schizotypal symptoms, in comparison with normal controls. With regard to earlier studies that reported an association between depressive and disruptive disorders with future schizophrenia spectrum pathology in general (Kim-Cohen et al., 2003; Rubino et al., 2009; Ambelas, 1992; Meyer et al., 2005), the current finding further specifies that these disorders are only associated with negative schizotypal symptoms in adult life in the present study.

Of note is the finding that children and adolescents with sexual and gender identity disorders and 'other conditions that may be a focus of clinical attention' demonstrate high levels of negative schizotypal symptoms in adulthood. The association between sexual and gender identity disorders and the development of subclinical symptoms within the schizophrenia spectrum has only sparsely been addressed (De Cuypere, 1993; Finney, Brandsma, Tondow, & Lemaistre, 1975), which is probably due to the extremely low prevalence of the disorder for both males (1 of 12,000) and females (1 of 30,000; Bakker, Van Kesteren, Gooren, & Bezemer, 1993). Replication of this finding is important to evaluate its stability. As of yet, no studies report about the risk for schizophrenia symp-

tomatology in adulthood of the childhood condition 'other conditions that may be a focus of clinical attention'. This category is used when the problem identified is either unrelated to a separate mental disorder, or is significant enough to require attention separate from the mental disorder, and is taken to constitute a 'milder' type of psychiatric problem, but the current report of high levels of negative schizotypal symptomatology suggests otherwise. More specifically, the present group of 44 children consists in majority of subjects diagnosed with relational problems (*n*=27) and with a phase of life problem (*n*=14) at juvenile age, suggesting the existence of interaction and social problems. The association between social impairment and the risk for development of schizophrenia spectrum pathology has been extensively addressed by retrospective studies (Foerster, Lawis, Owen, & Murray, 1991; Rossi, Pollice, Daneluzzo, Marinangeli, & Stratta, 2000; Watt & Lubensky, 1976; Zigler et al. 1977) and birth cohort studies (Bearden et al., 2000; Crowe, Done, & Sacker, 1995; Davidson et al., 1999; Malmberg et al., 1998).

Although anxiety disorder in childhood or adolescence has been associated with the development of psychopathology at the extreme end of the schizophrenia spectrum, i.e., schizophrenia and psychosis, in earlier studies (Kim-Cohen et al., 2003; Ambelas, 1992; Meyer et al., 2005), the present study did not find any association between this disorder and specific future schizotypal symptoms. Since this is the first study to report on specific schizotypal symptoms, this issue needs further investigation.

Obviously, the nature of the associations between psychiatric disorders in childhood and adolescence and adult disorganized and/or negative schizotypal symptoms needs further investigation. With regard to disorganized schizotypal symptoms, the results of some studies suggest that impaired thinking appears to reflect poorer communication skills (Van der Gaag, Caplan, Van Engeland, Loman, & Buitelaar, 2005), while others suggest that impaired thinking originates from deficits in executive functioning (Barneveld, De Sonneville, Van Rijn, Van Engeland, & Swaab, 2013; Kerns, 2007). In addition, in light of Bleuler's distinction between fundamental symptoms (i.e., basic or primary symptoms that are direct manifestations of the morbid condition) and accessory symptoms (i.e. secondary symptoms which represent an adaptation to the primary disturbance; Bleuler, 1961; Raskin, 1975), it needs to be clarified whether negative schizotypal symptoms might (partly) be the consequence of a variety of other factors, such as neuroleptic side effects, living with a chronic disorder, environmental understimulation (Flaum & Andreasen, 1995), or the effect of environmental stressors that these children with psychopathology might experience, which, when combined with a relevant genetic risk for neuropsychiatric disorders, might result in adult-onset neuropsychiatric disorders, such as psychotic depression (Niwa et al., 2013).

To rule out any effect of age, we covaried for age in the analyses of risk for the development of schizophrenia spectrum pathology. Hence, the association between psychiatric disorders of childhood and adolescence and adult schizotypal traits was independent of age.

Strengths and limitations of the study

Inherent to a long follow-up period (15.3 years), the present study suffered from attrition, being able to followup on 35% of the original sample. Nevertheless, the number of 731 subjects in the final sample is considered to be substantial and representative. The background variables of the participants were quite similar to that of the non-participants, with slightly more female and older participants at follow-up and a slightly higher intelligence in comparison to the non-responders. Further, since the present study concerns a clinically referred sample, the current findings might pertain to those subjects who presented with considerable and progressive juvenile neurobehavioral impairments and not to those subjects who were relatively inconspicuous as a child. Moreover, since the mean age of participants was 27.9 (*SD*=5.7) years, not all subjects may have passed the (full) period of risk for schizophrenia spectrum psychopathology, the level of schizotypal symptomatology might therefore be underestimated. Because we did not assess schizotypal symptoms in childhood, it was therefore not possible to determine whether these symptoms have increased in severity at follow-up. In addition, the screening by self-report does carry some limitations, as compared with interviews or observations. Self-report questionnaires might not ensure sufficient sensitivity and specificity for specific schizotypal signs such as an odd or guarded appearance, an expression of aloofness, or poor eye contact, and restricted affect (Kendler, 1988). In future studies, direct observation of these specific symptoms might be a way to address these additional questions. Besides these limitations, the current follow-up study suited the purpose to illustrate the complex dynamics of psychopathology in childhood or adolescence and the development of symptoms within the schizophrenia spectrum. We feel confident to state that it seems important for clinicians to be aware of the higher risk for schizotypal symptomatology in adulthood following childhood psychiatric disorders and that specific patterns of adult schizotypal symptomatology are associated with different types of juvenile psychiatric disorder. Thus, future research is necessary to address the mechanisms underlying this risk.

References

Ambelas, A. (1992). Preschizophrenics: adding to the evidence, sharpening the focus. *Br J Psychiatry,* 160(3), 401–404.

American Psychiatric Association. (1980). *Diagnostic and Statistical Manual of Mental Disorders* (3rd edition). Washington DC: American Psychiatric Association Press.

American Psychiatric Association. (1987). *Diagnostic and Statistical Manual of Mental Disorders (3rd revised edition*). Washington DC: American Psychiatric Association Press.

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders (4th edition).* Washington DC: American Psychiatric Association Press.

Bakker, A., Van Kesteren, P.J.M., Gooren, L.J.G., & Bezemer, P.D. (1993). The prevalence of transsexualism in the Netherlands. *Acta Psychiatr Scand,* 87(4), 237–238.

Barneveld, P.S., De Sonneville, L.M.J., Van Rijn, S., Van Engeland, H., & Swaab, H. (2013). Impaired response inhibition in autism spectrum disorders, a marker of vulnerability for schizophrenia spectrum disorders? *J Int Neuropsychol Soc*, 21, 1–10.

Bearden, C.E., Rosso, I.M., Hollister, J.M., Sanchez, L.E., Hadley, T., & Cannon, T.D. (2000). A prospective cohort study of childhood behavioral deviance and language abnormalities as predictors of adult schizophrenia. *Schizophr Bull*, 26(2), 395–410.

Bleuler, E. (1961). *Dementia praecox or the group of schizophrenias.* English translation. New York: International Universities Press.

Chapman, L.J., Chapman, J.P., Kwapil, T.R., Eckblad, M., & Zinser, M.C. (1994). Putatively psychosis-prone subjects 10 years later. *J Abnormal Psychol,* 103(2), 171–183.

Crow, T.J., Done, D.J., Sacker, A. (1995). Childhood precursors of psychosis as clues to its evolutionary origin. *Eur Arch Psychiatry Clin Neurosci,* 245(2), 61–69.

Davidson, M., Reichenberg, A., Rabinowitz, J., Weiser, M., Kaplan, Z., & Mark, M. (1999). Behavioral and intellectual markers for schizophrenia in apparently healthy male adolescents. *Am J Psychiatry,* 156(9), 1328–1335.

De Cuypere, G. (1993). Schizophrenia and symptomatic transsexualism: two case reports*. Eur Psychiatry*, 8, 163–167.

De la Serna, E., Baeza, I., Toro, J., Andres, S., Puig, O., Sanchez-Guistau, V., Romero, S., Bernardo, M., & Castro-Fornieles, J. (2010). Relationship between clinical and neuropsychological characteristics in child and adolescent first degree relatives of subjects with schizophrenia. *Schizophr Res*, 116(2–3), 159–167.

Dykens, E., Volkmar, F., & Glick, M. (1991). Thought disorder in highfunctioning autistic adults. *J Autism Dev Disord*, 21(3), 291–301.

Finney, J.C., Brandsma, J.M., Tondow, M., & Lemaistre, G. (1975). A study of transsexuals seeking gender reassignment *Am J Psychiatry*, 132(9), 962–964.

Flaum, M., & Andreasen, N. (1995). The reliability of distinguishing primary versus secondary negative symptoms. *Compr Psychiatry*, 36(6), 421–427.

Foerster, A., Lawis, S., Owen, M., & Murray, R. (1991). Pre-morbid adjustment and personality in psychosis. *Br J Psychiatry*, 158(2), 171–176.

Frances, A.J., First, M.B., & Pincus, H.A. (1995). *DSM-IV guidebook*. Washington DC: American Psychiatric Press.

Hoenig, J. (1995). Schizophrenia. In: Berrios, G.E. & Porter, R. (Eds.). *A history of clinical psychiatry: the origin and history of psychiatric disorders.* New York: New York University Press.

Hollis, C. (1995). Child and adolescent (juvenile onset) schizophrenia. A case control study of premorbid developmental impairments. *Br J Psychiatry,* 166(4), 489–495.

Kendler, K.S. (1988). Familial aggregation of schizophrenia and schizophrenia spectrum disorders. Evaluation of conflicting results. *Arch Gen Psychiatry*, 45(4), 377–383.

Kerns, J.G. (2007). Verbal communication impairments and cognitive control components in people with schizophrenia. *J Abnorm Psychol*, 116(2), 279–289.

Keshavan, M.S., Sujata, M., Mehra, A., Montrose, D.M., & Sweeney, J.A. (2002). Psychosis proneness and ADHD in young relatives of schizophrenia patients. *Schizophr Res*, 59(1), 85–92.

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-back of a prospective-longitudinal cohort. *Arch Gen Psychiatry,* 60(7), 709–717.

Konstantareas, M.M., & Hewitt, T. (2001). Autistic disorder and schizophrenia: diagnostic overlaps. *J Autism Dev Disord*, 31(1), 19–28.

Larsen, F.W. & Mouridsen, S.E. (1997). The outcome in children with childhood autism and Asperger syndrome originally diagnosed as psychotic. A 30-year follow-up study of subjects hospitalized as children. *Eur Child Adolesc Psychiatry*, 6(4), 181-190.

Liddle, P.F. (1987). The symptoms of chronic schizophrenia. A reexamination of the positive and negative dichotomy. *Br J Psychiatry*, 151, 145.

Malmberg, A., Lewis, G., David, A., & Allebeck, P. (1998). Premorbid adjustment and personality in people with schizophrenia. *Br J Psychiatry,* 172(4), 308–313.

Meehl, P.E. (1989). Schizotaxia revisited. *Arch Gen Psychiatry,* 46(10), 935–944.

Menkes, M., Rowe, J., & Menkes, J. (1967). A 25 year follow-up study on the hyperkinetic child with minimal brain dysfunction. *Pediatrics*, 39(3), 393–399.

Meyer, S.E., Bearden, C.E., Lux, S.R., Gordon, J.L., Johnson, J.K., O'Brien, M.P., Niendam, T.A., Loewy, R.L., Ventura, J., & Cannon, T.D. (2005). The psychosis prodrome in adolescent patients viewed through the lens of DSM-IV. *J Child Adolesc Psychopharmacol*, 15(3), 434–451.

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.

Murray, R.M., & Lewis, S.W. (1987). Is schizophrenia a neurodevelopmental disorder? *Br Med Journal*, 295, 681–682.

Niwa, M., Jaaro-Peled, H., Tankou, S., Seshadri, S., Hikida, T., Matsumoto, Y., Cascella, N.G., Kano, S., Ozaki, N., Nabeshima, T., & Sawa, A. (2013). Adolescent stress–induced epigenetic control of dopaminergic neurons via glucocorticoids. *Science*, 339(6117), 335–339.

Pine, D.S., Alegria, M., Cook, E.H., Costello, E.J., Dahl, R.E., Koretz, D., Merikangas, K.R, Reiss, A.L., & Vitiello, B. (2002). Advances in developmental science and DSM-V. In: Kupfer, D.J., First, M.B., & Regier, D. E. (Eds.). *A research agenda for DSM-V* (pp. 85–122). Washington DC: American Psychiatric Association.

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.

Raine, A., Reynolds, C., Lencz, T., Scerbo, A., Triphon, N., & Kim, D. (1994). Cognitive-perceptual, interpersonal, and disorganized features of schizotypal personality. *Schizophr Bull,* 20(1), 191–201.

Raine, A. (2006). Schizotypal personality: neurodevelopmental and Psychosocial Trajectories. *Annu Rev Clin Psychol,* 2, 291–326.

Raskin, D.E. (1975). Bleuler and schizophrenia. *Br J Psychiatry*, 127(3), 231–234.

Reynolds, C.A., Raine, A., Mellingen, K., Venables, P.H., & Mednick, S.A. (2000). Three-factor model of schizotypal personality: invariance across culture, gender, religious affiliation, family adversity, and psychopathology. *Schizophr Bull,* 26(3), 603–618.

Rossi, A., Pollice, R., Daneluzzo, E., Marinangeli, M.G., & Stratta, P. (2000). Behavioral neurodevelopment abnormalities and schizophrenic disorder: a retrospective evaluation with the Childhood Behavior Checklist (CBCL). *Schizophr Res*, 44(2), 121–128.

Rubino, I.A., Frank, E., Croce Nanni, R., Pozzi, D., Lanza di Scalea, T., & Siracusano, A. (2009). A comparative study of Axis I antecedents before age 18 of unipolar depression, bipolar disorder and schizophrenia. *Psychopathology*, 42(5), 325–332.

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.

Schuklenk, U. (2001). Helsinki declaration revisions. *Issues Med Ethics*, 9(1), 29.

Sheehan, D.V., Lecrubier, Y., Sheenan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G.C. (1998). The mini-international neuropsychiatric interview (M.I.N.I): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry,* 59(Suppl 20), 22–33, quiz 34-57.

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(8), 1474–1484.

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. (2002). Two-group multivariate analysis of variances. In: Stevens, J. (Ed.). *Applied multivariate statistics for the social science, 4th edition* (p.197). New Jersey: Lawrence Erlbaum Associates.

Suhr, J.A., & Spitznagel, M.B. (2001). Factor versus cluster models of schizotypal traits. I: a comparison of unselected and highly schizotypal samples. *Schizophr Res*, 52(3), 231–239.

Trevisi, M., Talamo, A., Bandinelli, P.L., Ducci, G., Kotzalidis, G.D., Santucci, C., Manfredi, G., Girardi, N., & Tatarelli, R. (2012). Insight and awareness as related to psychopathology and cognition. *Psychopathology*, 45(4), 235–243.

Tsuang, M.T., Stone, W.S., Tarbox, S.I., & Faraone, S.V. (2002). An integration of schizophrenia with schizotypy: identification of schizotaxia and implications for research on treatment and prevention. *Schizophr Res*, 54(1), 169–175.

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), 197–201.

Vollema, M.Q., & Hoijtink, H. (2000). The multidimensionality of selfreport 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.M., & Kahn, R.S. (2002). Does the schizotypal personality questionnaire reflect the biological-genetic vulnerability to schizophrenia? *Schizophr Res*, 54(1–2), 39–45.

Watt, N.,& Lubensky, A.W. (1976). Childhood roots of schizophrenia. *J Consult Clin Psychol*, 44(3), 363–375.

Weinberger, D.R. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry*, 44(7), 660–669.

Zeitlin, H. (1986*). The natural history of psychiatric disorder in children: a study of individuals known to have attended both child and adult psychiatric departments of the same hospital.* Oxford University Press, Oxford.

Zigler, E., Levine, J., & Zigler, B. (1977). Pre-morbid social competence and paranoid-non paranoid status in female schizophrenic patients. *J Nerv Ment Dis,* 164(5), 333–339.

Chapter 4

School-associated problem behavior in childhood and adolescence and development of adult schizotypal symptoms: a follow-up of a clinical cohort

Fagel, S.S.A.A, De Sonneville, L.M.J., Van Engeland, H., & Swaab, H. Specificity of teacher ratings of problem behavior for development of adult schizotypal symptoms: a follow-up of a clinical cohort. *Accepted for publication in the Journal of Abnormal Child Psychology.*

Abstract

How school-associated behavioral problems in childhood and adolescence precede distinctive adult schizotypal symptoms was examined. Gender specific findings were explored. 159 patients of the Department of Child and Adolescent Psychiatry of the University Medical Centre Utrecht, the Netherlands, were reassessed after 11.6 (*SD*=3.1) years for adult schizotypal symptoms. Severity of behavioral symptoms in childhood and adolescence using Teacher Report Form (TRF; Verhulst et al., 1997) and adult schizotypal symptoms using Schizotypal Personality Questionnaire-Revised (Raine, 1991) were examined by Spearman's bivariate correlations. Multiple regression analyses were performed to determine the combined predictive value of significant TRF subscales for schizotypal symptomatology. Moderation was tested by adding the interactions of gender with TRF subscales to the models. Disregarding gender, correlational analyses revealed that TRF total problems, in specific thought problems, social problems, and attentional problems were associated with disorganized schizotypal symptoms in adult life. TRF thought problems was also associated with future positive schizotypal symptoms. When gender was taken into account, for boys only thought problems was associated with adult positive schizotypal symptoms, whereas for girls externalizing problems, specifically attentional and aggressive problems, were associated with the higher levels of adult disorganized schizotypal symptoms. Moderated regression analyses provided

trend significant evidence confirming that in girls externalizing problems were positively associated with general and disorganized schizotypal symptoms. When using teachers as informants, it was found that juvenile behavioral abnormalities were differentially associated with type of adult schizotypal symptoms, with these associations being further modified by gender.

Introduction

Schizophrenia spectrum pathology is considered a persistent and lifelong condition with varying expression across the lifespan. Consequently, childhood behavioral indicators that are associated with the development of psychopathology at the extreme end of the schizophrenia spectrum, i.e., schizophrenia and psychosis, have been intensively studied throughout the years. As a result, literature provides evidence for a wide range of childhood behaviors being associated with the risk for future development of schizophrenia. However, the majority of subjects at risk based on childhood behaviors do not meet the criteria for a schizophrenia spectrum disorder in adulthood, but tend to manifest subclinical schizophrenia-like abnormalities (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Raine, 1991; Tsuang, Stone, Tarbox, & Faraone, 2002), i.e., schizotypal symptoms. Although these schizotypal symptoms are a milder manifestation on the continuum of schizophrenia spectrum pathology, these symptoms may have a very profound effect on a subject's quality of life, as, apart from the risk of development of schizophrenia (Vollema, Sitskoorn, Appels, & Kahn, 2002), severe functional impairments across a broad range of domains can be found, such as academic, social, and occupational dysfunctioning (Chapman et al., 1994; Gooding, Tallent, & Matts, 2005; Kwapil, 1998). The investigation of childhood behavior and its association with adult schizotypal symptoms therefore constitutes a valid and noteworthy, yet relatively understudied, area of exploration with strong implications for clinical practice and research.

Longitudinal studies so far have resulted in the identification of a very broad spectrum of childhood behaviors that are associated with the development of schizophrenia spectrum disorders. Retrospective studies for example, found social impairments to be especially present in subjects who later developed disorders within the schizophrenia spectrum (Foerster, Lawis, Owen, & Murray, 1991; Rossi, Pollice, Dane-luzzo, Marinangeli, & Stratta 2000; Watt & Lubensky, 1976; Zigler, Levine, & Zigler, 1977). Genetic high-risk (HR) studies reported that high risk 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 more depression (Cunningham, Miller, Lawrie, & Johnstone, 2005), compared to children and adolescents without genetic risk for schizophrenia spectrum pathology. In addition, birth cohort studies have found evidence for developmental precursors of schizophrenia spectrum disorders in four behavioral domains: delay in neuromotor development (Fish, Marcus, Hans, Auerbach, & Perdue, 1992; Jones, Rodgers, Murray, & Marmot, 1994; Crow, Done, & Sacker, 1995; Cannon et al., 1999; Walker, Lewis, Loewy, & Palyo, 1999; Rosso et al., 2000), delays in aspects of language development (DeLisi et al., 1991; Jones et al., 1994; Bearden et al., 2000), problems in the area of social functioning (Crow et al., 1995; Malmberg, Lewis, David, & Allebeck, 1998; Davidson et al., 1999; Bearden et al., 2000), and high levels of aggressive behavior (Miller et al., 2002).

So far, to our knowledge, only two longitudinal studies have studied adult outcome of childhood behavioral indicators for schizophrenia spectrum pathology using comparison groups of patients diagnosed with affective disorders (Dworkin, Lewis, Cornblatt, & Erlenmeyer-Kimling, 1994), and anorexia (Muratori, Salvadori, D'Arcangelo, Viglione, & Picchi, 2005), respectively. This approach led to the affirmation of the finding that social problems precede schizophrenia spectrum disorders in adulthood (Dworkin et al., 1994; Muratori et al., 2005), and to the identification of specific childhood problems in more restricted behavioral domains: the regulation of thought (Muratori et al., 2005), and regulation of attention (Muratori et al., 2005).

In addition, behavioral problems in childhood and adolescence of future patients with schizophrenia spectrum pathology have been found to differ between boys and girls. For example, studies have reported that boys exhibit more aggression (Welham et al., 2009), social problems (Salokangas, 1983; Welham et al., 2009), and thought problems (Welham et al., 2009), whereas girls prior to their schizophrenia diagnosis were more likely to be rated as withdrawn, unforthcoming, and depressed (Done, Crow, Johnstone, & Sacker, 1994). Hence, it is possible that the gender of the child may moderate associations between behavioral problems and adult schizotypal symptomatology; however, additional research is needed to fill this gap in the literature.

All of the cited studies have used intra-familial sources, i.e., in majority parent report. Studies using an extra-familiar source, i.e., teacher's reports, in assessing behavioral problems in children are scarce. Although parents form an important source (Van der Valk, Van den Oord, Verhulst, & Boomsma, 2001; Arseneault et al., 2003; Bartels et al., 2003),

situational variation in children's behaviors at home and at school makes teachers an important source of information (Polderman, Posthuma, De Sonneville, Verhulst, & Boomsma, 2006). For example, teachers may have a unique view on problems that are specific to the classroom or other school situations, such as problems in the social interactions with other children, or task-oriented situations (Polderman et al., 2006). Teachers also have an advantage over parents in their wide exposure to children of the same age, which makes them able to compare the child's behavior with that of many same-aged peers (Verhulst et al., 1997). Thus far, only one study has used data from teachers to examine how juvenile school-associated problem behavior is associated with the development of adult schizophrenia spectrum pathology (Olin et al., 1997). They found that children who later developed schizotypal personality disorder were hypersensitive to criticism in comparison with HR children who were not mentally ill in adulthood.

The present study is a follow-up study of a clinical cohort and investigates the development of adult schizotypal symptoms in relation to school-associated behavioral problems in childhood and adolescence. In line with the results of other studies (Amminger et al., 1999; Miller et al., 2002; Johnstone, Ebmeier, Miller, Owens, & Lawrie, 2005; Muratori et al., 2005; Scott et al., 2009), it is hypothesized that severity of school-associated behavioral problems is associated with higher levels of adult schizotypal symptoms. The cited comparative studies further suggest that childhood problems in the social domain (Dworkin et al., 1994; Muratori et al., 2005), in both regulation of thought (Muratori et al., 2005), and in attention regulation (Muratori et al., 2005) are particularly associated with adult schizotypal symptoms. Therefore, it is hypothesized that severity of school-associated behavioral problems in these behavioral domains in childhood and adolescence is 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 is further explored how different domains of school-associated behavioral problems are related to the three schizotypal symptom domains. Finally, as symptoms of future schizophrenia spectrum pathology are highly variable in their clinical presentation between boys and girls (Done et al., 1994; Salem & Kring, 1998; Welham et al., 2009), this study examined whether the association between juvenile school-associated behavioral problems and adult schizotypal symptoms was moderated by gender.

Methods

Sample and procedure

This study is part of a longitudinally prospective study designed to evaluate both global and clinical outcomes in adulthood of children and adolescents with psychopathology, referred during 1984 to 2004 (T1), to the Department of Child and Adolescent Psychiatry at the University Medical Centre of Utrecht (UMCU), the Netherlands. Children and adolescents 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 axis I DSM diagnosis before or at T1 of child psychotic disorder (schizophrenia or any other psychotic disorder), bipolar disorder or dissociative disorder, (4) no DSM diagnosis of mental retardation (IQ < 70) at T1, (5) presence of a Teacher Report Form (TRF; Verhulst et al., 1997) at T1. In total, 451 patients were eligible for follow-up. They were sent a letter informing them about the aims of the study and checking their willingness to participate in the study. The patients who did not respond were contacted by phone when they could be traced in the public phone registry to explain the aim of the study and to encourage participation. A total of 292 patients declined participation, resulting in a final sample of 159 (75 male and 84 female) adult patients. These patients were distributed across six broad DSM diagnostic categories at T1, i.e., Affective disorders (20.1%), Attention-deficit and disruptive behavior disorders (16.4%), Pervasive Developmental Disorders (16.4%), Eating disorders (18.2%), No diagnosis (3.1%), and a category consisting of low prevalence disorders such as Communication disorders, Tic-disorders, Other disorders of infancy, childhood and adolescence and Deferred diagnoses (25.8%). Using standardized scores of Wechsler Intelligence Scales at time of juvenile assessment (T1); i.e., WPPSI (Wechsler, 1967), WISC (Wechsler, 1949), WISC-R (Wechsler, 1974), WISC-III (Wechsler, 1991), WAIS (Wechsler, 1955) or WAIS-R (Wechsler, 1981), the intelligence level of the group was within the normal range with a total IQ of 104.2 (*SD*=15.6), a performance IQ of 103.5 (*SD*=15.8), and a verbal IQ of 103.8 (*SD*=15.4). Subjects were reassessed after a mean period of 11.6 years (*SD*=3.1), at a mean age of 24.4 years (*SD*=4.1) at T2. All subjects voluntarily agreed to participate in this study and signed an informed consent form. The ethical principles of the Helsinki Declaration (Schuklenk, 2001) were followed and approval was obtained from the Medical Ethical Committee of the University Medical Centre of Utrecht (number 05-319/K).

Representativeness

To check whether the participants assessed at this follow-up were representative of the subjects eligible for follow-up, age and gender distributions as well as the distribution of TRF scores were compared between participants and nonparticipants. Chi-square analyses revealed that proportionally more participants appeared to be female (52.8% female participants versus 30.5% female nonparticipants), (F(1,451)=21.750, p<.001). Differences between participants and nonparticipants on other background variables were evaluated by univariate analyses of variances (ANOVA). This revealed that participants were somewhat older at T1 (M=12.3; *SD*=3.5 vs. M=11.2; *SD*=3.3), (F(1,436)=11.307, p<.001, η_p^2=.025) and at T2 (M=24.4; *SD*=4.1 vs. M=22.2; *SD*=3.5), (F(1,449)=34.419, p<.001, η_p^2=.071). Participants had a higher Total IQ score at T1 (M=104.2; *SD*=15.6 versus M=99.6; *SD*=13.6), (F(1,231)=5.507, p=.020, η_p^2=.023) and a higher Performance IQ (M=103.5; *SD*=15.8 versus M=99.4; *SD*=14.2), (F(1,227)=4.080, p=.045, η_p^2=.018). No difference was found on Verbal IQ (M=103.8; *SD*=15.4 versus M=100.3; *SD*=14.7), (p=.096). Differences were found on two TRF subscales; those lost to follow-up had a higher score on rule breaking behavior (M=57.2; *SD*=8.2 versus M=59.7; *SD*=8.8), (F(1,364)=7.058, p=.008, η_p^2=.019), and aggressive behavior (M=59.1; *SD*=9.5 versus M=62.2; *SD*=10.9), (F(1,364)=11.538, p<.001, η_p^2=.031).

School-associated behavioral problems in childhood and adolescence

School-associated behavioral symptoms at time of referral were evaluated using the Dutch translation of the Teacher Report Form (TRF) at T1 for which good reliability and validity have been obtained (Verhulst et al., 1997). The TRF is an extensively used questionnaire to assess a broad range of emotional and behavioral problems in children and adolescents from the age of five to eighteen years. The TRF consists of 120 items that are scored on a three point scale ranging from zero (not true) to two (very true) by teachers who have known a pupil in a school setting for at least two months. The TRF provides standardized composite T-scaled scores for behavioral problems on eight specific problem scales, i.e., withdrawn behavior, anxious and depressed behavior, somatic complaints, social problems, aggressive behavior, rule breaking behavior, attention

problems, and thought problems. The first three problem scales are summed to compute the internalizing problems score, and the aggressive and rule-breaking behavior scores are summed to obtain the externalizing problems score. Total behavior problems include scales for social, thought, and attention problems that are neither internalizing nor externalizing problems. Higher scores are indicative for higher levels of problems.

Adult schizotypal symptoms

Adult schizotypal symptoms were assessed 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, 1987) criteria for schizotypal personality disorder (Raine, 1991). In the study of Raine (1991) 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 (χ^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. 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 has been found to be invariant to gender, ethnicity, religion, and social background (Reynolds, Raine, Mellingen, Venables, & Mednick, 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 family members diagnosed with schizophrenia. The SPQ has high internal reliability (0.91), test-retest reliability (0.82), convergent validity (0.59 to 0.81), discriminant validity (0.63), and criterion validity, 0.68) (Raine, 1991). Higher scores on the SPQ-R indicate higher levels of schizotypal symptoms.

Statistical analysis

To control for possible confounding effects, the association of three background varia-

bles, i.e., IQ at T1, age at T1 and age at T2, with SPQ total and factor scores was explored. None of these variables appeared to be significantly associated with SPQ total or factor scores (.077<p<.901). In addition, possible differences between boys and girls on age at T1 and T2, SPQ total and factor scores, and TRF total, internalizing, externalizing, and eight subscales scores were analyzed using MANOVA. Partial eta squared (η_p^2) was used to estimate effect sizes, with η_p^2~0.03 representing a weak effect, η_p^2~0.06 representing a moderate effect and η_p^2≥0.14 significantly a large effect (Cohen, 1992). Because the SPQ total and factor scores were all positively skewed, the strength of the relation with TRF subscales, internalizing, externalizing and total scores were examined by computing bivariate Spearman's correlation analysis (small effect size: r_s=0.1−0.23; medium: r_s=0.24−0.36; large: r_s≥0.37; Cohen, 1992). To explore gender specific characteristics, these analyses were replicated for boys and girls separately. The TRF subscales, internalizing, externalizing or total scores that showed significant correlations were entered in multiple regression analyses using the Enter method, to determine their combined predictive value for the development of adult schizotypal symptoms in general and each of its three factor scores. To test whether gender modified the associations between the TRF (subscales internalizing, externalizing and total score) and the SPQ (factors and total score), moderated multiple regression analyses were performed by adding the interaction term(s) (gender * TRF total/TRF factor/TRF subscale scores) to the model. To construct robust models for testing interactions and reducing multicollinearity all continuous predictor variables were centered (Cronbach, 1987). In order to adjust the type 1 error, i.e. alpha, for multiple testing, alpha was set to .005, two-tailed, for all analyses. Statistical analyses were performed using the Statistical Package for the Social Sciences 18.0 (SPSS Inc, Chicago, Il, USA).

Results

Sample characteristics of the total study sample and gender specific subgroups

Table 1 shows means and *SD*s for the age at T1 and T2 and behavioral data for the total study sample as well as gender specific subgroups. The MANOVA of gender with age at T1, age at T2, TRF scores and SPQ scores revealed a significant medium effect of Group, (F(16,142)=4.206, p<.001, η_p^2=.322) on age at T1, T2, and TRF attention, aggressive, and externalizing problem scores. This effect was due to boys being younger than

Table 1. Age at T1 and T2, and behavioral variables at T2 of the total study sample and gender specific subgroups.

		Total sample (*n*=159)	**Male sample (*n*=75)**	**Female sample (*n*=84)**
		M (*SD*)	*M (SD)*	*M (SD)*
Age	at T1	12.5 (3.6)	10.8 (3.4)	13.9 (3.2)
	at T2	24.4 (4.1)	23.4 (3.8)	25.3 (4.3)
SPQ[a]	Total score	26.9 (19.3)	25.4 (18.2)	28.3 (20.2)
	Positive factor	8.8 (7.1)	8.2 (6.3)	9.4 (7.7)
	Negative factor	12.8 (10.0)	11.9 (9.6)	13.6 (10.4)
	Disorganized factor	5.3 (4.6)	5.3 (4.9)	5.4 (4.4)
TRF[b]	Total problems	61.3 (10.0)	63.1 (9.5)	59.8 (10.2)
	Internalizing problems	61.1 (10.5)	59.8 (9.3)	62.3 (11.4)
	Externalizing problems	57.2 (10.7)	59.6 (11.4)	55.1 (9.5)
	Withdrawn behavior	61.5 (10.4)	61.3 (10.6)	61.7 (10.2)
	Anxious/depressed behavior	60.9 (9.7)	59.0 (8.4)	62.6 (10.4)
	Social problems	61.6 (9.3)	62.7 (9.5)	60.6 (9.0)
	Attentional problems	59.7 (9.2)	62.6 (9.4)	57.2 (8.1)
	Thought problems	63.2 (11.6)	64.3 (11.9)	62.3 (11.4)
	Somatic complaints	56.0 (8.5)	55.2 (8.1)	56.7 (8.9)
	Aggressive behavior	59.1 (9.5)	61.8 (10.7)	56.8 (7.6)
	Rule breaking behavior	57.2 (8.2)	58.6 (7.8)	55.8 (8.3)

[a]SPQ= Schizotypal Personality Questionnaire; [b]TRF= Teacher Report Form.

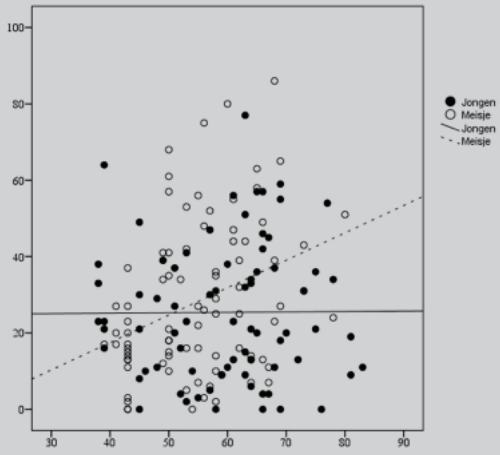
Table 2. Spearman's rank order correlations between TRF Total, broad band and subscale scores (left column) and SPQ Total and factor scores (rows) for the total study sample and gender specific groups.

	Total schizotypal symptoms			Positive schizotypal symptoms		
	Total *n*=159	**Males *n*=75**	**Females *n*=84**	**Total *n*=159**	**Males *n*=75**	**Females *n*=84**
Internalizing problems	.159	.197	.098	.146	.186	.090
Externalizing problems	.139	.006	.309*	.168	.098	.267
Withdrawn behavior	.102	.180	.034	.047	.123	-.006
Somatic complaints	.115	.006	.203	.164	.089	.213
Anxious and depressive behavior	.130	.158	.081	.131	.159	.084
Social problems	.183	.249	.131	.170	.234	.120
Thought problems	.242*	.303	.178	.230*	.332*	.132
Attention problems	.133	.042	.249	.093	.014	.184
Rule breaking behavior	.187	.126	.261	.217	.207	.239
Aggressive behavior	.117	-.012	.300	.147	.078	.262
Total problems	.190	.151	.260	.186	.197	.207

* significant at $p \leq .005$.

	Negative schizotypal symptoms			Disorganized schizotypal symptoms		
	Total *n*=159	**Males *n*=75**	**Females *n*=84**	**Total *n*=159**	**Males *n*=75**	**Females *n*=84**
	.117	.215	-.001	.226*	.230	.220
	.045	-.062	.211	.223*	.075	.411*
	.097	.224	-.017	.169	.193	.145
	.092	.013	.157	.067	-.081	.203
	.073	.151	-.023	.211	.233	.201
	.125	.233	.030	.272*	.282	.257
	.181	.279	.091	.291*	.296	.280
	.076	.026	.179	.244*	.129	.372*
	.102	.077	.162	.218	.148	.298
	.030	-.078	.209	.200	.054	.402*
	.112	.126	.155	.290*	.204	.393*

Figure 1. Moderation effect of gender with TRF externalizing problems for SPQ total en disorganized symptoms



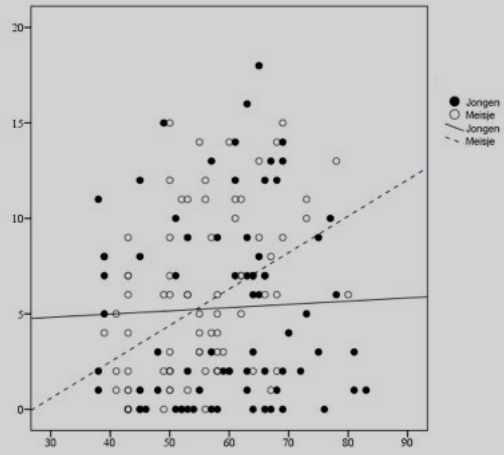


Table 3 Regression analyses for testing the moderation models (*n*=159)

Criterion variable	*Predictor variable*	*F*	R^2	β	*p*
SPQ total score	TRF externalizing problems	3.984	.072	.006	.953
	Gender			.117	.143
	TRF externalizing problems * gender			.256	.015*
SPQ positive factor	TRF thought problems	4.070	.073	.295	.008**
	Gender			-.057	.607
	TRF thought problems * gender			.106	.174
SPQ disorganized factor	TRF attention problems	2.683	.081	-.092	.459
	TRF aggressive problems			-.037	.741
	Gender			.078	.342
	TRF attention problems * gender			.106	.449
	TRF aggressive problems * gender			.163	.219
	TRF externalizing problems	4.622	.082	.039	.710
	Gender			.053	.501
	TRF externalizing problems * gender			.263	.012*
	TRF total problems	5.080	.090	.214	.070
	Gender			.051	.514
	TRF total problems * gender			.107	.358
* p<.05, ** p<.01					

girls at T1 (F(1,158)=34.027, p<.001,η_p^2=.178), and T2 (F(1,158)=9.113, p=.003, η_p^2=.055). In addition, boys had higher scores in comparison with girls on TRF attention problems (F(1,158)=15.041, p<.001, η_p^2=.087), and TRF aggressive behavior (F(1,158)=11.836, p=.001, η_p^2=.070). The difference in TRF externalizing problems between boys and girls did not reach significance (p=.007).

School-associated behavior problems during childhood and adolescence and adult schizotypal symptoms

TRF total problems (r_s=.290, p<.001), internalizing problems (r_s=.226, p=.004), externalizing problems (r_s=.223, p=.005), thought problems (r_s=.291, p<.001), social problems (r_s=.272, p<.001), and attention problems (r_s=.244, p=.002) correlated significantly with severity of adult disorganized schizotypal symptoms. Also significant correlations were found for TRF thought problems with adult schizotypal symptoms in general (r_s=.242, p=.002) and positive schizotypal symptoms (r_s=.230, p=.004) with adult disorganized schizotypal symptomatology. None of the TRF scales were correlated with negative schizotypal symptoms in adulthood (.023<p<.709). (See Table 2).

Within the total group, the multiple regression analysis (Enter method) of the constituting TRF subscales, i.e. social problems, thought problems, and attention problems produced a significant model (R^2=.094, F(3,155)=5.349, p=.002), but none of the three TRF subscales were significant as predictors (.113<p<.296).

Gender specific associations between school-associated behavior problems during childhood and adolescence and adult schizotypal symptoms

Testing for an interaction between gender and juvenile school-associated behavioral problems was done to examine the possible moderating effects of gender on development of schizotypal symptoms in adulthood. First, correlational analyses were conducted. Spearman's bivariate correlations for boys and girls separately showed different patterns. With regard to boys, only TRF thought problems was significantly associated with positive schizotypal symptoms (r_s=.332, p=.004). None of the TRF scales were significantly associated with severity of adult negative (.015<p<.91) or disorganized schizotypal symptoms (.01<p<.644). (See Table 2). With regard to girls, TRF total problems was significantly associated with adult disorganized schizotypal symptoms (r_s=.393, p<.001),

which was specifically due to externalizing problems (r_s=.411, p<.001), and on subscale level to attention problems (r_s=.372, p<.001), and aggressive behavior (r_s=.402, p<.001). A significant correlation was found for TRF externalizing problems (r_s=.309, p=.004) with severity of total schizotypal symptoms. None of the TRF scales were associated with positive or negative schizotypal symptoms in adulthood (.014<p<.956). (See Table 2).

The moderated regression analyses revealed a trend significant interaction between TRF externalizing problems and gender for the SPQ total and disorganized scores (See Table 3), such that the positive association of externalizing problems with general and disorganized schizotypal symptoms were evident for girls, but not for boys (See Figure 1). Thought problems was the only school-associated behavioral problem that was significantly related to the SPQ positive factor and was therefore selected for inclusion in regression analysis. The moderation model was found to approach significance, (F(3,155)=4.070, p=.008, η_p^2=.073),with a trend significant main effect for TRF thought problems, but neither for gender nor for the interaction term (See Table 3). With regard to TRF, aggressive problems and attention problems, and development of SPQ disorganized symptoms, the moderation model was found to approach significance (F(5,153)=2.683, p=.024, η_p^2=.081). However, none of the main effects and the interaction term were significant. (See Table 3).

Discussion

This study adds to the literature by using an extra-familial source to assess school-associated behavioral problems in children (TRF; Verhulst et al., 1997), and its association with adult schizotypal symptomatology in a population presenting with psychopathology at childhood or adolescence. It was found that juvenile behavioral abnormalities that are tied to a school´s environment and its specific demands were differentially associated with type of adult schizotypal symptoms. These associations were further modified by gender. Disregarding gender, teacher-reported thought problems in childhood was identified as the strongest indicator of future schizotypal symptoms, since it was significantly associated with disorganized and positive schizotypal symptoms. In addition, school-associated social problems and attention problems in childhood and adolescence were also identified as indicators of future disorganized schizotypal symptoms. However, when gender is taken into account, for girls school-associated externalizing problems, specifically attention and aggressive problems, were associated with the development of higher levels of adult disorganized schizotypal symptoms.

Severity of school-associated childhood and adolescent problems and adult schizotypal symptoms

Data suggest that subjects who are burdened by a broad range of behavioral problems in childhood and adolescence as reported by their teacher are at higher risk for disorganized schizotypal symptoms during adult life. This finding adds to earlier studies (Miller et al., 2002; Amminger et al., 1999; Muratori et al., 2005; Johnstone et al., 2005; Scott et al., 2009) that so far have mainly focused on intra-familial sources and have revealed that early problem behavior was associated with elevated risk for future schizophrenia spectrum pathology in general, without evaluating the specific association to distinctive domains of schizotypal symptoms.

Childhood thought problems and schizotypal symptoms

Within the total sample, higher levels of disordered thinking as assessed by the TRF in childhood were found to be associated with higher levels of future schizotypal symptoms within the domain of positive symptoms as well as within the domain of disorganized symptoms. If schizotypal symptoms are considered to represent a genetically related, milder variant of schizophrenia, lying on a continuum of schizophrenia spectrum pathology, this finding suggests that thought problems in childhood and adolescence as reported by their teachers is indicative for the development of specific behavior within the schizophrenia spectrum. This tentative conclusion adds to the well-known notion of Kreapelin (1919) and Bleuler (1961), who attributed, already a century ago, a central role in the development of schizophrenia spectrum disorders to 'impaired thinking'. Meehl (1962, 1990) further posited that associative loosing or what he called 'cognitive slippage' was the primary manifestation of a schizophrenia diathesis. The current results extend the insight into the outcome of cross-sectional (Johnston & Holzman, 1979; Arboleda & Holzman, 1985; Tompson, Asarnow, Goldstein, & Milkowitz, 1990) and more recent longitudinal studies (Muratori et al., 2005; Velthorst et al., 2009), revealing that children who will later develop schizophrenia spectrum pathology exhibit more severe school-associated thought problems, than high risk children who do not develop adult schizophrenia disorders later on, or children who do not eventually develop other non-psychotic psychiatric pathology. In addition to the results of these studies that have only used intra-familial sources to describe juvenile behavioral problems, in the present study it is found that out of a broad range of juvenile problem behaviors and within a

school's context, teacher reported levels of thought problems stand out as the factor being strongest associated with future disorganized and positive schizotypal symptoms. Consequently, interventions that can affect these school-associated thought problems may have crucial implications for long-term outcome in children and adolescents at high risk for the development of schizophrenia spectrum pathology.

The cognitive mechanisms that mediate the association between school-associated thought problems and distinctive schizophrenia spectrum symptomatology, however, need further investigation. Since especially disorganized behavior is associated with poor executive functioning (Cohen, Barch, Carter, & Servan-Schreiber, 1999; Moritz, Andresen, Naber, Krausz, & Probsthein, 1999; Kerns & Berenbaum, 2002; Kerns, 2006), impairments in executive functioning might be among other candidate markers of future adult symptoms of disorganization. With respect to positive schizotypal symptoms, such as delusions and hallucinations, these might be specifically associated with deficits in attention and information processing during development (Blackwood, Howard, Bentall, & Murray, 2001). For example, hallucinations were found to be associated with impairments in attentional processes and perceptions that lead to the intrusion of unintended information into conscious awareness (Bentall & Slade, 1985; Bentall, Kaney, & Dewey, 1991; Bentall, Baker, & Havers, 1991; Ventura, Thames, Wood, Guzik, & Hellemann, 2010). Additional research is warranted to determine whether these cognitive deficits mediate the association between positive and disorganized schizotypal symptoms in general and different facets of impaired thinking (Caplan, Guthrie, Tang, Komo, & Asarnow, 2000).

School-associated social and attentional problems in childhood and adolescence and adult schizotypal symptoms

Severity of social and attention problems in childhood and adolescence within a school's environment was associated with disorganized schizotypal symptoms in adulthood in the total sample. This adds to earlier findings of studies that, based on the use of intra-familial sources, have reported about the presence of childhood social problems in relation to the development of future schizophrenia spectrum pathology in comparison to typically developing controls (Jones et al., 1994; Tarbox & Pogue-Geile, 2008; Welham et al., 2009) as well as in comparison with subjects with affective disorder (Dworkin et al., 1994), and anorexia (Muratori et al., 2005). Muratori and colleagues (2005) also identified specific childhood problems in regulation of attention. However, these studies did not differentiate between specific schizotypal symptoms. Our study suggests a specific con-

nection between early social and attention problems that are tied to demands on school and disorganized behavior later in life.

School-associated behavioral indicators of future schizotypal symptoms in boys and girls

As the majority of studies focuses on general populations of high risk subjects with men being grossly overrepresented, the literature may have been biased from a male perspective. Because of the present follow-up study consisting of a sample of 75 boys and 84 girls who all sought psychiatric help during childhood or adolescence, it was therefore possible to delineate meaningful gender specific behavioral pathways of future schizotypal symptoms.

Surprisingly, in girls school-associated externalizing problems and not internalizing problems were associated with higher levels of exclusively disorganized schizotypal symptoms. These gender specific findings contrast earlier findings of externalizing problems being particularly associated with the development of future schizophrenia spectrum disorders in men (McGlashan & Bardenstein, 1990), and internalizing problems being related with future schizophrenia spectrum disorders in women (Goldstein & Link, 1988; Jones et al., 1994; Addington, Addington, & Patten, 1996; McGlashan et al., 1990; Yung, Phillips, Yuen, & McGorry, 2004; Johnstone et al., 2005). However, the use of an extra-familiar instead of an intra-familiar source to assess behavioral problems might explain present results. Agreement among informants can differ according to type of psychopathology (Achenbach, McConaughy, & Howell, 1987; Smith, 2007), with greater levels of correspondence for informants' ratings of externalizing problems when compared with informants' ratings of internalizing problems (Achenbach, McConaughy, & Howell, 1987; Duhig, Renk, Epstein, & Phares, 2000). This difference is often interpreted as suggesting that informant agreement is better for problems that are presumably less observable and depend more on interpretation by informants (internalizing problems) than problems that are more observable (externalizing problems) such as fighting or teasing. In addition, parents have been found to report higher levels of problem behavior than teachers and judge problem behavior of boys and girls differently from teachers (Van der Ende & Verhulst, 2005). For example, teachers report lower levels of externalizing behavior in boys as opposed to parents (Van der Ende & Verhulst, 2005). Further investigation of gender specific behavioral problems using different informants is therefore warranted.

It was found that certain types of school-associated juvenile behavior appeared

to be associated with the development of specific symptoms of schizophrenia spectrum pathology.

The regression analysis demonstrated that the combination of the three subscales improved the predictive power (R^2) relative to the separate correlations (r^2). However, the improvement was modest (9.4% vs. 8.4% for thought problems that showed the highest correlation).

Strengths and limitations

The long follow-up period of 11.6 (*SD*=3.1) years of the current cohort was highly suitable to investigate how school-associated behavioral problems in childhood and adolescence were related with distinctive adult schizotypal symptoms. In addition, the present sample showed clearly elevated levels of SPQ total score as compared to the typically developing controls reported by Fagel and colleagues (2013) (M=26.9; *SD*=19.3 vs. M=17.3; *SD*=12.6). This underscores severity of schizotypal symptomatology of the present sample. Inherent to this long follow-up period, this study suffered from attrition which resulted in follow-up data available for 159 (35%) of the subjects. However, analyses of the background variables at T1 revealed that participants and non-participants were quite similar, with slightly higher Full scale IQ and Performance IQ and less severe rule breaking and aggressive behavior of the participants in comparison with the non-participants. It remains unknown, however, how the non-participants developed at T2. Further, since the present study concerns a clinically referred sample, the current findings might pertain to those subjects who presented with considerable and progressive juvenile neurobehavioral impairments and not to those subjects who were relatively inconspicous as a child. Then, the mean age of participantsat follow up was 24.4 (*SD*=5.1) years. As a result not all subjects may have passed the complete period of risk for schizophrenia spectrum pathology. In addition, the screening by self-report does carry some limitations, as compared with interviews. For example, self-report questionnaires might not ensure sufficient sensitivity and specificity for specific schizotypal signs such as an odd or guarded appearance, an expression of aloofness, or poor eye contact, and restricted affect (Kendler, 1988) and people may not be accurate in their self-judgments of appearance and speech (Raine, 1991). However, the SPQ has high reliability and validity. This may be because some of the questions assessing signs were worded so that the subject reports on external corroboration of these signs (e.g., “People sometimes comment on my unusual mannerisms and habits” or “People sometimes find it hard to understand

what I am saying") rather than relying solely on self-analysis. Schizotypal individuals therefore seem to have no significant loss of insight that would affect their self-perceptions and thus invalidate the results on subscales of schizotypal signs (Raine, 1991). Although the TRF is not intended to replace the full assessment of a child's functioning including clinical interviews, it should be noted that in addition to information from parents about a child's behavior, teacher information is a valuable additional source of information (Van der Ende & Verhulst, 2005). Within a school's structured setting, teachers are in a unique situation to compare the behavior of one child with the behavior of many other same-aged, older or younger children, and to judge whether the behavior of the child is appropriate for his or her age. However, as parents may have a possible rater bias by lacking internal standards to determine 'normal' levels of behavior, teachers may too have their own kinds of 'bias' (Polderman et al., 2006). Besides these limitations, the current follow-up study suited the purpose to illustrate the complex dynamics of school-associated behavioral problems in childhood and adolescence and the development of distinctive adult schizotypal symptoms.

From a clinical point of view, clinicians should be aware of the higher risk for schizotypal symptomatology in adulthood following school-associated juvenile behavioral problems, and that specific patterns of adult schizotypal symptomatology are asso-ciated with different types of juvenile behavioral problems.

References

Achenbach, T. M., McConaughy, S.H., & Howell, C.T. (1987). Child/adolescent behavioral and emotional problems: Implications of cross informant correlations for situational specificity. *Psychol Bull*, 101, 213–232.

Addington, D., Addington, J., & Patten, S. (1996). Gender and affect in schizophrenia. *Can J Psychiatry*, 41(5), 265–268.

American Psychiatric Association (1987). *Diagnostic and Statistical Manual of Mental Disorders (3rd revised ed)*. Washington DC: American Psychological Association Press.

Amminger, G.P., Pape, S., Rock, D., Roberts, S., Ott, S., Squires-Wheeler, E., Kestenbaum, C., & Erlenmeyer-Kimling, L. (1999). Relationship between childhood behavioral disturbance and later schizophrenia in the New York High-Risk project. *Am J Psychiatry*, 156(4), 525-530.

Arboleda, C., & Holzman, P. (1985). Thought disorder in children at risk for psychosis. *Arch Gen Psychiatry*, 42(10), 1004-1013.

Arseneault, L., Moffitt, T.E., Caspi, A., Taylor, A., Rijsdijk, F.V., Jaffee, S.R., Ablow, J.C., & Measelle, J.R. (2003). Strong genetic effects on cross-situational antisocial behavior among 5-year-old children according to mother, teachers, examiner–observers, and twins' self-reports. *J Child Psychol Psychiatry,* 44(6), 832–848.

Ayalon, M., & Merom, H. (1985). The teacher interview. *Schizophr Bull*, 11(1), 117-120.

Bartels, M., Hudziak, J.J., Boomsma, D.I., Rietveld, M.J.H., Van Beijsterveldt, C.E.M., & Van den Oord, E.J.C.G. (2003). A study of parent ratings of internalizing and externalizing problem behavior in 12-year-old twins. *J Am Acad Child Adolesc Psychiatry,* 42(11), 1351–1359.

Bearden, C., Rosso, I., Hollister, J., Sanchez, L., Hadley, T., & Cannon, T. (2000). A prospective cohort study of childhood behavioral deviance and language abnormalities as predictors of adult schizophrenia. *Schizophr Bull*, 26(2), 395-410.

Bentall, R., & Slade, P. (1985). Reality testing and auditory hallucinations: a signal detection analysis. *Br J Clin Psychol*, 24(Pt 3), 159–169.

Bentall, R., Kaney, S., & Dewey, M. (1991). Paranoia and social reasoning: an attribution theory analysis. *Br J Clin Psychol*, 30(Pt 1), 13–23.

Bentall, R., Baker, G., & Havers, S. (1991). Reality monitoring and psychotic hallucinations. *Br J Clin Psychol*, 30(Pt 3), 213–222.

Blackwood, N., Howard, R., Bentall, R., & Murray, R. (2001). Cognitive neuropsychiatric models of persecutory delusions. *Am J Psychiatry,* 158(4), 527–539.

Bleuler, E. (1961). *Dementia praecox or the group of schizophrenias.* English translation. New York: International Universities Press.

Cannon, M., Jones, P., Huttunen, M., Tanskanen, A., Rabe-Hesketh, S., & Murray, R. (1999). School performance in Finnish children and later development of schizophrenia: a population-based longitudinal study. *Arch Gen Psychiatry,* 56(5), 457-463.

Caplan, R., Guthrie, D., Tang, T., Komo, S., & Asarnow, R.F. (2000). Thought disorder in childhood schizophrenia: replication and update of concept. *J Am Acad Child Adolesc Psychiatry*, 39(6), 771-778.

Chapman, L.J., Chapman, J.P., Kwapil, T.R., Eckblad, M., & Zinser, M.C. (1994). Putatively psychosis-prone subjects 10 years later. *J Abnorm Psychol*, 103(2), 171- 183.

Cohen, J. (1992). A power primer. *Psychol Bull,* 112(1), 155–159.

Cohen, J., Barch, D., Carter, C., & Servan-Schreiber, D. (1999). Context-processing deficits in schizophrenia: converging evidence from three theoretically motivated cognitive tasks. *J Abnorm Psychol*, 108(1), 120–133.

Cronbach, L.J. (1987). Statistical tests for moderator varables: flaws in analyses recently proposed. *Psychol Bull*, 102(3), 414–417.

Crow, T.J., Done, D.J., & Sacker, A. (1995). Childhood precursors of psychosis as clues to its evolutionary origin. *Eur Arch Psychiatry Clin Neurosci*, 245(2), 61-69.

Cunningham, D., Miller, O., Lawrie, S., & Johnstone, E. (2005). Pathogenesis of schizophrenia: a psychopathological perspective. *Br J Psychiatry*, 186, 386-393.

Davidson, M., Reichenberg, A., Rabinowitz, J., Weiser, M., Kaplan, Z., & Mark, M. (1999). Behavioral and intellectual markers for schizophrenia in apparently healthy male adolescents. *Am J Psychiatry*, 156(9), 1328-1335.

DeLisi, L., Boccio, A., Rliordan, H., Hoff, A., Dorfman, A., McClelland, J., Kushner, M., Van Eyl, O., & Oden, N. (1991). Familial thyroid disease and delayed language development in first admission patients with schizophrenia. *Psychiatry Res*, 38(1), 39-50.

Done, D.J., Crow, T.J., Johnstone, E.C., & Sacker, A. (1994). Childhood antecedents of schizophrenia and affective illness: social adjustment at ages 7 and 11. *Br Med Journal*, 309(6956), 699-703.

Duhig, A. M., Renk, K., Epstein, M. K., & Phares, V. (2000). Interparental agreement on internalizing, externalizing, and total behavior problems: A meta-analysis. *Clin Psychol Sci Pract*, 7, 435–453.

Dworkin, R., Lewis, J., Cornblatt, B., & Erlenmeyer-Kimling, L. (1994). Social competence deficits in adolescents at risk for schizophrenia. *J Nerv Ment Dis,* 182(2), 103-108.

Fagel, S.S.A.A., Swaab, H., De Sonneville, L.M., Van Rijn, S., Pieterse, J.K., Scheepers, F., & Van Engeland, H. (2013). Development of schizotypal symptoms following psychiatric disorders in childhood or adolescence. *Eur Child Adolesc Psychiatry.* In Press.

Fish, B. (1987). Infant predictors of the longitudinal course of schizophrenic development. *Schizophr Bull*, 13(3), 395-409.

Fish, B., Marcus, J., Hans, S., Auerbach, J.G., & Perdue, S. (1992). Infants at risk for schizophrenia: sequelae of a genetic neurointegrative defect. *Arch Gen Psychiatry*, 49(3), 221-35.

Foerster, A., Lawis, S., Owen, M., & Murray, R. (1991). Pre-morbid adjustment and personality in psychosis. *Br J Psychiatry*, 158, 171-176.
Goldstein, J.M., & Link, B.G. (1988). Gender and the expression of schizophrenia. *Psychiatry Res*, 22(2), 141-155.

Gooding, D.C., Tallent, K.A., & Matts, C.W. (2005). Clinical status of at-risk individuals 5 years later: further validation of the psychometric high-risk strategy. *J Abnormal Psychol*, 114(1), 170-175.

Goodman, S., 1987. Emory university project on children of disturbed parents. *Schizophr Bull*, 13(3), 411-423.

Johnston, M., & Holzman, P. (1979). *Assessing schizophrenic thinking* (pag 56-101). San Francisco: Jossey-Bass.

Johnstone, E., Ebmeier, K., Miller, P., Owens, D., & Lawrie, S. (2005). Predicting schizophrenia: findings from the Edinburgh High-Risk Study. *Br J Psychiatry,* 186, 18-25.

Jones, P., Rodgers, B., Murray, R., & Marmot, M. (1994). Child development risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet*, 344(8934), 1398–1402.

Kendler, K. (1988). Familial aggregation of schizophrenia and schizophrenia spectrum disorders. Evaluation of conflicting results. *Arch Gen Psychiatry*, 45(4), 377-383.

Kerns, J., & Berenbaum, H. (2002). Cognitive impairments associated with formal thought disorder in people with schizophrenia. *J Abnorm Psychol*, 111(2), 211–224.

Kerns, J. (2006). Schizotypy facets, cognitive control, and emotion. *J Abnorm Psychol,* 115(3), 418–427.

Kraepelin, E. (1919). *Dementia praecox and paraphrenia,* Barclay, R. (trans). Chicago: Chicago Medical Book.

Kwapil, T.R. (1998). Social anhedonia as a predictor of the development of schizophrenia spectrum disorders. *J Abnorm Psychol*, 107(4), 558-65.

Malmberg, A., Lewis, G., David, A., & Allebeck, P. (1998). Premorbid adjustment and personality in people with schizophrenia. *Br J Psychiatry*, 172, 308-313; discussion 314-315.

McGlashan, T.H., & Bardenstein, K.K.. (1990). Gender differences in affective, schizoaffective, and schizophrenic disorders. *Schizophr Bull*, 16(2), 319–329.

Mednick, S., & Schulsinger, F. (1968). Some premorbid characteristics related to breakdown in children with schizophrenic mothers. *Psychiatry Res*, 6, 267-291.

Meehl, P.E. (1962). Schizotaxia, schizotypy, schizophrenia. *Am Psychology*, 17, 827–838.

Meehl, P.E. (1990). Toward an integrated theory of schizotaxia, schizotypy, and schizophrenia. *J Pers Disord*, 4, 1–99.

Miller, P.M., Byrne, M., Hodges, A., Lawrie, S.M., & Johnstone, E.C. (2002). Childhood behaviour, psychotic symptoms and psychosis onset in young people at high risk of schizophrenia: early findings from the Edinburgh high risk study. *Psychol Med*, 32(1), 173-179.

Moritz, S., Andresen, B., Naber, D., Krausz, M., & Probsthein, E. (1999). Neuropsychological correlates of schizotypal disorganization. *Cogn Neuropsychiatry*, 4(4), 343–349.

Muratori, F., Salvadori, F., D'Arcangelo, G., Viglione, V., & Picchi, L. (2005). Childhood psychopathological antecedents in early onset schizophrenia. *Eur Psychiatry*, 20(4), 309–314.

Nagler, S., & Glueck, Z. (1985). The Clinical Interview. *Schizophr Bull*, 11(1), 38-47.

Olin, S., Raine. A., Cannon, T., Pamas, J., Schulsinger, F., & Mednick, S. (1997). *Schizophr Bull*, 23(1), 93-103.

Polderman, T.J., Posthuma, D., De Sonneville, L.M.J., Verhulst, F.C., & Boomsma, D.I. (2006). Genetic analyses of teacher ratings of problem behavior in 5-year-old twins. *Twin Res Hum Genet*, 9(1), 122-130.

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.

Raine, A., Reynolds, C., Lencz, T., Scerbo, A., Triphon, N., & Kim, D. (1994). Cognitive-perceptual, interpersonal, and disorganized features of schizotypal personality. *Schizophr Bull*, 20(1), 191-201.

Raine, A. (2006). Schizotypal personality: neurodevelopmental and psychosocial trajectories. *Annu Rev Clin Psychol*, 2, 291–326.

Reynolds, C., Raine, A., Mellingen, K., Venables, P., & Mednick, S. (2000). Three-factor model of schizotypal personality: invariance across culture, gender, religious affiliation, family adversity, and psychopathology. *Schizophr Bull*, 26(3), 603–618.

Rossi, A., Pollice, R., Daneluzzo, E., Marinangeli, M., & Stratta, P. (2000). Behavioral neurodevelopment abnormalities and schizophrenic disorder: a retrospective evaluation with the Childhood Behavior Checklist (CBCL). *Schizophr Res*, 44(2), 121–128.

Rosso, I., Bearden, C., Hollister, J., Gasperoni, T., Sanchez, L., Hadley, T., & Cannon, T. (2000). Childhood neuromotor dysfunction in schizophrenia patients and their unaffected siblings: a prospective cohort study. *Schizophr Bull*, 26(2), 367-378.

Salem, J.E., & Kring, A.M. (1998). The role of gender differences in the reduction of Etiologic heterogeneity in schizophrenia. *Clin Psychol Rev*, 18(7), 795-819.

Salokangas, R.K.R. (1983). Prognostic implications of the sex of schizophrenic patients. *Br J Psychiatry*, 142, 145-151.

Schuklenk, U. (2001). Helsinki declaration revisions. *Issues Medical Ethics*, 9(1), 29.

Scott, J., Martin, G., Welham, J., Bor, W., Najman, J., O'Callaghan, M., Williams, G., Aird, R., & McGrath, J. (2009). Psychopathology during childhood and adolescence predicts delusional-like experiences in adults: a 21-year birth cohort study. *Am J Psychiatry*, 166(5), 567–574.

Smith, S. R. (2007). Making sense of multiple informants in child and adolescent psychopathology: A guide for clinicians. *JPA*, 25, 139–149.

Tarbox, S.I., & Pogue-Geile, M.F. (2008). Development of social functioning in preschizophrenia children and adolescents: A systematic review. *Psychol Bull*, 134(4), 561-583.

Tompson, M., Asarnow, J., Goldstein, M., & Milkowitz, D.J. (1990). Thought disorder and communication problems in schizophrenia and depressed children and their parents. *J Child Psychol Psychiatry*, 19(2), 159-168.

Tsuang, M., Stone, W., Tarbox, S., & Faraone, S. (2002). An integration of schizophrenia with schizotypy: identification of schizotaxia and implications for research on treatment and prevention. *Schizophr Res*, 54(1-2), 169-175.

Van der Ende, J., & Verhulst, F.C. (2005). Informant, gender and age differences in ratings of adolescent problem behavior. *Eur Child Adolesc Psychiatry*, 14(3), 117–126.

Van der Valk, J.C., Van den Oord, E.J.C.G., Verhulst, F.C., & Boomsma, D.I. (2001). Using parental ratings to study the etiology of 3-year-old twins' problem behaviors: Different views or rater bias? *J Child Psychol Psychiatry*, 42(7), 921–931.

Velthorst, E., Nieman, D., Becker, H., Van de Fliert, R., Dingemans, P., Klaassen, R., De Haan, L., Van Amelsvoort, T., & Linszen, D. (2009). Baseline differences in clinical symptomatology between ultra high- risk subjects with and without a transition to psychosis. *Schizophr Res*, 109(1-3), 60–65.

Ventura, J., Thames. A., Wood, R., Guzik, L., & Hellemann, G. (2010). Disorganization and reality distortion in schizophrenia: A meta-analysis of the relationship between positive symptoms and neurocognitive deficits. *Schizophr Res*, 121(1-3), 1–14.

Verhulst, F.C., Van der Ende, J., & Koot, H.M. (1997). *Manual for the Teacher's Report Form* (Dutch translation). Department of Child and Adolescent Psychiatry, Rotterdam, The Netherlands.

Vollema, M. & 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., Sitskoorn, M., Appels, M., & Kahn, R. (2002). Does the schizotypal personality questionnaire reflect the biological-genetic vulnerability to schizophrenia? *Schizophr Res*, 54(1-2), 39-45.

Walker, E., Lewis, N., Loewy, R., & Palyo, S. (1999). Motor dysfunction and risk for schizophrenia. Dev Psychopathol, 11(3), 509–523.
Watt, N., & Lubensky, A. (1976). Childhood roots of schizophrenia. *J Consult Clin Psychol*, 44(3), 363-375.

Wechsler, D. (1949). *Wechsler Intelligence Scale for Children (WISC)*. San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1955). *Manual for the Wechsler Adult Intelligence Scale (WAIS).* New York: The Psychological Corporation.

Wechsler, D. (1967). *Wechsler Preschool and Primary Scale of Intelligence (WPPSI).* New York: The Psychological Corporation.

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

Wechsler, D. (1981). *Manual for the Wechsler Adult Intelligence Scale-Revised (WAIS-R).* New York: The Psychological Corporation.

Wechsler, D. (1991). *Manual for the Wechsler Intelligence Scale for Children, Third Edition (WISC-III).* San Antonio, TX: The Psychological Corporation.

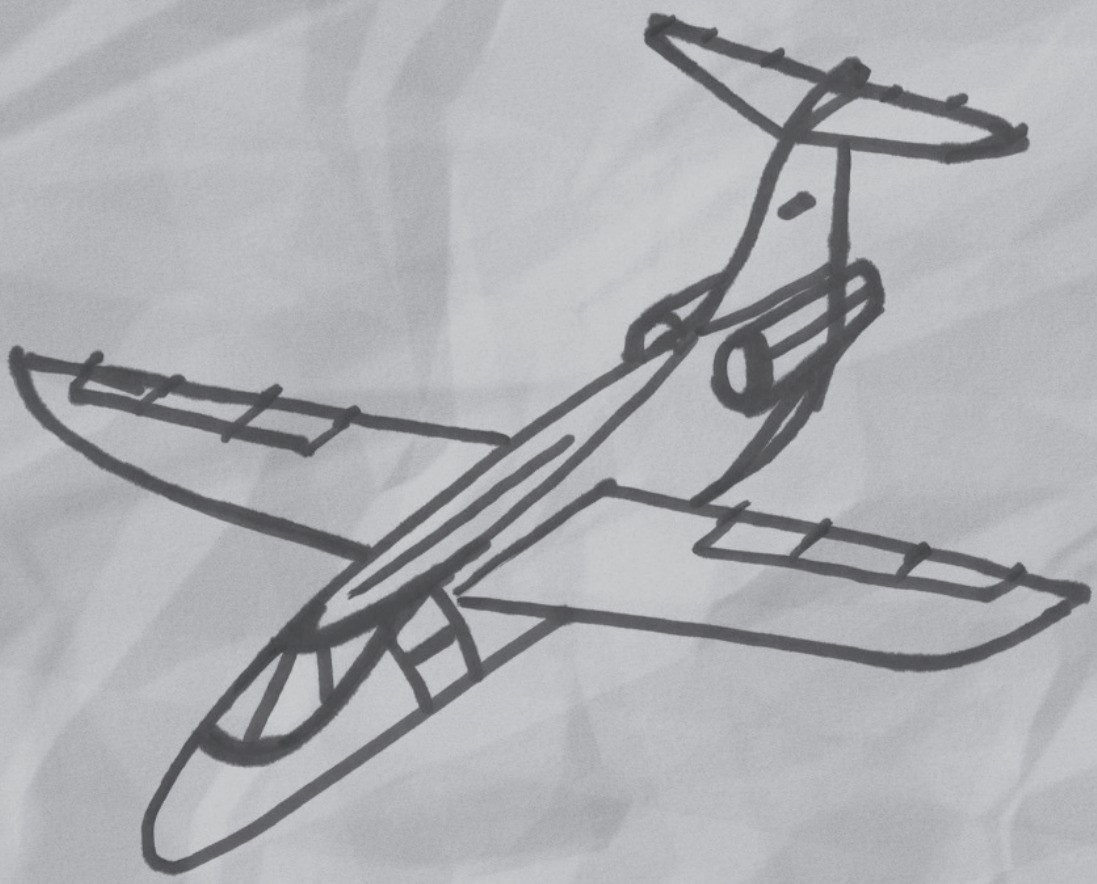
Weintraub, S., Prinz, R., & Neale, J. (1978). Peer evaluations of the competence of children vulnerable to psychopathology. *J Abnorm Child Psychol*, 6(4), 461-473.

Welham, J., Scott, J., Williams, G., Najman, J., Bor, W., O'Callaghan, M., & McGrath, J. (2009). Emotional and behavioural antecedents of young adults who screen positive for non-affective psychosis: a 21-year birth cohort study. *Psychol Med*, 39(4), 625-634.

Yung, A.R., Phillips, L.J., Yuen, H.P., & McGorry, P.D. (2004). Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. *Schizophr Res*, 67(2-3), 131– 142.

Zigler, E., Levine, J., & Zigler, B. (1977). Pre-morbid social competence and paranoid-non paranoid status in female schizophrenic patients. *J Nerv Ment Dis*, 164(5), 333-339.

Chapter 5



Adult schizotypal symptoms following juvenile psychopathology: no relation with juvenile intellectual functioning

Fagel, S.S.A.A., De Sonneville, L.M.J., Van Engeland, H., & Swaab, H. Adult schizotypal symptoms following juvenile psychopathology: no relation with juvenile intellectual functioning. *Under review*.

Abstract

Because of the frequent finding that the developmental course of patients with disorders such as schizophrenia or psychosis is often marked by a significantly lower level of premorbid intelligence in comparison with healthy controls, the association between intellectual functioning in juvenile psychopathology and adult schizotypal symptoms, including the role of sex, was examined. 317 patients of the Department of Child and Adolescent Psychiatry of the University Medical Centre Utrecht, the Netherlands, were reassessed after 13.2 (*SD*=5.2) years for adult schizotypal symptoms by using the Schizotypal Personality Questionnaire-Revised (SPQ-R; Vollema & Hoijtink, 2002; Raine, 1991). The relation between intellectual functioning in juvenile psychopathology and adult schizotypal symptoms was examined by Spearman´s bivariate correlations. No evidence was found for general or specific domains of intelligence in juvenile psychopathology being related to general and specific adult schizotypal symptomatology. This result also held when boys and girls were studied separately. The absence of associations between juvenile intelligence and adult schizotypal symptomatology in a sample of subjects presenting with juvenile psychopathology might be interpreted as juvenile intellectual markers not being suitable to predict development of milder symptoms within the schizophrenia spectrum.

Introduction

Schizophrenia spectrum pathology is composed of multiple conditions that are characterized by distortions of cognitive and perceptual reality, collectively known as positive symptoms, interpersonal withdrawal (negative symptoms), and disorganized speech and behavior (disorganized symptoms) (Liddle, 1987; Suhr, 2001). These conditions have different gradients 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 (Meehl, 1989). Because there is evidence for neurodevelopmental origins being part of its etiology in (at least) a subgroup of patients (Weinberger, 1987; Murray & Lewis, 1987), 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 patients that developed disorders within the schizophrenia spectrum in adulthood, such as schizophrenia (Woodberry, Giuliano, & Seidman, 2008; Cannon, Bearden, Hollister, Rosso, Sanchez, & Hadley, 2000; Mortensen, Sorensen, Jensen, Reinisch, & Mednick, 2005; Ott et al., 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 may relate to this general impairment. While the results of the army cohort study of David and colleagues (1997), the birth cohort study of Seidman et al. (2006), the genetic high-risk study of Ott et al. (1998), and the meta-analysis of Aylward, Walker and Bettes (1984) found that pre-schizophrenic children were especially marked by deficits in verbal intelligence in comparison to typically developing controls, the results of the clinical follow-up study of Amminger et al. (2000), and the birth cohort study of Jones, Rodgers, Murray and Marmot (1994) have pinpointed deficits in nonverbal juvenile intelligence in pre-schizophrenic children in comparison to typically developing controls as precursors. Then again, the results of the genetic high-risk study of Sørensen, Mortensen, Parnas and Mednick (2006), the birth cohort study of Cannon and colleagues (2000), and the meta-analysis of Khandaker, Barnett, White and Jones (2011) are suggestive for verbal as well as non-verbal juvenile capacities being equally affected in patients with schizophrenia when compared to typically developing controls.

Similar inconsistency in results is found when looking at subdomains of intellectual functioning. Some studies have found that persons who developed disorders

within the schizophrenia spectrum had lower scores on subtests pertaining to juvenile verbal intelligence when compared with typically developing controls. For example, the prospective birth cohort study of Seidman and colleagues (2006) reported lower scores on Information and digit span at child age in persons who developed schizophrenia in adulthood. The prospective high-risk study of Sørensen and colleagues (2010) found lower scores on similarities in persons who developed disorders such as schizophrenia, schizotypal personality disorder, delusional disorder, paranoid personality disorder, schizotypal disorder, and paranoid psychosis when compared with typically developing controls. On the other hand, studies have also shown that this unfavorable development is associated with weaknesses in non-verbal components of intelligence in childhood or adolescence. For example, the prospective cohort study of Niendam, Bearden, Rosso, Sanchez and Hadley (2003) found pre-schizophrenic subjects having lower scores on Coding in comparison with their unaffected siblings. This deficit in coding on child age was also found in the cohort study of Sørensen and colleagues (2006) in persons who developed disorders such as schizophrenia, schizotypal personality disorder, and other disorders within the schizophrenia spectrum in comparison with typically developing controls. The prospective high-risk study of Sørensen and colleagues (2010) reported lower scores in the subtest mazes, and object assembly being associated with the development of schizophrenia in comparison with typically developing controls.

These studies have exclusively investigated disorders within the schizophrenia spectrum which might arguably account for the inconsistencies in results. Schizophrenia spectrum pathology is a very heterogeneous condition, with substantial variability within each diagnostic group of schizophrenia spectrum patients (Kendell, 1987; Pfol, 1986). 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 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 the development of schizophrenia spectrum pathology is to focus on more homogeneous symptoms within the spectrum. Since it is found that the majority of individuals at risk to develop schizophrenia spectrum pathology will not show manifest illness (Meehl, 1990; Gottesman, 1982; Raine, 1991; Chapman, 1994; Tsuang, 2002), but will rather present with milder schizotypal symptoms, it would be relevant to examine precursors of milder features of schizophrenia spectrum pathology along its dimensions. In particular this strategy has recently been promoted as a way to provide important insights into the origins and mechanisms of schizophrenia (Raine, 2006).

Thus far, 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 (Barrantes-Vidalatal, 2002) and positive schizotypal symptoms (Barrantes-Vidalatal, 2002; Matheson & Langdon, 2008). With regard to specific subdomains of intellectual functioning Noguchi and colleagues (2008) showed that lower verbal intelligence was associated with positive symptoms. To our knowledge, no study as yet has longitudinally investigated how intellectual functioning in children and adolescents with psychopathology is associated with the development of distinctive symptoms of schizophrenia spectrum pathology in adulthood.

It has been shown that lower premorbid intelligence is also linked to numerous other psychiatric disorders, such as depression (Koenen et al., 2009; Zammit et al., 2004), affective disorders (Koenen et al., 2009; Urfer-Parnas et al., 2010), adjustment disorders (Mortensen et al., 2005), personality disorders (Mortensen et al., 2005; Urfer-Parnas et al., 2010), alcohol and substance-use-related disorders (Mortensen et al., 2005), neurotic and stress disorders (Urfer-Parnas et al., 2010), and psychiatric illness in general (Koenen et al., 2009). Since the relationship between premorbid intelligence and the development of adult schizophrenia spectrum pathology is only investigated in patients by comparison to typically developing controls, a more promising approach may be to investigate how intelligence and schizotypal symptoms are related independent of general psychopathology, i.e., focusing on level of intellectual functioning and degree and type of schizotypal symptoms.

Finally, there is general agreement that women and men with schizophrenia differ in onset age (Sartorius et al., 1978; Lewine, 1981; Loranger, 1984), and life course (Lewine, 1985; Goldstein, Tsuang, & Faraone, 1989; Westermeyer, Harrow & Marengo, 1989). However, few studies have examined sex differences in intellectual functioning prior to the onset of disorders within the schizophrenia spectrum (Aylward, Walker, & Bettes, 1984; Weiser et al., 2000). The vast majority of studies indicate better premorbid functioning during childhood among females (compared to males) who later developed schizophrenia (Goldberg, Cold, Torrey, & Weinberger, 1995; Walker & Lewine, 1993; Walder et al., 2008). Noticeably absent from the literature are efforts to examine sex differences in intellectual functioning in predicting distinctive symptoms of schizophrenia spectrum pathology. The investigation of such differences is important for understanding the etiology of schizophrenia spectrum pathology.

The present follow-up study aims to investigate how intellectual (dys) functioning in childhood and adolescence is associated with the development of adult distinc-

tive schizotypal symptoms in a cohort of subjects presenting with juvenile psychopathology. In line with the result of the cross-sectional study of Noguchi and coleagues (2008) investigating intellectual functioning and its relation with distinctive schizotypal symptoms, it is hypothesized that lower levels of general intellectual functioning in childhood and adolescence, in particular verbal intelligence, will be most strongly linked to adult schizotypal symptoms and especially positive and negative symptoms. Whether this relation is valid for specific intellectual subdomains is further explored, as well as the role of sex.

Methods

Sample and procedure

This study is part of a longitudinally prospective study designed to evaluate both global and clinical outcomes in adulthood of patients, referred during 1984 to 2004 (T1), to the Department of Child and Adolescent Psychiatry at the University Medical Centre of Utrecht (UMCU), the Netherlands. 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) presence of axis I diagnosis based on Diagnostic Statistical Manual (DSM) criteria of the American Psychiatric Association (APA, 1980, 1987, 1994), (4) no axis II DSM diagnosis (APA, 1980, 1987, 1994) of mental retardation (IQ<70) at T1, (5) no axis I DSM diagnosis before or at T1 with child psychotic disorder, schizophrenia or another psychotic disorder, bipolar disorder or dissociative disorder, and (6) juvenile intellectual assessment at T1. There were 912 non-retarded patients who were eligible for follow-up. They were sent a letter informing them about the aims of the study and checking their willingness to participate in the study. The patients who did not respond were contacted by phone when they could be traced in the public phone registry, to explain the aim of the study and to encourage participation. 317 (153 male and 164 female) adult patients were traced and were willing to participate. Subjects were reassessed after a mean period of 13.2 years (*SD*=5.2), at the mean age of 25.7 years (*SD*=4.7) at T2, with subjects assessed at T1 at 3 to 12 years (*n*=155) being reassessed at the mean age of 25.0 years (M=4.5) and subjects assessed at T1 at 13 to 18 years (*n*=162) being reassessed at the mean age of 26.2 years (*SD*=5.0). With a Full Scale IQ (FSIQ) score of the total group of 103.1 (*SD*= 14.7) the subjects perfectly fit in the normal intelligence range. All subjects voluntarily agreed to participate in this study and signed an informed consent form. The ethical principles of the Helsinki Declaration (Schuklenk, 2001) were followed and approval was obtained from the

Table 1. Number of participants per juvenile DSM diagnostic category (*n*=317)

Juvenile DSM diagnostic categories of the participants	***n***
Eating disorders	55
Pervasive Developmental Disorders	50
Depressive disorders	35
Attention Hyperactivity Disorders	34
Disruptive disorders	27
Anxiety disorders	24
Other conditions that may be a focus of clinical attention	20
Sexual and Gender Identity disorders	13
Deferred diagnosis	12
Other disorders of infancy, childhood, or adolescence	12
Adjustment disorders	11
Somatoform disorders	7
Learning disorders	5
Elimination disorder	5
Tic-disorders	4
Communication disorder	1
Non-specific psychiatric disorder (non-psychotic)	1
Substance-related disorder	1

Table 2. Means and *SD*'s for age at T1, T2, SPQ scores and IQ scores of the total study sample and sex specific subgroups.

	Total group (*n*=319)	**Males (*n*=153)**	**Females (*n*=164)**
	M (SD)	*M (SD)*	*M (SD)*
Age at T1	12.4(3.3)	11.2(3.2)	13.6(2.9)
Age at T2	25.7(4.8)	26.0(5.0)	25.3(4.5)
SPQ total score	27.4(19.1)	27.3(17.5)	27.4(20.5)
SPQ positive factor	9.1(7.5)	8.6(6.3)	9.6(8.4)
SPQ negative factor	12.9(9.6)	13.0(9.4)	12.8(9.9)
SPQ disorganized factor	5.4(4.7)	5.7(5.0)	5.0(4.4)
Full scale IQ	103.1(14.7)	101.9(15.3)	104.2(14.1)
Verbal IQ	102.4(14.5)	101.1(13.8)	103.6(15.1)
Information	10.0(3.1)	10.4(3.2)	9.7(3.0)
Similarities	10.5(2.9)	10.1(3.0)	10.8(2.9)
Arithmetics	10.2(3.2)	10.1(3.2)	10.3(3.1)
Vocabulary	10.0(2.8)	10.2(2.9)	9.7(2.8)
Comprehension	10.0(2.8)	9.8(2.7)	10.3(2.9)
Digit span	9.3(3.0)	8.9(2.9)	9.7(3.2)
Performance IQ	103.3(16.1)	102.3(17.9)	104.2(14.3)
Picture completion	9.5(3.0)	9.9(2.9)	9.2(3.1)
Picture arrangement	10.5(3.1)	10.8(3.2)	10.4(2.9)
Block design	10.5(3.3)	10.7(3.6)	10.3(3.1)
Object assembly	10.2(3.4)	10.1(3.7)	10.3(3.2)
Digit symbol	9.9(3.3)	9.0(3.1)	10.8(3.2)

Medical Ethical Committee of the University Medical Centre of Utrecht (number 05-319/K). Table 1 represents the number of participants by juvenile DSM diagnostic category. Table 2 represents the background variables of participants.

Representativeness

To check representativeness of the sample, age, intelligence scores and sex distribution of participants and nonparticipants were compared. Chi-square analysis revealed that proportionally more participants appeared to be females (51.7% female participants versus 34.6% females in the nonparticipants group), (χ^2(1,912)=25.121, p<.001). Multivariate analysis of variances (MANOVA) revealed that participants had a slightly higher Verbal IQ (VIQ) (M=102.4; *SD*=14.5 vs. M=99.3; *SD*=14.0), (F(1,888)=9.802, p=.002, η_p^2=.011) and Full Scale IQ (M=103.1; *SD*=14.7 vs. M=100.5; *SD*=14.0), (F(1,888)=6.562, p=.011, η_p^2=.007). No differences between participants and those lost to follow-up were found for age at T1 (F(1,888)=.474, p=.491), age at T2 (F(1,888)=1.626, p=.203) and Performance IQ (PIQ) (F(1,888)=1.159, p=.282).

Intellectual assessment in childhood and adolescence

Cognitive functioning was evaluated using standardized scores of Wechsler Intelligence Scales at time of juvenile assessment; i.e. WPPSI (Wechsler, 1967), WISC (Wechsler, 1949), WISC-R (Wechsler, 1974) or WISC-III (Wechsler, 1991) was administered to subjects aged younger than 16 years and WAIS (Wechsler, 1955) or WAIS-R (Wechsler, 1981) was administered to subjects aged 16 years and older. FSIQ, VIQ, and PIQ scores were computed. WISC and WAIS versions comprised an overlap in eleven Wechsler subscales; i.e., information, vocabulary, comprehension, similarities, arithmetic, digit span, picture completion, block design, coding, picture arrangement, and object assembly. standardized scores were calculated for these eleven subscales, and five subtests were omitted because they were not included in both Wechsler versions (mazes, matrix reasoning, symbol search, geometrical figures, and letter-number sequencing).

Adult schizotypal symptoms

Adult schizotypal symptoms were measured using the Schizotypal Personality Questionnaire-Revised (SPQ-R; Raine, 1991; Vollema & Hoijtink, 2000). The SPQ-R is a self-report measure of schizotypal symptoms, modeled on the Diagnostic and Statistical Manual of Mental Disorders (APA, 1987) criteria for schizotypal personality disorder (Raine, 1991). In the study of Raine (1991) 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 (χ^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. 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 has been found to be invariant to sex, ethnicity, religion, and social background (Reynolds, Raine, Mellingen, Venables, & Mednick, 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. The SPQ has high internal reliability (0.91), test-retest reliability (0.82), convergent validity (0.59 to 0.81), discriminant validity (0.63), and criterion validity, 0.68) (Raine, 1991). Higher scores on the SPQ-R indicate higher levels of schizotypal symptoms, with a range of 0 to 100 for the SPQ total score, 0 to 38 for the SPQ positive factor, 0 to 43 for the SPQ negative factor, and 0 to 19 for the SPQ disorganized factor.

Statistical analysis

To control for possible confounding effects, the association of three background variables, i.e., age at T1 age at T2, and time interval between T1 and T2, with SPQ total and factor scores was explored. None of these variables appeared to be significantly associated with SPQ total or factor scores (.130<p<.970). In addition, to analyze possible differences between boys and girls on background and SPQ and IQ variables, a MANOVA was performed with background (age at T1 and T2) and SPQ total, factor scores and IQ full scale and subscale scores as dependent variables. Partial eta squared (η_p^2) was used to estimate effect sizes, with η_p^2~0.03 representing a weak effect, η_p^2~0.06 representing a

moderate effect and $\eta_p^2 \geq 0.14$ representing a large effect (Cohen, 1992). Because the SPQ total and factor scores were all positively skewed, the strength of the relation with IQ full scale, and subscale scores were examined by computing bivariate Spearman's correlation analysis (small effect size: r_s=0.1−0.23; medium: r_s=0.24−0.36; large: $r_s \geq 0.37$) (Cohen, 1992). To explore sex specific characteristics, these analyses were replicated for boys and girls separately. In order to adjust the type 1 error for multiple testing, Sidak adjustment for correlated outcomes was performed and alpha was lowered to .002, two-tailed for all analyses. $p<.01$ was adopted as trend-level significant. Statistical analyses were performed using the Statistical Package for the Social Sciences 20.0 (SPSS Inc, Chicago, Il, USA).

Results

Sample characteristics of the total study sample and sex specific subgroups

Table 2 shows means and *SD*s for the age at T1 and T2 and SPQ and IQ variables for the total study sample as well as sex specific subgroups. The MANOVA of sex with age at T1, age at T2, IQ scores and SPQ scores revealed a significant and large multivariate effect of Sex ($F(19,297)=7.105$, $p<.001$, $\eta_p^2=.312$). The univariate analyses showed that males were younger than females at T1 ($F(1,315)=47.230$, $p<.001$, $\eta_p^2=.130$), and had lower scores in comparison with females on Substitution ($F(1,315)=25.805$, $p<.001$, $\eta_p^2=.076$).

Intelligence in childhood and adolescence and adult schizotypal symptoms of the total group

Performing Spearman's bivariate correlations for juvenile intelligence scores and SPQ Total and Factor scores, revealed significant correlations between lower scores on Arithmetics (r_s=.-148, p=.008), Vocabulary (r_s=-.153, p=.006), and FSIQ (r_s=-.144, p=.010) and higher levels of positive schizotypal symptoms. None of the other juvenile intelligence scores were associated with severity of SPQ total and factor scores ($.017<p<.968$). (See Table 3).

Sex specific associations between juvenile intelligence and adult schizotypal symptoms

The Spearman's bivariate correlations for boys and girls separately revealed the following results. With regard to boys, only Comprehension was trend significantly correlated with positive schizotypal symptoms (r_s=-.214, p=.008). None of the other juvenile intelligence scores were associated with severity of SPQ total and factor scores (.022<p<.931). With regard to girls, none of the juvenile intelligence scores were significantly associated with SPQ total and factor scores (.016<p<.883). (See Table 3). However, none of the aforementioned intelligence scores remained significant after correction for multiple comparisons.

Discussion

The present follow-up study revealed no evidence for general and specific domains of intelligence in juvenile psychopathology being related to the development of general and distinctive schizotypal symptomatology in adulthood. These results also held when boys and girls were studied separately.

The absence of associations between intellectual functioning in children and adolescents with juvenile psychopathology and adult schizotypal symptomatology was surprising, since longitudinal studies have well-established that intellectual functioning in childhood or adolescence is lower in patients that develop disorders within the extreme end of the schizophrenia spectrum in adulthood, such as schizophrenia (Cannon, Bearden, Hollister, Rosso, Sanchez, & Hadley, 2000; Mortensen, Sorensen, Jensen, Reinisch, & Mednick, 2005; Ott et al., 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). Furthermore, studies have reported better premorbid functioning during childhood and adolescence among females (compared to males) who later develop schizophrenia (Goldberg et al, 1995; Walker & Lewine, 1993; Walder et al., 2008). However, several issues are important to consider when interpreting the present results in light of the existing literature.

First, the present outcome is the result of a correlational analysis in individuals who all show juvenile psychopathology. The present absence of associations between intelligence and extent of schizotypal symptoms might be interpreted as that intellectual markers, such as identified in comparison studies using normal controls, do not play a

Table 3. Spearman's rank order correlations between juvenile intelligence and SPQ Total and factor scores for total sample and gender specific subgroups

	Total schizotypal symptoms			Positive schizotypal symptoms		
	Total	**Males**	**Females**	**Total**	**Males**	**Females**
Full scale intelligence	-.096	-.019	-.169	-.144*	-.128	-.170
Verbal intelligence	-.086	-.019	-.147	-.134	-.114	-.166
Information	-.009	.071	-.080	-.034	.052	-.103
Similarities	.012	.078	-.043	-.010	.036	-.056
Arithmetics	-.094	-.090	-.095	-.148*	-.134	-.167
Vocabulary	-.135	-.085	-.185	-.153*	-.114	-.188
Comprehension	-.138	-.185	-.095	-.141	-.214*	-.188
Digit span	-.041	-.024	-.055	-.072	-.063	-.090
Performance intelligence	-.072	-.027	-.122	-.108	-.118	-.110
Picture completion	.021	.166	-.101	-.017	.077	-.084
Picture arrangement	-.050	-.044	-.047	-.055	-.080	-.021
Block design	-.040	-.031	-.050	-.098	-.110	-.081
Object assembly	-.059	-.061	-.051	-.045	-.054	-.035
Digit symbol	-.018	-.055	.008	-.024	-.101	.012

** Trend significant at p≤.01*

	Negative schizotypal symptoms			Disorganized schizotypal symptoms		
	Total	**Males**	**Females**	**Total**	**Males**	**Females**
	-.095	-.010	-.171	-.020	.068	-.106
	-.087	-.007	-.157	-.010	.051	-.063
	-.025	.039	-.087	.034	.077	-.014
	-.010	.052	-.059	.050	.127	-.012
	-.044	-.040	-.041	-.075	-.068	-.069
	-.140	-.100	-.180	-.068	.002	-.143
	-.136	-.162	-.115	-.090	-.115	-.053
	-.014	.010	-.028	-.042	-.039	-.035
	-.065	-.011	-.121	-.021	.041	-.092
	.026	.157	-.085	.053	.170	-.066
	-.055	-.051	-.049	-.022	.012	-.063
	-.014	-.006	-.024	-.004	.016	-.029
	-.062	-.071	-.047	-.046	-.034	-.045
	.002	.006	.009	-.065	-.073	-.051

substantial role in the development of schizotypal symptoms.

Second, with the present study focusing on dimensions of schizotypal symptoms instead of on disorders within the extreme end of the schizophrenia spectrum, the current results might be suggestive for intellectual markers being too subtle to detect vulnerability in milder forms of schizophrenia spectrum pathology, i.e., schizotypal symptomatology, and may only be found relevant for the extremes of the spectrum, i.e., when looking at the development of schizophrenia or psychosis (Park et al., 2012).

Third, while the majority of studies using psychiatric samples are characterized by a relatively low intelligence level, the level of intelligence of the present sample fitted perfectly within national norms, i.e., normal range, with Full scale IQ M=103.1 (*SD*=14.7). As a result, this might have restricted the number and magnitude of the significant correlations and might preclude generalizability of findings to more impaired populations.

Strengths and limitations of the study

The long follow-up period of 13.2 (*SD*=5.2) years of the current cohort was highly suitable to investigate long-term associations between level of intelligence in childhood or adolescent psychopathology and (development of) distinctive adult schizotypal symptoms. Inherent to this long follow-up period, this study suffers from attrition which resulted in follow-up data available for 35% of the subjects. However, analyses of the background variables at T1 revealed that the participants and non-participants were quite similar, with slightly higher Full scale and Verbal IQ of the participants in comparison with the non-participants and a slight overrepresentation of female subjects in the group of participants. It remains, however, unknown how the non-participants developed at T2. Since the mean age of participants at follow up was 25.7 (*SD*=4.8) years, not all subjects may have passed the complete period of risk for schizophrenia spectrum pathology, which may have led to an underestimation of level of schizotypal symptomatology. Because we did not assess schizotypal symptoms at T1, it was not possible to determine that these symptoms have increased in severity at follow-up. In addition, the screening by a self-reported questionnaire might carry some limitations as compared with interviews. For example, self-report questionnaires might not ensure sufficient sensitivity and specificity for specific schizotypal signs such as an odd or guarded appearance, an expression of aloofness, or poor eye contact, and restricted affect (Kendler, 1988) and people may not be accurate in their self-judgments of appearance and speech (Raine, 1991). However, the SPQ has high reliability and validity, which might be due to some of the questions

assessing signs are worded so that the subject reports on external corroboration of these signs rather than relying solely on self-analyses. Schizotypal individuals therefore seem to have no significant loss of insight that would affect their self-perceptions and thus invalidate the results on subscales of schizotypal signs (Raine, 1991).

References

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (3rd ed.).* (1980). Washington, DC: American Psychiatric Association Press.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (3rd revised ed.).* (1987). Washington, DC: American Psychiatric Association Press.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (4th ed.).* (1994). Washington, DC: American Psychiatric Association Press.

Amminger, G., Schlögelhofer, M., Lehner, T., Ott, S., Friedrich, M., & Aschauer, H. (2000). Premorbid performance IQ deficit in schizophrenia. *Acta Psychiatr Scand,* 102(6), 414–422.

Aylward, E., Walker, E., & Bettes, B. (1984). Intelligence in schizophrenia: Meta-analysis of the research. *Schizophr Bull,* 10(3), 430-459.

Barrantes-Vidal, N., Fananas, L., Rosa, A., Caparros, B., Riba, M.D., & Obiols, J.E. (2002). Neurocognitive, behavioural and neurodevelopmental correlates of schizotypy clusters in adolescents from the general population. *Schizophr Res,* 61, 293–302.

Blakesley, R.E., Mazumdar, S., Dew, M.A., Houck, P.R., Tang, G., Reynolds, C.F., & Butters, M.A. (2009). Comparisons of methods for multiple hypothesis testing in neuropsychological research. *Neuropsychology,* 23(2), 255–264.

Cannon, T.D., Bearden, C., Hollister, J.M., Rosso, I.M., Sanchez, L.E., & Hadley, T. (2000). Childhood cognitive functioning in schizophrenia patients and their unaffected siblings. *Schizophr Bull,* 26(2), 379–393.

Chapman, L.J., Chapman, J.P., Kwapil, T.R., Eckblad, M., & Zinser, M.C. (1994). Putatively psychosis-prone subjects 10 years later. *J Abnormal Psycho*l, 103(2), 171-183.

Cohen, J. (1992). A power primer. *Psychol Bull,* 112(1), 155–15.

David, A.S., Malmberg, A., Brandt, L., Allebeck, P., & Lewis, G. (1997). IQ and risk for schizophrenia: a population-based cohort study. *Psychol Med,* 27(6), 1311–1323.

De la Serna, E., Baeza, I., Toro, J., Andrés, S., Puig, O., Sánchez-Guistau, V., Romero, S., Bernardo, M., & Castro-Fornieles, J. (2010). Relationship between clinical and neuropsychological characteristics in child and adolescent first degree relatives of subjects with schizophrenia. *Schizophr Res,* 116(2-3), 159-67.

Goldberg, T., Cold, J., Torrey, F., & Weinherger, D. (1995). Sex differences and neurocognition in schizophrenia (abstract). *Schizophr Res*, 15, 118.

Goldstein, J.M., Tsuang, M.T. & Faraone, S.V. (1989). Gender and schizophrenia: Implications for understanding the heterogeneity of the illness. *Psychiatry Res*, 28, 243-253.

Gottesman, I.I., & Shields, J.A. (1982). *Schizophrenia, the epigenetic puzzle.* Cambridge: Cambridge University Press.

Jones, P., Rodgers, B., Murray, R. & Marmot, M. (1994). Child developmental risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet*, 334(8934), 1393-1402.

Kendell, R.E. (1987). S*chizophrenia: clinical features.* In: Michels, R., & Cavenar, J. (Eds.). Psychiatry, Vol 1. Philadelphia: JB Lippincott.

Kendler, K.S. (1988). Familial aggregation of schizophrenia and schizophrenia spectrum disorders. Evaluation of conflicting results. *Arch Gen Psychiatry*, 45(4), 377-383.

Kendler, K., McGuire, M., Gruenberg, A.M., O'Hare, A., Spellman, M., & Walsh, D. (1993). The Roscommon family study: I. methods, diagnosis of probands, and risk of schizophrenia in relatives. *Arch Gen Psychiatry*, 50(7), 527–540.

Khandaker, G.M., Barnett, J.H., White, I.R., Jones, P.B. (2011). A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. *Schizophr Res*, 132(2-3), 220-7.

Koenen, K.C., Moffitt, T.E., Roberts, A.L., Martin, L.T., Kubzansky, L., Harrington, H., Poulton, R., & Caspi, A. (2009). Childhood IQ and adult mental disorders: a test of the cognitive reserve hypothesis. *Am J Psychiatry*, 166(1), 50–57.

Lewine, R.R.J. (1981). Sex differences in schizophrenia: Timing or subtype? *Psychol Bull*, 90, 432-444.

Lewine, R.R.J. (1985). Schizophrenia: An amotivational syndrome in men. *Can J Psychiatry,* 30, 316-318.

Liddle, P.F. (1987). The symptoms of chronic schizophrenia. A reexamination of the positive and negative dichotomy. *Br J Psychiatry,* 151, 145.

Loranger, A.W. (1984). Sex difference in age at onset of schizophrenia. *Arch Gen Psychiatry*, 41, 157-161.

Matheson, S., & Langdon, R.(2008). Schizotypal traits impact upon executive working memory and aspects of IQ. *Psychiatry Res*, 159(1-2), 207-14.

McGrath, J. (2008). Dissecting the heterogeneity of schizophrenia outcomes. *Schizophr Bull,* 34, 247-8.

Meehl, P.E. (1989). Schizotaxia revisited. *Arch Gen Psychiatry*, 46(10), 935–944.

Meehl, P.E. (1990). Toward an integrated theory of schizotaxia, schizotypy, and schizophrenia. *J Pers Disord,* 4, 1-99.

Menkes, M.M., Rowe, J.S., & Menkes, J.H. (1967). A twenty-five year follow-up study on the hyperkinetic child with minimal brain dysfunction. *Pediatrics*, 39(3), 393-9.

Mortensen, E.L., Sorensen, H.J., Jensen, H.H., Reinisch, J.M., & Mednick, S.A. (2005). IQ and mental disorder in young men. *Br J Psychiatry*, 187, 407–415.

Murray, R.M., & Lewis, S.W. (1987). Is schizophrenia a neurodevelopmental disorder? *Br Med Journal*, 295, 681-82.

Niendam, T.A., Bearden, C.E., Rosso, I.M., Sanchez, L.E., & Hadley, T. (2003). A prospective study of childhood neurocognitive functioning in schizophrenic patients and their siblings. *Am J Psychiatry,* 160 (11), 2060–2062.

Noguchi, H., Hori, H., & Kunugi, H. (2008). Schizotypal traits and cognitive function in healthy adults. *Psychiatry Res*, 161(2), 162–169.

Ott, S.L., Spinelli, S., Rock, D., Roberts, S., Amminger, G.P., & Erlenmeyer-Kimling, L. (1998). The New York High-Risk Project: social and general intelligence in children at risk for schizophrenia. *Schizophr Res*, 31(1), 1–11.

Park, S., Hong, J.P., Lee, H.B., Samuels, J., Bienvenu, O.J., Chung, H.Y., Eaton,W.W., Costa, P.T. Jr., & Nestadt, G. (2012). Relationship between personality disorder dimensions and verbal memory functioning in a community population. *Psychiatry Res,* 196(1), 109-114.

Pfohl, B., & Andreasen, N. (1986). *Schizophrenia: diagnosis and classification*. In: Hales, F.A. (Ed.): Psychiatry update, Vol. 5 (pp. 38–51). Washington DC: American Psychiatric Press.

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.

Raine, A., Reynolds, C., Lencz, T., Scerbo, A., Triphon, N., & Kim, D. (1994). Cognitive- perceptual, interpersonal, and disorganized features of schizotypal personality. *Schizophr Bull*, 20(1), 191-201.

Raine, A. (2006). Schizotypal personality: neurodevelopmental and psychosocial trajectories. *Annu Rev Clin Psychol*, 2, 291–326.

Reynolds, C., Raine, A., Mellingen, K., Venables, P., & Mednick, S. (2000). Three-factor model of schizotypal personality: invariance across culture, gender, religious affiliation, family adversity, and psychopathology. *Schizophr Bull,* 26(3), 603–618.

Sartorius, N., Jablensky, A., Stromgren, E., & Shapiro, R. (1978). Validity of diagnostic concepts across cultures. In: Wynne, L.C., Cromwell, R.L., & Matthysse, S. (Eds). *The Nature of Schizophrenia: New Approaches to Research and Treatment* (pp. 657-669). New York: John Wiley & Sons, Inc.

Schuklenk, U. (2001). Helsinki declaration revisions. *Issues Med Ethics,* 9(1), 29.

Seidman, L.J., Buka, S.L., Goldstein, J.M., & Tsuang, M.T. (2006). Intellectual decline in schizophrenia: Evidence from a prospective birth cohort 28 year follow-up study. *J Clin Exp Neuropsychol,* 28(2), 225–242.

Sidak, Z. (1967). Rectangular confidence regions for the means of multivariate normal distributions. *J Am Stat Assoc*, 62, 626–633.

Sørensen, H.J., Mortensen, E.L., Parnas, J., & Mednick, S.A. (2006). Premorbid neurocognitive functioning in schizophrenia spectrum disorder. *Schizophr Bull*, 32(3), 578–583.

Sørensen, H.J., Mortensen, E.L., Schiffman, J., Ekstrøm, M., Denenney, D., & Mednick, S.A. (2010). Premorbid IQ and adult schizophrenia spectrum disorder: Verbal performance subtests. *Psychiatry Res*, 178(1), 23–26.

Suhr, J.A., & Spitznagel, M.B. (2001). Factor versus cluster models of schizotypal traits. I: a comparison of unselected and highly schizotypal samples. *Schizophr Res*, 52(3), 231–239.

Tsuang, M., Stone, W., Tarbox, S., & Faraone, S. (2002). An integration of schizophrenia with schizotypy: identification of schizotaxia and implications for research on treatment and prevention. *Schizophr Res*, 54(1), 169-175.

Urfer-Parnas, A., Mortensen, E.L., Saebye, D., & Parnas, J. (2010). Premorbid IQ in mental disorders: a Danish draft-board study of 7486 psychiatric patients. *Psychol Med,* 40(4), 547–556.

Vollema, M., & Hoijtink, H. (2000). The multidimensionality of self-report schizotypy in a psychiatric population: an analysis using multidimensional rasch models. S*chizophr Bull*, 26(3), 565-575.

Vollema, M., Sitskoorn, M., Appels, M., & Kahn, R. (2002). Does the schizotypal personality questionnaire reflect the biological-genetic vulnerability to schizophrenia? *Schizophr Res,* 54(1-2), 39-45.

Walder, D.J., Mittal., V., Trotman, H.D., McMillan, A.L., & Walker, E.F. (2008). Neurocognition and conversion to psychosis in adolescents at high-risk. *Schizophr Res*, 101, 161–168.

Walker, E., & Lewine, R. (1993). Sampling biases in studies of gender and schizophrenia. *Schizophr Bull,* 19, 1-7.

Wechsler, D. (1949). *Wechsler Intelligence Scale for Children (WISC).* San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1955). *Manual for the Wechsler Adult Intelligence Scale (WAIS).* New York: Psychological Corporation.

Wechsler, D. (1967). *Wechsler Preschool and Primary Scale of Intelligence (WPPSI).* New York: The Psychological Corporation.

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

Wechsler, D. (1991). *Manual for the Wechsler Intelligence Scale for Children, Third Edition (WISC-III).* San Antonio, TX: Psychological Corporation.

Wechsler, D. (1981). *Manual for the Wechsler Adult Intelligence Scale-Revised (WAIS-R).* New York: The Psychological Corporation.

Weinberger, D.R. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry,* 44(7), 660-669.

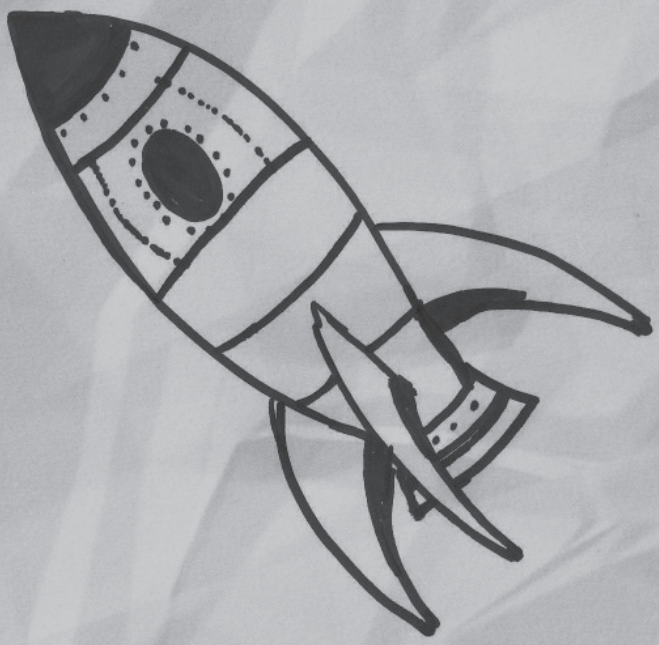
Weiser, M., Reichenberg, A., Rabinowitz, J., Kaplan, Z., Mark, M., Nahon, D., & Davidson, M. (2000). Gender differences in premorbid cognitive performance in a national cohort of schizophrenic patients. *Schizophr Res,* 45(3), 185-90.

Westermeyer, J.F., Harrow, M., & Marengo, J.T. (1989). Gender and outcome in schizophrenia and depression. *Presented at the Annual Meeting of the American Psychiatric Association,* San Francisco, CA.

Woodberry, K.A., Giuliano, A.J., & Seidman, L.J. (2008). Premorbid IQ in schizophrenia: a meta-analytic review. *Am J Psychiatry*, 165(5), 579-87.

Zammit, S., Allebeck, P., David, A.S., Dalman, C., Hemmingsson, T., Lundberg, I., & Lewis, G. (2004). A longitudinal study of premorbid IQ score and risk of developing schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses. *Arch Gen Psychiatry*, 61(4), 354–360.

Chapter 6



General discussion

The majority of children and adolescents at risk for a schizophrenia spectrum disorder does not meet the criteria for a schizophrenia spectrum disorder in adulthood, but tends to manifest subclinical schizophrenia-like abnormalities (Chapman, Chapman, Kwapil, Eckblad, and Zinser, 1994; Raine, 1991; Tsuang, Stone, Tarbox, and Faraone, 2002), i.e., schizotypal symptoms. The investigation of how behavioral and intellectual (dys)functioning develops into adult schizotypal symptoms, and how these schizotypal symptoms affect a person's QoL therefore constitutes a valid and noteworthy, yet relatively understudied, area of exploration with strong implications for clinical practice and research. Moreover, with most studies only including typically developing controls for comparison and 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, and other psychiatric disorders in adulthood, such as ADHD (De la Serna et al., 2010; Keshavan et al., 1967; Rubino et al., 2009), anxiety and depressive disorders (Kim-Cohen et al., 2003; Meyer et al., 2005; Zammit et al., 2004; Koenen et al., 2009) have also been associated with juvenile behavioral and intellectual markers, it is presently unclear whether the identified abnormalities are specifically indicative for the development of symptoms within the schizophrenia spectrum or might be predictive of development of psychopathology in general. We therefore investigated juvenile behavioral and intellectual precurors of schizotypal symptoms and the patient's QoL, selecting a broad sample of patients who all sought psychiatric care during child age. Further, as the clinical presentation of symptoms of future disorders at the extreme of the schizophrenia spectrum are different in boys and girls (Done, Crow, Johnstone, and Sacker, 1994; Salem and Kring, 1998; Welham et al., 2009), the specificity of the reported behavioral and intellectual problems in relation to schizotypal symptoms in adulthood for both boys and girls is further explored.

In sum, the current series of studies aimed to identify to what extent behavioral

and emotional problems and its underlying mechanisms in juvenile psychopathology are associated with the development of adult schizotypal symptoms and what the impact of these symptoms is on a person's Quality of Life. In addition, it is studied whether the outcome is different for boys and girls.

In contrast to earlier studies that have mainly evaluated QoL comparing psychiatric patients with typically developing controls, the study that is reported in chapter two focused on the question whether and how the presence of adult schizotypal symptoms influences the level of objective and subjective QoL using a sample of patients covering a wide spectrum of psychiatric disorders. It was found that each schizotypal dimension, i.e., positive, negative and disorganized schizotypal symptoms, unfavorably affected each domain of objective QoL. However, impoverished subjective QoL, and in particular dissatisfaction with social contacts, was predominantly related to negative schizotypal symptoms. These findings show that the presence of schizotypal symptomatology in subjects alters QoL in an unfavorable way. Negative schizotypal symptoms most strongly affected OQoL and SQoL.

In chapter three we studied how and to what extent children and adolescents with a broad range of psychiatric disorders presented with schizotypal symptoms in adulthood. We therefore used the nosological approach embodied in the Diagnostic and Statistical Manual (DSM) of the American Psychiatric Association (APA, 1980; 1987; 1994) at the time of juvenile assessment. Albeit all children and adolescents with psychiatric diagnoses scored higher on general schizotypal symptoms than typically developing controls when they were adults, the differences were only significant for five psychiatric categories, namely Pervasive Developmental Disorders (PDD), Attention Deficit Hyperactivity Disorders (ADHD), Deferred diagnosis, Sexual and Gender Identity Disorders and Depressive disorders. For three psychiatric disorders, i.e., PDD, ADHD, and Deferred diagnosis, the levels of both disorganized and negative symptoms in adulthood were higher. Four other groups of children with psychiatric disorders showed higher scores on negative schizotypal symptoms in adulthood. These groups were Sexual and Gender Identity disorders, Depressive disorders, Disruptive disorders, and 'Other conditions that may be a focus of clinical attention'. No significantly higher levels were found for positive schizotypal symptoms in adulthood. Therefore we concluded that individuals with juvenile psychiatric problems were more likely to develop negative and disorganized schizotypal symptoms in adulthood when compared to normal controls and that specific patterns of adult schizotypal symptomatology were associated with different types of juvenile psychiatric disorders.

Whereas in chapter three the nosological approach of the DSM was applied,

in chapter four we opted for a dimensional approach. In addition to the vast majority of studies using information from parents about a child's behavior, we studied how behavioral problems in childhood and adolescence as reported by their teachers precede distinctive schizotypal symptoms in adulthood. It was further examined whether the outcome was different for boys and girls. We found that five out of eight behavioral subscales as measured by the Teacher Report Form (TRF; Verhulst, Van der Ende, & Koot, 1997) were associated with disorganized schizotypal symptoms. Thought problems and rule breaking behavior in childhood were associated with positive schizotypal symptoms in adulthood. Remarkably, thought problems and positive and disorganized schizotypal symptoms were only associated in boys, while in girls externalizing problems were associated with disorganized symptoms. We therefore concluded that thought problems (observed by the teacher) were identified as strongest behavioral indicator of future schizotypal symptoms, especially in boys and that subjects burdened by a broad range of behavioral problems in childhood and adolescence are likely to be the ones that will show the most severe adult disorganized symptoms.

In chapter five it was studied whether level of intellectual (dys)functioning in juvenile psychopathology was associated with the development of adult distinctive schizotypal symptomatology, whether this relation was valid for specific intellectual subdomains, and whether this relation held for schizotypal symptoms in general or for specific schizotypal symptom domains. Again, the role of gender was explored. We found no evidence for general and specific domains of intelligence in juvenile psychopathology being related to the development of general or distinctive schizotypal symptomatology in adulthood. This was true for boys as well as for girls. The absence of associations between intellectual functioning in children and adolescents with juvenile psychopathology and adult schizotypal symptomatology was surprising since longitudinal studies have well-established that intellectual functioning in childhood or adolescence is lower in patients that develop disorders at the extreme end of the schizophrenia spectrum in adulthood, such as schizophrenia (Cannon, Bearden, Hollister, Rosso, Sanchez, & Hadley, 2000; Mortensen, Sorensen, Jensen, Reinisch, & Mednick, 2005; Ott et al., 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). Studies have reported better premorbid functioning during childhood and adolescence among females (compared to males) who later develop schizophrenia (Goldberg et al., 1995; Walker, 1993; Walder, Mittal, Trotman, McMillan, & Walker, 2008). Because of the present findings are concerning a sample only consisting of patients who presented with juvenile psychopathology, the absence of associations might be interpreted as follows. First, the

present results are based on the study of individuals who all show juvenile psychopathology. However, juvenile intellectual markers have also been identified in relation to the development of other psychiatric disorders, such as ADHD (De la Serna et al. 2010; Menkes, Rowe, & Menkes, 1967), anxiety and depressive disorders (Zammit et al., 2004; Koenen et al., 2009). In addition, premorbid intelligence and the development of adult schizophrenia spectrum pathology has only been investigated among schizophrenic patients who were compared to typically developing controls. Therefore the present absence of associations might be interpreted as telling us that intellectual markers are related to psychopathology in general rather than being specific for the development of schizotypal symptoms. In addition, with the present study focusing on subclinical schizotypal symptoms instead of disorders at the extreme end of the schizophrenia spectrum, the current results suggest that intellectual markers are too subtle to detect developmental risk in milder forms of schizophrenia spectrum pathology, i.e., schizotypal symptomatology, and may only be found at the extremes of the spectrum, i.e., when looking at the development of schizophrenia or psychosis (Park et al., 2012).

So in conclusion, the results of the present studies show how schizotypal symptoms may develop following all kinds of childhood problems and how these symptoms unfavorably influence a person's quality of life. It is important for clinicians to be aware of the higher risk for schizotypal symptomatology in adulthood following juvenile psychopathology and juvenile behavioral problems and to be aware of the risk that psychopathology may manifests itself in changing symptom patterns over time.

Comparison with other follow-up studies

In this section possible explanations for the present findings, as well as methodological limitations of the study, are discussed.

One of the main factors distinguishing the present study from the majority of other longitudinal studies is that these studies were primarily based on individuals with disorders at the extreme end of the schizophrenia spectrum, such as schizophrenia or psychosis. By applying a nosological approach, these studies start with the assumption that disorders either are present or absent, based on present-versus-absent judgments of each critical feature (Verhulst et al., 1995). However, this approach is often criticized for its inability to classify subthreshold traits and symptoms. Moreover, the majority of individuals at risk does not show a disorder at the extreme end of the schizophrenia spectrum,

but rather tends to manifest a host of subclinical schizophrenia-like abnormalities (Raine, 1991; Chapman et al., 1994; Tsuang et al., 2002), i.e., schizotypal symptoms, that also impair daily functioning. With the present studies investigating behavioral and intellectual (dys)functioning in childhood or adolescence and its association with adult schizotypal symptoms and how these affect QoL therefore constitutes a valid and noteworthy, yet relatively understudied, area of exploration with strong implications for clinical practice and research.

Second, schizophrenia spectrum pathology is a very heterogeneous condition, with a variety of diagnostic criteria and definitions (Kendell, 1987; Pfol & Andreasen, 1986). The variability within schizophrenia spectrum pathology is even more underscored by the fact that patients generally yield a greater score variance compared to normal controls (Shakow, 1963). One approach that might progress insight into the mechanisms that facilitate development of schizophrenia spectrum pathology is therefore the investigation of more homogeneous symptom clusters of schizophrenia spectrum pathology, i.e., positive (hallucinations and delusions), negative (emotional and behavioral disturbances), and disorganized symptoms (difficulty in pursuing a logical train of thought and understanding and utilizing information). Following this approach, the present results revealed more insight in that specific symptoms of schizophrenia spectrum pathology were associated with different types of juvenile psychiatric disorders and behavioral abnormalities, and that negative schizotypal symptomatology most strongly affected OQoL and SQoL. These findings underscore that the investigation of type of schizotypal symptomatology matters.

Another important factor relates to the type of sample of the present study that only consisted of individuals with juvenile psychopathology. This choice contrasts the majority of studies using typical developing controls for comparison and might explain the relatively small effects that we found across the different studies. However, the study of individuals with juvenile psychopathology is of marked importance, since similar juvenile behavioral and intellectual markers have been identified in relation to other psychiatric disorders, such as ADHD (De la Serna et al., 2010; Keshavan, Sujata, Mehra, Montrose, & Sweeney, 2002; Menkes et al., 1967; Rubino et al., 2009), anxiety and depressive disorders (Kim-Cohen et al., 2003; Meyer et al., 2005; Zammit et al., 2004; Koenen et al., 2009), and QoL is also lower in general psychopathology (Lehman, 1983). The present results show that even in a group of patients who all show psychiatric problems, several juvenile behavioral problems and psychiatric disorders in particular are more at risk for development of schizotypal symptomatology in adult life and that level of schizotypal symptoms, in particular negative symptoms most strongly affected OQoL and SQoL. No associations

were found between juvenile intelligence and the development of adult schizotypal symptoms within the present sample of subjects presenting with juvenile psychopathology.

A third issue relates to the decision to explore outcome in relation to gender. The majority of studies focused on general populations of subjects with men being grossly overrepresented, and this may have biased literature from a male perspective. The sample sizes of the present studies enabled to delineate meaningful associations between behavioral and intellectual (dys)functioning and future schizotypal symptomatology in relation to gender. This distinction has led to important insight into gender specific results. For example, with regard to behavioral abnormalities in childhood and adolescence as reported by the child's teachers, thought problems and positive and disorganized schizotypal symptoms were only associated in boys, while in girls externalizing problems were associated with disorganized symptoms. These findings show that it is important to examine gender specific indicators of schizophrenia spectrum pathology.

Limitations

First, inherent to the long follow-up period of no less than eleven to fifteen years, the present study suffered from attrition. Dependent on the criteria that were applied in the study, this has led to different numbers of patients that were included for follow-up in each study. Nevertheless, the numbers of subjects in the samples were considered to be substantial and representative, with the background variables of the participants being quite similar to that of the nonparticipants.

Second, although we were able to control for several important background variables in the present study, we were not able to take aspects into account that are known to delay, if not prevent, the development of disorders at the extreme end of the schizophrenia spectrum (McGlashan et al., 2006; McGorry et al, 2002; Morrison et al., 2004), such as the application of pharmacotherapy, or psychological and psychosocial interventions. This might have influenced the present findings.

A third issue relates to the mean age of the participants in adulthood. Since the participants were in their mid twenties, not all subjects may have passed the (full) period of risk for schizophrenia spectrum psychopathology. Therefore, the level of schizotypal symptomatology might have been underestimated. Future studies using a longer follow-up period might reveal insight into this issue.

A fourth issue concerns the screening by self-report that does carry some limitations, as compared with interviews. For example, self-report questionnaires might not ensure sufficient sensitivity and specificity for specific schizotypal signs such as an odd or guarded appearance, an expression of aloofness, or poor eye contact, and restricted affect (Kendler, 1988) and people may not be accurate in their self-judgments of appearance and speech (Raine, 1991). However, the SPQ has high reliability and validity and schizotypal individuals seem to have no significant loss of insight, in that it would affect their self-perceptions and thus invalidate the results on subscales of schizotypal signs (Raine, 1991).

A fifth issue relates to the level of intelligence in the present sample. While the majority of studies using psychiatric samples are characterized by a relatively low level of intelligence, the level of intelligence of the current sample was relatively high and fits perfectly within the normal range. With regard to the study of how intellectual functio-ning in childhood and adolescence is associated with adult schizotypal symptoms, this might have restricted the number and magnitude of the significant correlations.

Finally, the present study concerns a clinically referred sample. The findings might therefore pertain to those subjects who presented with considerable juvenile behavioral impairments and not to those subjects who were relatively inconspicuous as a child.

Besides these limitations, the present study suited the purpose to illustrate the complex dynamics of psychopathology and intellectual functioning in childhood and adolescence and the development of symptoms within the schizophrenia spectrum and how this affects a subjects' quality of life. In the next section clinical implications of the present study will therefore be addressed.

Clinical and research implications

For intervention and prevention purposes it is of importance to know which and to what extent behavioral abnormalities and intellectual domains are especially important as predictor for later development of schizotypal symptomatology. In addition, it is important to know how these symptoms affect a person's life. Although we have strategically focused on more homogeneous symptoms within the heterogenetic course of schizophrenia spectrum pathology, we should note that although we did find some clues to the development of schizotypal symptomatology, the effects of these findings were relatively small. Clinicians should therefore interpret the reported findings as being a small step

forward in the unraveling of the developmental course of what Bleuler characterized as the ´Group of Schizophrenias` (Bleuler, 1911).

On the other hand, the present findings did show that even across the long follow-up period of eleven to fifteen years, the investigation of more homogeneous symptoms within the spectrum has progressed insight in that some behavioral problems and aspects of intellectual (dys)functioning in juvenile psychopathology were indeed associated with the development of schizotypal symptomatology. This result has progressed insight into the mechanisms that facilitate schizophrenia spectrum pathology and provides several important implications for clinical and research purposes.

First, these results stress the importance to acknowledge the developmental and heterogenetic course of behavioral problems in childhood and adolescence and the importance to follow patients across the lifespan. This is an important message for clinical practice, that from a historical context of clinical specialization has devoted their practice and research to disorders of childhood or adulthood (Frances, First, & Pincus, 1995) which has led to an arbitrary bifurcation in conceptualization and classification of mental disorders across developmental stages (Pine et al., 2002). In addition, our results stress the challenge that has been articulated in the recent article of Van Os (2013). Van Os proposes that the challenge in the years to come is to understand how the earliest expressions of psychopathology form part of a dynamic circuit of symptoms that affect and reinforce each other, gradually differentiating across stages of psychopathology into more specific, but still largely overlapping, clinical syndromes.

Second, the finding that subjects with juvenile psychopathology were more likely to develop severe adult schizotypal symptomatology as compared to typically developing subjects stresses the importance to acknowledge the developmental and heterogenetic course of psychiatric disorders in childhood and adolescence and the importance of intervention strategies for the prevention of continuity of psychopathology into adulthood.

Third, the present findings revealed that it seems important for clinicians to be aware of the higher risk for schizotypal symptomatology in adulthood following some psychiatric disorders of childhood and adolescence in particular. This is especially important to target future intervention strategies.

Fourth, it was demonstrated that teachers can be considered valuable informants on the behavior of children. Although the use of multiple informants (and therefore teacher reports) in assessing psychopathology has already become general practice in child and adolescent psychiatry, this finding stresses the importance of incorporating teacher reports in clinical research on the development of adult psychopathology.

Fifth, the finding that both Subjective as well as Objective QoL within a group of subjects with juvenile psychopathology is diminished in accordance to the level of schizotypal symptomatology stresses the severity of schizotypal symptomatology in relation to psychopathology in general.

Sixth, that especially negative schizotypal symptomatology was found to unfavorably affect a person's Subjective QoL is an important finding, which might bring us closer to an effective intervention for the impairments of schizophrenia spectrum pathology.

Seventh, because the present findings show that gender matters in relation to the development of schizotypal symptomatology, the investigation of the development of psychopathology as well as clinical practice ought to take account of the possible differences that exist in the development of schizotypal symptomatology between boys and girls.

References

American Psychiatric Association. (1980). *Diagnostic and Statistical Manual of Mental Disorders (3rd ed.)*. Washington DC: American Psychiatric Association Press.

American Psychiatric Association. (1987). *Diagnostic and Statistical Manual of Mental Disorders (3rd revised ed.).* Washington DC: American Psychiatric Association Press.

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders (4th ed.)*. Washington DC: American Psychiatric Association Press.

Bleuler, E. (1911). *Dementia Praecox or the Group of Schizophrenias.* New York: International Universities Press.

Chapman, L.J., Chapman, J.P., Kwapil, T.R., Eckblad, M., & Zinser, M.C. (1994). Putatively psychosis-prone subjects 10 years later. *J Abnormal Psychol*, 103(2), 171-183.

De la Serna, E., Baeza, I., Toro, J., Andrés, S., Puig, O., Sánchez-Guistau, V., Romero, S., Bernardo, M., & Castro-Fornieles, J. (2010). Relationship between clinical and neuropsychological characteristics in child and adolescent first degree relatives of subjects with schizophrenia. *Schizophr Res,* 116(2-3), 159-167.

Done, D.J., Crow, T.J., Johnstone, E.C., & Sacker, A. (1994). Childhood antecedents of schizophrenia and affective illness: social adjustment at ages 7 and 11. *Br Med Journal,* 309, 699-703.

Frances, A.J., First, M.B., & Pincus, H.A. (1995). *DSM-IV guidebook.* Washington DC: American Psychiatric Press.

Kendell, R.E. (1987). Schizophrenia: clinical features. In: Michels, R. & Cavenar, J. (Eds.). *Psychiatry, Vol 1.* Philadelphia: JB Lippincott.

Kendler, K. (1983). Overview: a current perspective on twin studies of schizophrenia. *Am J Psychiatry,* 140, 1413-1425.

Keshavan, M.S., Sujata, M., Mehra, A., Montrose, D.M., & Sweeney, J.A. (2002). Psychosis proneness and ADHD in young relatives of schizophrenia patients. *Schizophr Res*, 59(1), 85-92.

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-back of a prospective-longitudinal cohort. *Arch Gen Psychiatry,* 60(7), 709-717.

Koenen, K.C., Moffitt, T.E., Roberts, A.L., Martin, L.T., Kubzansky, L., Harrington, H., Poulton, R., & Caspi, A. (2009). Childhood IQ and adult mental disorders: a test of the cognitive reserve hypothesis. *Am J Psychiatry*, 166, 50–57.

Lehman, A.F. (1983). The well-being of chronic mental patients: assessing their quality of life. *Arch Gen Psychiatry,* 40(4), 369-373.

McGlashan, T.H., Zipursky, R.B., Perkins, D., Addington, J., Miller, T., Woods, S.W., Hawkins, K.A., Hoffman, R.E., Preda, A., Epstein, I., Addington, D., Lindborg, S., Trzakkoma, Q., Tohen, M., & Breier, A. (2006). Randomized, double-blind trial of Olanzapine versus placebo in patients prodromally symptomatic for psychosis. *Am J Psychiatry,* 163, 790-799.

McGorry, P.D., Yung, A.R., Phillips, L.J., Yuen, H.P., Francey, S., Cosgrave, E.M., Germano, D., Bravin, J., McDonald, T., Blair, A., Adlard, S., & Jackson, H. (2002). Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. *Arch Gen Psychiatry*, 591, 921-928.

Menkes, M., Rowe, J., & Menkes, J. (1967). A 25 year follow-up study on the hyperkinetic child with minimal brain dysfunction. *Pediatrics*, 39(3), 393-399.

Meyer, S.E., Bearden, C.E, Lux, S.R., Gordon, J.L., Johnson, J.K., O'Brien, M.P., Niendam, T.A., Loewy, R.L., Ventura, J., & Cannon, T.D. (2005). The psychosis prodrome in adolescent patients viewed through the lens of DSM-IV. *J Child Adolesc Psychopharmacol*, 15(3), 434-451.

Morrison, A.P., French, P., Walford, L., Lewis, S.W., Kilcommons, A., Green, J., Parker. S., & Bentall, R.P. (2004). Cognitive therapy for the prevention of psychosis in people at ultra-high risk: randomized controlled trial. *Br J Psychiatry*, 185, 291-297.

Pfohl, B., & Andreasen, N. (1986). Schizophrenia: diagnosis and classification. In: Hales, F.A. (Ed.): *Psychiatry update*, vol. 5, pp. 38–51. Washington DC, American Psychiatric Press.

Pine, D.S., Alegria, M., Cook, E.H., Costello, E.J., Dahl, R.E., Koretz, D., Merikangas, K.R., Reiss, A.L., & Vitiello, B. (2002). Advances in developmental science and DSM-V. In: Kupfer, D.J., First, M.B., & Regier, D.E. (Eds.). *A research agenda for DSM-V* (pp. 85–122). Washington, DC: American Psychiatric Association.

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.

Rubino, I.A., Frank, E., Croce Nanni, R., Pozzi, D., Lanze di Scalea, T., & Siracusano, A. (2009). A comparative study of Axis I antecedents before age 18 of unipolar depression, bipolar disorder and schizophrenia. *Psychopathology*, 42, 325-332.

Salem, J.E., & Kring, A.M. (1998). The role of gender differences in the reduction of etiologic heterogeneity in schizophrenia. *Clin Psychol Rev*, 18(7), 795–819.

Shakow, D. (1963). Psychological Deficit in Schizophrenia. *Behavioral Science*, 8(4), 275.

Tsuang, M., Stone, W., Tarbox, S., & Faraone, S. (2002). An integration of schizophrenia with schizotypy: identification of schizotaxia and implications for research on treatment and prevention. *Schizophr Res,* 54, 169-175.

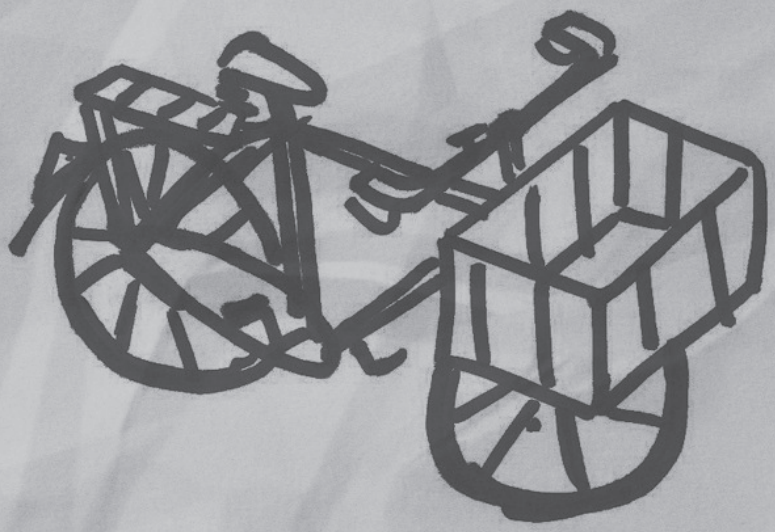
Trevisi, M., Talamo, A., Bandinelli, P.L., Ducci, G., Kotzalidis, G.D., Santucci, C., Manfredi, G., Girardi, N., & Tatarelli, R. (2012). Insight and awareness as related to psychopathology and cognition. *Psychopathology*, 45(4), 235-43.

Verhulst, F.C., Van der Ende, J., & Koot, H.M. (1997). *Manual for the Teacher's Report Form* (Dutch translation). Department of Child and Adolescent Psychiatry, Rotterdam, the Netherlands.

Verhulst, F.C., & Achenbach, T.M. (1995). Empirically based assessment and taxonomy of psychopathology: cross-cultural applications. A review. *Eur Child Adolesc Psychiatry,* 4, 61-76.

Welham, J., Scott, J., Williams, G., Najman, J., Bor, W., O'Callaghan, M., & McGrath, J. (2009). Emotional and behavioural antecedents of young adults who screen positive for non-affective psychosis: a 21- year birth cohort study. *Psychol Med*, 39, 625-634.

Zammit, S., Allebeck, P., David, A.S., Dalman, C., Hemmingsson, T., Lundberg, I., Lewis, G. (2004). A longitudinal study of premorbid IQ score and risk of developing schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses. *Arch Gen Psychiatry*, 61, 354–360.



Summary

Schizophrenia spectrum pathology is composed of multiple conditions that are characterized by distortions of cognitive and perceptual reality, collectively known as positive symptoms (delusions and hallucinations), negative symptoms (emotional and behavioral disturbances), and disorganized symptoms (difficulty in pursuing a logical train of thought and understanding and utilizing infomration; Kaplan, Sadock, & Grebb, 1994). These conditions have different 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 (Meehl, 1989). They are considered to be persistent and lifelong and are supposed to present themselves differently at different ages. Consequently, developmental origins of schizophrenia spectrum pathology have been intensively studied throughout the years. This has led to the identification of many different behavioral and intellectual factors that can be associated with the development of disorders within the schizophrenia spectrum, such as schizophrenia and psychosis. However, the etiology of these disorders remains unclear. Presently, there are still no effective treatments for most aspects of schizophrenia spectrum pathology and its functional impairments. A possible 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 treatment, and sometimes even have full remission of alle symptoms and full recovery even to the premorbid level of functioning (McGrath, 2008). Moreover, the majority of at-risk individuals based on childhood behaviors does not meet the criteria for a schizophrenia spectrum disorder in adulthood, but tends to manifest subclinical schizophrenia-like abnormalities (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Raine, 1991; Tsuang, Stone, Tarbox, & Faraone, 2002), i.e., schizotypal symptoms. The investigation of childhood behavior and its association with adult schizotypal symptoms therefore constitutes a valid and noteworthy, yet relatively understudied, area

of exploration with strong implications for clinical practice and research. Finally, since psychiatric problems are known to unfavorably affect a person's quality of life and many juvenile behavioral and intellectual markers are also associated with the development of other psychiatric problems than schizophrenia spectrum pathology, the question remains unanswered in what way these aforementioned behavioral and intellectual markers may be associated with the development of distinctive adult schizotypal symptoms in a cohort of subjects presenting with juvenile psychopathology.

The present serie of studies therefore investigated how quality of life was related to distinctive adult schizotypal symptoms (chapter two) and how juvenile behavioral and intellectual (dys) functioning was associated with distinctive adult schizotypal symptoms (chapter three to five) in a sample of patients who all sought psychiatric help at child age.

The subjects of the study were children who came for psychiatric assessment to the department of Child and Adolescent Psychiatry at the University Medical Centre Utrecht, the Netherlands, during 1984 to 2004. Subjects who were aged 18 years or older at follow-up (2006 to 2010) were, when possible, traced and encouraged to participate in the study. The participants were assessed for adult schizotypal symptoms using the Schizotypal Personality Questionnaire-Revised (Raine, 1991; Vollema, & Hoijtink, 2000). Quality of life was evaluated using a questionnaire concerning global and clinical outcome in adult life which was developed at the Department of Child and Adolescent Studies of Leiden University. Based on the publication of Corrigan and Buican (1995) Quality of life was discriminated between Objective quality of life (OQoL), i.e., evaluating the patients' living conditions, and Subjective quality of life (SQoL), i.e., evaluating the patients' appraisal of these conditions.

In chapter two it was found that level of schizotypal symtomatology unfavorably affected each domain of OQoL. Impoverished SQoL, and in particular dissatisfaction with social contacts, was predominantly related to negative schizotypal symptoms. This finding is of importance for clinical practice, since it shows that level of schizotypal symptoms, and in particular negative symptoms most strongly affected OQoL and SQoL.

In chapter three and chapter four it was studied how and to what extent behavioral abnormalities in childhood and adolescence were associated with the development of schizotypal symtpomatology in adulthood. In chapter three the nosological approach of the Diagnostic and Statistical Manual (DSM; American Psychiatric Association, 1980; 1987; 1994) was applied. Albeit all children and adolescents with psychiatric diagnosies scored higher on general schizotypal symptoms than typically developing controls in adulthood, the differences were only significant for persons presenting with the follo-

wing psychiatric problems, namely Pervasive Developmental Disorders (PDD), Attention Deficit Hyperactivity Disorders (ADHD), Deferred diagnosis, Sexual and Gender Identity Disorders, and Depressive Disorders. In addition, children presenting with problems such as PDD, ADHD, and Deferred diagnosis, were more likely to develop both disorganized and negative schizotypal symptoms in adulthood. Four other groups of children showed higher scores on negative schizotypal symptoms in adulthood, i.e., children diagnosed with Sexual and Gender Identity Disorders, Depressive disorders, Disruptive disorders, and 'Other condition that may be a focus of clinical attention'. None of children with psychiatric disorders showed higher levels of positive schizotypal symptoms in comparison with typically developing controls. These results clearly show that individuals with juvenile psychiatric problems are more likely to develop negative and disorganized schizotypal symptoms in adulthood when compared to typically developing controls and that how symptoms can change across the lifespan, i.e., that specific patterns of adult schizotypal symptomatology can be associatied with different types of juvenile psychiatric disorders.

In chapter four a dimensional approach was applied to study how and to what extent behavioral problems within a school's context are associated with the development of adult schizotypal symptoms. It was further examined whether this was specific for boys and girls. To assess behavioral problems within a schools' context, we used the Teacher Report Form (TRF; Verhulst, Van der Ende, & Koot, 1997), a measurement instrument in which the teacher reports about eight different behaviors of the child. It was found that five of eight behavioral subscales were associated with disorganized schizotypal symptoms in adulthood. Problems in the area of thinking as well as rule breaking behavior were further associated with the development of positive symptoms in adulthood. When boys and girls were studied separately, the problems in the area of thinking and positive and disorganized symptoms were only associated in boys, while externalizing problems, i.e., disruptive, hyperactive, and aggressive behaviors, were associated with the development of disorganized schizotypal symptoms in girls. Based on these results, we can conclude that school-associated thought problems were identified as strongest behavioral indicator of future schizotypal symptoms, especially in boys, and that subjects burdened by a broad range of behavioral problems in childhood and adolescence are the ones to show most severe adult disorganized symptoms.

In chapter five it was studied wheter level of intellectual (dys) functioning in juvenile psychopathology was associated with the development of adult distinctive schizotypal symtpomatomaology. Further, the role of gender was explored. We found no evidence for general and specific domains of intelligence in juvenile psychopathology

being related to the development of general and distinctive adult schizotypal symptoms. This was true for boys as well as for girls. The absence of associations was surprising since studies so far have well-established that intellectual functioning in childhood and adolescence is lower in patients who develop disorders such as schizophrenia and psychosis. What might explain present absence of associations is that the current study only investigated subjects who all showed juvenile psychopathology instead of using typically developing controls for comparison. In addition, the development of schizophrenia-like symptoms was studied instead of development of disorders at the extreme end of the schizophrenia spectrum. The present results might therefore be interpreted as intellectual markers being non-specific and to subtle to detect in milder forms of schizophrenia spectrum pathology, i.e., schizotypal symptoms.

In conclusion, the results of the present studies show how schizotypal symptoms may develop following child psychiatric psychopathology and how these symptoms unfavorably influence a persons' quality of life. It is important for clinicians to be aware of the complex dynamics of psychopathology and the higher risk for adult schizotypal symptomatology following behavioral problems and psychiatric disorders at child and adolescent age.

References

American Psychiatric Association. (1980). *Diagnostic and Statistical Manual of Mental Disorders (3th ed.)*. Washington, DC: American Psychiatric Association Press.

American Psychiatric Association. (1987). *Diagnostic and Statistical Manual of Mental Disorders (3th revised ed.).* Washington, DC: American Psychiatric Association Press.

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders (4th ed.).* Washington, DC: American Psychiatric Association Press.

Chapman, L.J., Chapman, J.P., Kwapil, T.R., Eckblad, M., & Zinser, M.C. (1994). Putatively psychosis-prone subjects 10 years later. *J Abnormal Psychol*, 103, 171-183.

Corrigan, P.W., & Buican, B. (1995). The construct validity of subjective quality of life for the severely mentally ill. *J Nerv Ment Dis,* 183(5), 281-285.

Kaplan, H.I., Sadock, B.J., & Grebb, J.A. (1994). *Kaplan and Sadock's synopsis of psychiatry, 7th ed.* In: Kaplan, H.I., & Sadock, B.J. (Eds.). Baltimore, MD: Williams & Wilkins.

McGrath, J. (2008). Dissecting the heterogeneity of schizophrenia outcomes. *Schizophr Bull*, 34, 247-8.

Meehl, P.E. (1989). Schizotaxia revisited. *Arch Gen Psychiatry*, 46(10), 935–944.

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

Tsuang, M., Stone, W., Tarbox, S., & Faraone, S. (2002). An integration of schizophrenia with schizotypy: identification of schizotaxia and implications for research on treatment and prevention. *Schizophr Res,* 54, 169-175.

Verhulst, F.C., Van der Ende, J., & Koot, H.M. (1997). *Manual for the Teacher's Report Form (Dutch translation)*. Department of Child and Adolescent Psychiatry, Rotterdam, the Netherlands.

Vollema, M., & Hoijtink, H. (2000). The multidimensionality of self-report schizotypy in a psychiatric population: an analysis using multidimensional rasch models. *Schizophr Bull*, 26, 565-575.

Samenvatting (Summary in Dutch)

schizofrene spectrum pathologie manifeert zich meestal in de volwassen leeftijd, maar kan zich gedurende de levensloop met verschillende symptomen manifesteren. Inmiddels zijn er door de jaren heen vele gedragsmatige en intellectuele factoren in verband gebracht met het ontwikkelen van de meest extreme stoornissen (bv. schizofrenie en psychose) binnen dit schizofrene spectrum. Echter blijft de oorzaak van deze stoornissen nog steeds onduidelijk, waardoor er tot op heden geen effectieve behandelingen voor de meeste symptomen (en gevolgen) van schizofrenie en psychose zijn. Mogelijkerwijs is de variëteit aan symptomen die personen met schizofrene spectrum pathologie kenmerken hiervan de oorzaak. Zo kan het zijn dat de ene patiënt met schizofrenie slecht te behandelen is, terwijl de andere patiënt met schizofrenie gebaat blijkt te zijn met bepaalde behandelingen en zelfs kan herstellen tot het premorbide niveau van functioneren (het niveau van functioneren voorafgaand aan de manifestatie van de symptomen; McGrath, 2008). Een manier om inzicht te verwerven in de oorsprong van deze psychopathologie is om meer homogene symptomen binnen het schizofrene spectrum, zoals positieve symptomen (wanen en hallucinaties), negatieve symptomen (afgevlakt affect en het tonen van affect dat niet toepasselijk is bij de omstandigheden) en gedesorganiseerde symptomen (moeite hebben met het aanhouden van een logische gedachtegang en het begrijpen en gebruiken van informatie; Kaplan, 1994) te onderzoeken. Verder ontwikkeld de meerderheid van de mensen met symptomen in het schizofrene spectrum geen stoornis zoals schizofrenie of psychose, maar subklinische schizofrenie-achtige kenmerken hiervan (Chapman, Chapman, Kwapik, Eckblad, & Zinser, 1994; Raine, 1991; Tsuang, Stone, Tarbox, & Faraone, 2002), zoals schizotypische klachten. Hierdoor is het zeer informatief om te onderzoeken welke jeugdige indicatoren geassocieerd kunnen worden met het ontwikkelen van specifieke subklinische klachten binnen het schizofrene spectrum (schizotypische symptomen) op volwassen leeftijd. Tenslotte is het bekend dat het hebben van psychiatrische problematiek an sich een negatief effect heeft op de kwaliteit van leven van personen, dus de vraag hoe specifiek

uitkomsten voor schizotypische symptomen zijn is nog niet beantwoord. Het huidige onderzoek heeft zich daarom op de volgende vragen gericht. In hoeverre hebben verschillende schizotypische symptomen op de volwassen leeftijd een effect op de kwaliteit van leven van mensen (hoofdstuk twee)? In welke mate kunnen jeugdige gedragsmatige en intellectuele factoren geassocieerd worden met het ontwikkelen van schizotypische symptomen op volwassen leeftijd (hoofdstuk drie t/m vijf)? Dit is onderzocht in een groep volwassenen die allen psychiatrische hulp op kinderleeftijd zochten.

De onderzoeksgroep bestaat uit kinderen die allen in de periode 1984 tot en met 2005 voor uiteenlopende gedrags- en emotionele problemen voor een psychiatrisch consult bij de afdeling Kinder-en Jeugd Psychiatrie van het Universitair Medisch Centrum Utrecht zijn geweest. In de periode 2006 tot en met 2010 zijn de kinderen die inmiddels de volwassen leeftijd bereikt hadden (de leeftijd waarop schizotypische symptomen kunnen ontwikkelen) opgespoord en benaderd om middels vragenlijsten inzicht te krijgen in hun kwaliteit van leven en om de aanwezigheid en ernst van schizotypische symptomen te onderzoeken.

In hoofdstuk twee werd gevonden dat de ernst van de schizotypische symptomen een ongunstig effect had op de kwaliteit van leven van mensen die in de kindertijd psychische problemen hadden. Daarbij kwam naar voren dat zowel de leefsituatie van patiënten (Objectieve kwaliteit van leven), als ook het oordeel van personen hierover (Subjectieve kwaliteit van leven) negatief beïnvloed werd. De ernst van de negatieve schizotypische symptomen en dan met name de waardering van de sociale contacten hing samen met een ongunstig effect op de beleving van de kwaliteit van leven. Dit is een relevante bevinding voor de klinische praktijk, omdat het aantoont dat de ernst van de schizotypische symptomen en met name negatieve schizotypische symptomen, in direct verband staat met een slechtere leefsituatie en de waardering hiervan.

In hoofdstuk drie en hoofdstuk vier is onderzocht welke gedragsproblemen op de kinderleeftijd geassocieerd kunnen worden met het ontwikkelen van schizotypische symptomen op volwassen leeftijd. In hoofdstuk drie gebruikten we hiervoor de nosologische benadering zoals deze wordt toegepast middels de Diagnostic and Statsical Manual (DSM; American Psychiatric Association, 1980; 1987; 1994). Hierbij vergeleken we in eerste instantie de groep waarbij een psychiatrische diagnose op de kinderleeftijd was gesteld met een controlegroep zonder psychiatrische problematiek op volwassen leeftijd. De onderzoeksgroep bleek in zijn geheel meer schizotypische symptomen op volwassen leeftijd te vertonen dan de controlegroep. Daarnaast bleken vijf groepen significant meer schizotypische symptomen te vertonen in vergelijking met zich normaal ontwikkelende personen. Deze groepen waren de de volwassenen met op kinderleeftijd gediagnosticeerde

problemen binnen het autisme spectrum, een aandachtstekortstoornis, een uitgestelde diagnose, een sexuele of genderidentiteitsstoornis of een depressieve stoornis. Daarnaast vertoonden kinderen met een autisme spectrum stoornis, aandachtstekortstoornis en uitgestelde diagnose meer negatieve en gedesorganiseerde schizotypische symptomen op volwassen leeftijd dan zich normaal ontwikkelende kinderen. Verder vertoonden kinderen met een sexuele of genderidentiteitsstoornis, depressieve stoornis, disruptieve stoornis of 'andere stoornissen die een focus van klinische zorg kunnen zijn' meer negatieve schizotypische symptomen in vergelijking met zich normaal ontwikkelende personen. Geen van de kinderpsychiatrische groepen vertoonde meer positieve schizotypische symptomen op volwassen leeftijd dan de controle groep. De resultaten geven goed inzicht in welke psychiatrische klachten in de kindertijd samenhangen met schizotypsiche symptomen in de volwassenheid. Het blijkt dat de groep individuen met kinderpsychiatrische problematiek als geheel meer negatieve en gedesorganiseerde schizotypische symptomen ontwikkelen op volwassen leeftijd dan zich normaal ontwikkelende personen en dat specifieke kinderpsychiatrische problematiek geassocieerd kan worden met specifieke patronen van schizotypische symptomen op volwassen leeftijd.

Naast de nosologische benadering die de DSM hanteert, pasten wij in hoofdstuk vier een dimensionele benadering toe. Zodoende konden wij onderzoeken welke gedragsmatige problematiek in de kinder- en jeugdleeftijd samenhangt met het ontwikkelen van schizotypische symptomen op volwassen leeftijd. Daarbij werd onderzocht in welke mate dit voor jongens en meisjes specifiek was. Binnen deze studie werd gebruik gemaakt van de Teacher Report Form (TRF; Verhulst, Van der Ende, & Koot, 1997), een meetinstrument waarbij de leerkracht rapporteert over acht uiteenlopende gedragingen van een kind. Het bleek dat een hogere score op vijf van de acht gedragsschalen geassocieerd waren met het ontwikkelen van meer gedesorganiseerde schizotypische symptomen op volwassen leeftijd. Als we jongens en meisjes apart onderzochten, bleek dat bij jongens denkproblemen en grensoverschrijdend gedrag zoals gerapporteerd door de leerkrachten verband hield met het ontwikkelen van meer positieve en gedesorganiseerde schizotypische symptomen op volwassen leeftijd. Bij meisjes bleken externaliserende problemen geassocieerd te zijn met het ontwikkelen van gedesorganiseerde symptomen, zoals onsamenhangende, verwarde spraak of chaotisch gedrag. Op basis van deze resultaten kunnen we concluderen dat denkproblemen de sterkste indicator zijn voor toekomstige schizotypische symptomen en dat individuen met een brede range aan gedragsproblematiek in de kindertijd degenen zijn die het meeste risico hebben op het ontwikkelen van gedesorganiseerde symptomen op volwassen leeftijd.

In hoofdstuk vijf werd binnen de groep met kinderpsychiatrische problematiek

onderzocht in welke mate intellectueel (dis)functioneren in de kindertijd geassocieerd kon worden met de ontwikkeling van schizotypische symptomen op volwassen leeftijd. Daarnaast werd de rol van geslacht onderzocht. Er werd geen bewijs gevonden dat algemene of specifieke domeinen van intelligentie binnen deze kinderpsychiatrische groep geassocieerd konden worden met het risico op de ontwikkeling van (specifieke) schizotypische symptomen op volwassen leeftijd. Dit was zowel bij jongens als bij meisjes het geval. Deze uitkomst was verrassend omdat eerdere studies aantoonden dat een lagere intelligentie en specifieke subdomeinen van intelligentie samenhangen met een risico op het ontwikkelen van stoornissen zoals schizofrenie en psychose. Omdat het huidige onderzoek zich heeft gericht op personen die allen psychiatrische problematiek vertoonden op kinderleeftijd en op schizotypische symptomen in tegenstelling tot eerdere onderzoeken die zich op stoornissen binnen het schizofrene spectrum richten, kan het ontbreken van een verband er op duiden dat intellectuele markers mogelijker wijs niet specifiek zijn voor het ontwikkelen van mildere symptomen binnen het schizofrene spectrum.

Eindconclusie

De resultaten van dit proefschrift geven inzicht in de ontwikkeling van schizotypische symptomen vanuit kinderpsychiatrische problematiek en hoe deze symptomen de kwaliteit van leven op volwassen leeftijd ongunstig beinvloeden. Deze bevindingen geven aanleiding om in de klinische praktijk extra bewust te zijn van de verschillende manieren waarop psychopathologie zich in de verschillende fasen van de ontwikkeling kan manifesteren.

References

American Psychiatric Association. (1980). *Diagnostic and Statistical Manual of Mental Disorders (3th ed.)*. Washington, DC: American Psychiatric Association Press.

American Psychiatric Association. (1987). *Diagnostic and Statistical Manual of Mental Disorders (3th revised ed.).* Washington, DC: American Psychiatric Association Press.

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders (4th ed.).* Washington, DC: American Psychiatric Association Press.

Chapman, L.J., Chapman, J.P., Kwapil, T.R., Eckblad, M., & Zinser, M.C. (1994). Putatively psychosis-prone subjects 10 years later. *J Abnormal Psychol,* 103, 171-183.

Corrigan, P.W., & Buican, B. (1995). The construct validity of subjective quality of life for the severely mentally ill. *J Nerv Ment Dis*, 183(5), 281-285.

Kaplan, H.I., Sadock, B.J., & Grebb, J.A. (1994). Kaplan and Sadock's synopsis of psychiatry, 7th ed. In: Kaplan, H.I., & Sadock, B.J. (Eds). Baltimore, MD: Williams & Wilkins.

McGrath, J. (2008). Dissecting the heterogeneity of schizophrenia outcomes. *Schizophr Bull*, 34, 247-8.

Meehl, P.E. (1989). Schizotaxia revisited. *Arch Gen Psychiatry,* 46(10), 935–944.

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

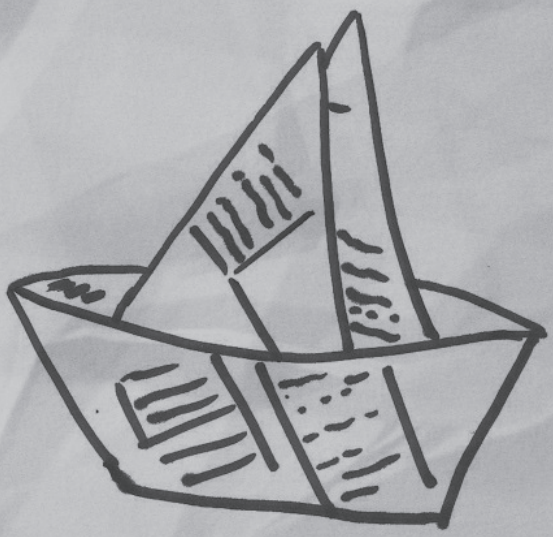
Tsuang, M., Stone, W., Tarbox, S., & Faraone, S. (2002). An integration of schizophrenia with schizotypy: identification of schizotaxia and implications for research on treatment and prevention. *Schizophr Res*, 54, 169-175.

Verhulst, F.C., Van der Ende, J., & Koot, H.M. (1997). *Manual for the Teacher's Report Form (Dutch translation)*. Department of Child and Adolescent Psychiatry, Rotterdam, the Netherlands.

Vollema, M., & Hoijtink, H. (2000). The multidimensionality of self-report schizotypy in a psychiatric population: an analysis using multidimensional rasch models. *Schizophr Bull*, 26, 565-575.

Curriculum Vitae

Selene Fagel was born on July 10th of 1981 in Hoofddorp, the Netherlands. After completing her secondary education in 1999 at the 'Norbertuscollege' in Roosendaal, she studied Psychology at the University Utrecht with a major in Clinical Neuropsychology. She obtained her degree in Psychology in 2005 after a research internship at the Free University under supervision of Dr. Martin Klein. In 2005 she started her PhD project at the department of Clinical Child and Adolescent Studies of Leiden University and the department of Child and Adolescent Psychiatry of the University Medical Centre Utrecht. This project, supervised by Prof. Herman van Engeland, Dr. Ir. Leo de Sonneville, and Prof. Hanna Swaab, resulted in the present thesis. During her work as a PhD student, she worked as a lecturer at the department of Clinical Child and Adolescent Studies from 2005 until 2011. From November 2011 until April 2013 she worked as a researcher at the department of Biological Psychology at the Free University under supervision of Dr. Christel Middeldorp. From April 2013 until November 2013 she worked as an assistant professor at the department of Clinical Child and Adolescent Studies of Leiden University. Currently, she holds a research position at The Dutch Inspectorate of Education. From 2008 until recent, she has combined her academic career as a trainer and education development manager at Tridata, Institute of Applied Statistics and Data-analysis. She is one of the main authors of a soon to be published book on Applied Statistics and lecturer of the training for Statistical Analist-A.



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List of publications

Fagel, S.S.A.A., De Sonneville, L.M.J., Van Engeland, H., & Swaab, H. (2013). School-associated problem behavior in childhood and adolescence and development of adult schizotypal symptoms: a follow-up of a clinical cohort. *J Abnorm Child Psychol.* Accepted for publication.

Barneveld, P.S., Swaab, H., Fagel, S.S.A.A., Van Engeland, H., & De Sonneville, L.M.J. (2013). 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. *Compr Psychiatry.* Epub ahead of print.

Fagel, S.S.A.A., Swaab, H., De Sonneville, L.M.J., Van Rijn, S., Pieterse, J.K., Scheepers, F., & Van Engeland, H. (2013). Development of schizotypal symptoms following psychiatric disorders in childhood or adolescence. *Eur Child Adolesc Psychiatry.* Epub ahead of print. DOI 10.1007/s00787-013-0409-7.

Fagel, S.S.A.A., Swaab, H., Van Engeland, H., & De Sonneville, L.M.J. How the presence of schizotypal symptoms affects objective and subjective quality of life: A follow-up of child and adolescent psychiatric patients into adulthood. *Under review.*

Fagel, S.S.A.A., De Sonneville, L.M.J., Van Engeland, H., & Swaab, H. Adult schizotypal symptoms following juvenile psychopathology: no relation with juvenile intellectual functioning. *Under review.*

Robben, R., Uitdehaag, B.M.J., Fagel, S.S.A.A., Taphoorn, M.J.B., Postma, T.J., Heimans, J.J.,& Klein M. (2011). Longitudinal proxy measurements in low-grade glioma: impact of cognitive deficits on patient-proxy agreement concerning patient's health-related quality of life. *Neuro Oncol*, 13;75.

Fagel, S.S.A.A., Van Engeland, H., De Sonneville, L.M.J., Pieterse, J., & Swaab. H. (2010). Specificity and severity of pre-psychotic juvenile behavior: a 20 year follow-up study. *Schizophr Res*, 117(2-3); 202.

Douw, L., Klein, M., Fagel, S.S.A.A., Van den Heuvel, J., Taphoorn, M.J.B., Aaronson, N.K., Postma, T., Vandertop, W.P., Mooij, J.J., Boerman, R.H., Beute, G.N., Sluimer, J.D., Slotman, B.J., Reijneveld, J.C., & Heimans, J.J. (2009). Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. *Lancet Neurol,* 8(9);810–818.

Van den Heuvel, J., Reijneveld, J.C., Fagel, S.S.A.A., et al. (2007). Late-delayed radiation injury and neurocognitive functioning in very long-term low-grade glioma survivors. *Neuro Oncol,* 9(4); 564.

Klein, M., Fagel, S.S.A.A., Taphoorn, M.J.B., Postma, T.J., & Heimans, J.J. (2006) Neurocognitive functioning in long-term low-grade glioma survivors: a six-year follow-up study. *Neuro Oncol,* 8(4); 302.