Associations between cognition and internalizing problems in young adults with early-onset schizophrenia: A 13-year follow-up study

Benedicte Strugstad

Master Thesis
Department of Psychology

THE UNIVERSITY OF OSLO

Spring 2017

Associations between cognition and internalizing problems in young adults with early-onset schizophrenia: A 13-year follow-up study

© Benedicte Strugstad

2017

Associations between cognition and internalizing problems in young adults with early-onset schizophrenia: A 13-year follow-up study

Benedicte Strugstad

http://www.duo.uio.no/

Abstract

Author: Benedicte Strugstad

Title: Associations between cognition and internalizing problems in young adults with early-onset schizophrenia: A 13-year follow-up study

Supervisor I: Professor Merete Glenne Øie; **Supervisor II:** Professor Bjørn Lau

Background: Cognition has increasingly been linked to outcome measures in schizophrenia, and to a greater extent to functional outcome than clinical outcome. Clinical outcome research in schizophrenia often focuses on psychotic symptoms, rather than on other emotional symptoms. Suicide ideation as a consequence of internalizing problems, such as anxiety, depression and somatic complaints, is common in individuals with early-onset schizophrenia (EOS). The present 13-year follow-up study examines the association between cognition and internalizing problems in adolescents with EOS by studying concurrent associations between cognition and internalizing problems at baseline (T1) and follow-up (T2), associations between internalizing problems at T1 and T2 and associations between cognition at T1 and internalizing problems at T2. The student has been involved in literature search, entering data in SPSS, statistical analyses, interpreting the results before finally writing the thesis.

Methods: Twelve individuals (8 male/4 female) with EOS and 30 healthy controls (16 male/14 female) were included in the study, and the participants were between 12 and 18 years of age at T1. Internalizing problems were measured with the Internalizing scale of the Child Behavior Checklist (CBCL) at T1 and the Adult Behavior Checklist (ABCL) at T2. Cognition measures included Auditory attention/working memory (Composite score of Seashore Rhythm Test, Digit Span forward and backward and Digit Span Distraction Test), Visuomotor processing (Composite score of Trail Making Test A, Trail Making Test B and Digit-Symbol Coding), Cognitive flexibility (WCST perseverative responses), and Verbal memory (CVLT long free recall).

Results: In the EOS group, there was a large, negative and significant correlation between Visuomotor processing and internalizing problems concurrently at T1. At T2, there was a large, negative correlation between Verbal memory and internalizing problems, while internalizing problems at T1 were not associated with internalizing problems at T2. Furthermore, a large, negative and significant correlation between Auditory attention/working memory at T1 and internalizing problems at T2 was found in the EOS group.

Conclusion: Due to the association between cognition and internalizing problems in individuals with EOS, a focus on improving the treatment of cognitive impairments is important in preventing internalizing problems and suicide ideation in young patients with schizophrenia.

Preface and acknowledgments

I was fascinated by neuropsychology already during the first semester of my psychology studies at the University of Oslo, and I knew early on that I wanted to specialize in this research field. I have always been intrigued by the miracles of the brain, and to get a chance to study its functions up close has been a joy.

Thank you so much to my principal supervisor, Professor Merete Glenne Øie, who has been a true inspiration, and offered guidance and direction every step of the way. Her enthusiasm, dedication, involvement and encouragement have been invaluable. I am very grateful to her for letting me use data from the 13-year longitudinal study on young people with early-onset schizophrenia. This has given me a unique opportunity to learn more about cognitive functioning in schizophrenia, and it has taught me much about an important disorder and its patient group.

I also appreciate deeply all the help on methods and statistics from my secondary supervisor Professor Bjørn Lau. In an inspiring way, he has taught me to enjoy working with SPSS, as well as contributing with important input, insight and reflection throughout this project. I would also like to thank Professor Kjetil Sundet who was always available whenever I needed assistance with the variables or interpreting the results.

During the work of my master's thesis, I have been involved in almost all aspects of the process. The entire project of finishing this thesis has been intense and time-consuming, but also very instructive and exceptionally rewarding.

Lastly, I want to extend warm thanks to my beloved partner for his great support throughout this process!

Benedicte Strugstad

Table of Contents

1 Introduction

1.1 Schizophrenia

The term schizophrenia is Greek and translates into “a split mind.” It was first introduced by Eugen Bleuler in 1908 as an extension of Kraepelins Dementia Praecox (Bleuler, 1911). By using the term schizophrenia, he meant to describe the separation of mental processes. Bleuler also attempted to categorize the disorder into different subtypes. His work was the foundation for the diagnostic criteria developed later (Birchwood, 2003). At the core of schizophrenia are the abnormal perception and thought processes, as well as the distinction between reality and delusions. The typical symptoms in schizophrenia can be categorized into positive and negative symptoms, in addition to cognitive impairments. Positive symptoms are thoughts and perceptions not normally present in healthy individuals, including examples such as hallucinations and delusions. Negative symptoms refer to the absence of thoughts, feelings or behavior such as flattened affect, apathy and physical retardation (Green & Harvey, 2014). Cognitive impairments refer to impairments in functions such as working memory, executive functioning, attention, memory or processing speed. In order to be diagnosed with schizophrenia, the person must have had hallucinations or delusions and negative symptoms for a month, and the symptoms must have made a significant impact on social or occupational life for at least six months (American Psychiatric Association, 2013).

Schizophrenia is a serious mental disorder, which has traditionally been viewed as having severe consequences for the people affected and their respective families. However, schizophrenia is no longer considered a deteriorating disorder (Lepage, Bodnar, & Bowie, 2014). Although some studies show recovery rates as low as 28%, others have shown rates to be as high as 77% (Lepage et al., 2014). The illness may persist over time, and may cause impairments in everyday functioning, in addition to a higher risk of suicide (Frangou, 2010). According to the World Health Organization, schizophrenia affects 21 million people worldwide (World Health Organization, 2016). In Norway, the incidence is estimated at 7-10 per 100,000 (Johannessen, 2002) and the presumed prevalence is estimated at 200/100,000, which means that more than 10,000 are in treatment for schizophrenia at any given time (Johannessen, 2002). The cost of health services (2012) connected to schizophrenia is estimated to be NOK 7.9 billion (Evensen et al., 2016). Schizophrenia has traditionally had a

higher prevalence in urban areas (Johannessen, 2002), and among males and it typically starts earlier in men (World Health Organization, 2016). The etiology of schizophrenia is complex, and believed to be a combination of brain pathology, genetics, environmental factors and interactions of all these factors (Fatemi & Folsom, 2009). The assumption that schizophrenia is a neurodevelopmental disorder has existed for more than two decades (Frangou, 2010).

1.2 The importance of early-onset schizophrenia

The most common age of onset of schizophrenia is from 18 to 25 years, the average age for men being 18-25 years and 25-35 years for females (Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012). Onset at an earlier stage does occur, though is rare. Early-onset schizophrenia (EOS) is defined as an occurrence of schizophrenia before the age of 18 (Frangou, 2006), and the prevalence of schizophrenia in adolescence is 1-2 per 1,000 (Rajji, Ismail, & Mulsant, 2009). A higher prevalence has been reported in men (Test, Burke, & Wallisch, 1990), although recent research has reported no differences in prevalence (Ordonez et al., 2016; Perala et al., 2007).

The DSM diagnostic criteria of schizophrenia do not distinguish between early-onset and young adulthood-onset, and it is believed that early-onset follows the same development of the illness as adult-onset. However, studies have shown that the premorbid impairments are worse, and that the clinical course is more severe in individuals with EOS (Frangou, 2006). A study showed that 52% of the patients with EOS had a chronic course of the illness, whereas only 25% in the adult-onset population had such a course (Remschmidt, 1993). Still, more recent research by Amminger and colleagues (2011) questions the assumption that EOS typically has a poor outcome (Amminger et al., 2011). Their results showed that early detection and specialized treatment for the first psychotic episode appear to be more effective at improving long-term functional outcomes in people with EOS than in those with adult-onset schizophrenia.

Adolescence is a time of considerable change, both in terms of hormonal and physical changes (Forbes & Dahl, 2010), but also in identity, self-consciousness and cognitive flexibility (Rutter & Rutter, 1993). Adolescents are about to enter adulthood, they are attending school, deciding on further education, and establishing important social networks. For EOS patients, an early onset of the illness is likely to limit social contact with peers,

which may halt their development in social and academic areas. Also, cognitive functions, especially executive functions, are still not fully developed in EOS patients, as opposed to adult-onset individuals (Best & Miller, 2010).

Most of the research on schizophrenia is on adult-onset. Research on patients with EOS is important, since it can provide valuable insight into the development and course of the disorder in a way that research on adult-onset cannot. Some advantages are obvious. The individuals have not had the illness for a long time, which means that the possible negative effects of the illness on cognition may be more limited (Frangou, Hadjulis, & Vourdas, 2008). Furthermore, possible confounding medication effects may be minimized (Moritz, Woodward, Krausz, Naber, & Group, 2002). EOS patients are not likely to have been hospitalized for long, which could be another advantage, since being in a mental health institution for a long time could possibly further reduce social competence and cognitive functioning (Øie, Sundet, & Ueland, 2011). Thus research on EOS may have less confounding variables than research on adult-onset samples. Furthermore it is important to acquire more insight into the causes of internalizing problems in this particularly vulnerable group of young individuals for prevention and treatment purposes. By identifying early predictors of later problems, treatment can start early and possibly influence the course, morbidity and mortality.

1.3 Outcome research in schizophrenia

The last few decades have witnessed a significant interest in identifying factors that can moderate or influence functional and clinical outcomes in people with schizophrenia, and especially in EOS (Diaz-Caneja et al., 2015). Despite increased interest, there is not much research, and the results are contradictory (Diaz-Caneja et al., 2015). In a systematic review it was found that the most replicated predictors of worse outcome in individuals with EOS are premorbid difficulties, greater symptom severity at baseline and longer duration without treatment (Diaz-Caneja et al., 2015).

Functional outcome in schizophrenia refers to the outcome in areas such as occupational, educational and social functioning, whereas clinical outcome refers to the outcome associated with course, treatment or symptom reduction/resolution (Diaz-Caneja et al., 2015). In schizophrenia research, symptoms refer to both positive and negative symptoms, but also to

symptoms associated with overall mental state or emotional well-being. Most of the studies on clinical outcome focus on a therapeutic response to neuroleptics, positive or negative symptoms, or to achieving a state of remission (Lepage et al., 2014). Depression in schizophrenia has also been the focus of attention to a great extent, due to the important role it plays, particularly in the prodromal phase of the illness (Häfner, Löffler, Maurer, Hambrecht, & Heiden, 1999). But even so, depressive symptoms are sometimes overlooked in schizophrenia due to a focus on the treatment of psychotic symptoms (Castle & Bosanac, 2012), and in many cases symptoms of depression are confused with negative symptoms such as social withdrawal and apathy (Castle & Bosanac, 2012). Although depression has been the attention of much schizophrenia research, the relationship between depression and schizophrenia is still unclear (Heald, Morris, & Soni, 2008). Moreover, a focus on emotional dysfunction in early-onset psychosis is rare (Sanchez-Gistau et al., 2015), and should be examined further.

1.4 What is "internalizing problems"?

The term "internalizing problems" refers to emotional disorders caused by difficulties regulating negative emotions (Graber, 2004). Internalizing problems may manifest itself as shy or withdrawn behavior, worrying, self-denigrating comments and low self-confidence and when difficulties last at least two weeks and begin to affect different aspects of life, a psychiatric disorder may be present (Terzian, Hamilton, & Ericson, 2011). In the 1960s, Achenbach and colleagues proposed an original taxonomy of childhood and adolescent disorders based on empirical evidence (Achenbach, 1966). The result was a model that divided behavior into broadband scales, the most prominent scales being Internalizing and Externalizing (Achenbach, 1966). The Child Behavior Checklist (CBCL), a parent-report form identifying behavior problems in children, was developed based on this taxonomy (Achenbach, 1991). Although behavioral problems were divided into these two distinct groups, it is not uncommon that internalizing and externalizing problems co-occur (Levesque, Levesque, & SpringerLink, 2011). Externalizing behavior refers to problems with aggression and acting out, while internalizing problems are more inner-directed, and refer to problems that generate unease, tension and suffering in the individual related to emotional domains (Whitcomb & Merrell, 2013). Achenbach (1991) categorized the Internalizing scale into three sub-scales: depressive symptoms, anxiety and somatic symptoms. These internalizing

conditions may appear as distinct symptoms, but there is strong evidence that they also exist in a comorbid or co-occurring relationship (Ackerson, 1942; Fish & Shapiro, 1964). The chances may be relatively high that a child or adolescent who has depressive symptoms also may experience anxiety, social withdrawal and physical concerns (Merrell, 2008). Based on this evidence, it makes sense to look at internalizing problems as a group of symptoms in research on adolescents with EOS, as opposed to only focusing on depression or anxiety.

Furthermore, internalizing problems as a concept has been linked to personality traits and temperamental profiles in adolescent populations (Forns, Abad, & Kirschner, 2011). Adolescents with internalizing problems can typically be characterized by a predominantly negative affect and a high degree of emotional instability. In interpersonal relations they are typically shy, inhibited and introverted. They may also be self-conscious and feel socially anxious (Forns et al., 2011). Their cognitive style is often dominated by preoccupation and indecisiveness, as well as a negative and pessimistic self-perception and problems with attention (Forns et al., 2011). The association between internalizing problems and personality traits supports the hypothesis that internalizing problems in adolescence may predict internalizing problems in the future, due to the stability of personality traits (Forns et al., 2011).

Several longitudinal studies have shown that internalizing problems in children from the general population predict mood and anxiety disorders (Petty et al., 2008). One study of 5-6-year-old children from the general population revealed that the CBCL Internalizing scale predicted mood and anxiety disorders after 1.5 years (Kroes et al., 2002). Mesman and Koot (2001) showed that the Internalizing scale predicted at least one DSM-IV anxiety or affective disorder eight years later in children from the general population (Mesman & Koot, 2001). The children were 2-3 years old at baseline and 10-11 years at follow-up (Mesman & Koot, 2001). Petty and colleagues (2008) also showed that the CBCL Internalizing scale predicted anxiety disorders in a 5-year follow-up study of 2-17-year-old children of parents with a panic disorder or major depression. In the same study, the CBCL Externalizing scale predicted disruptive behavior, but also major depression (Petty et al., 2008). A study analyzing childhood externalizing and internalizing behavior suggests that peer rejection may be a mediating factor in developing depression from externalizing problems (Keiley, Lofthouse, Bates, Dodge, & Pettit, 2003). In a longitudinal study on children and adolescents from the general population by Roza and colleagues (2003), both the CBCL Internalizing and

Externalizing scale proved to be significant independent predictors of mood disorders (Roza, Hofstra, Van der Ende, & Verhulst, 2003). However, when they were both included in the same model, the Internalizing scale did not predict mood disorders independently of the Externalizing scale (Roza et al., 2003). The aforementioned studies show that the Internalizing and Externalizing scales from the CBCL are predictive of anxiety and depression in children and adolescents at risk or from the general population. The focus in this study is on internalizing problems and not on externalizing behavior. The reasons for this choice are explained further in the following and more specifically in 1.6.

1.5 Schizophrenia and internalizing problems

Since internalizing problems include depression, anxiety and somatic complaints, each subgroup of symptoms is presented in the following, along with its relevance to schizophrenia in general, as little research exists on EOS specifically regarding this.

1.5.1 Schizophrenia and depression

It is well documented that depressive and anxiety symptoms are common comorbid features in individuals with schizophrenia (Birchwood, 2003). Bleuler (1911) claimed as early as 1908 that depressive mood swings are common in people with schizophrenia, and that affective distortions are more primary to the illness than hallucinations and delusions. The main characteristics of depression are depressed mood, lack of interest or pleasure in activities, loss of energy, feelings of guilt, lack of concentration, psychomotor retardation and suicidality (American Psychiatric Association, 2013). The prevalence of depression in people with schizophrenia varies in estimates from 6% to 75% (Siris & Bench, 2003), with the average prevalence estimated at 25% (Siris et al., 2001). The prevalence of depression in the normal population is estimated to be 5-7% (Kessler et al., 2003; Murphy, Laird, Monson, Sobol, & Leighton, 2000). The large variation in prevalence estimates for depression in schizophrenia is mainly due to some methodological challenges, such as: 1) whether diagnoses, syndromes or single symptoms are being studied; 2) whether point-, period- or lifetime prevalence rates are being considered, and 3) which stage in the illness the patient is in at the time (Häfner, Maurer, Trendler, An Der Heiden, & Schmidt, 2005).

In order to explain the presence of depression in schizophrenia, researchers have introduced a framework of three possible pathways (Birchwood, 2003). Firstly, retrospective studies reveal that first-episode psychosis is often preceded by social difficulty and emotional disorder going back to early adolescence (Poulton et al., 2000). There is now considerable evidence that social factors, such as urban living, deprivation and social status influence the clinical outcome of psychosis. These factors may also influence normal psychological development, and may lead to low self-esteem, difficulty in establishing relationships and to stress (Birchwood, 2003), and these factors could influence the development of depression (Fombonne, Wostear, Cooper, Harrington, & Rutter, 2001; Rutter & Sroufe, 2000).

The second way to explain depression in schizophrenia is as an integral part of the disorder. Häfner, Riecher-Rössler and Hambrecht (1992) discovered that 18% of people with schizophrenia had concurrent depressive and psychotic symptoms, and that 21% of the sample were already depressed when they developed their first psychotic episode (Häfner et al., 1992). More recently Birchwood, Iqbal, Chadwick and Trower (2000) found that more than 50% of the patients had depressive symptoms in the residual- or post-psychotic phase (Birchwood, Iqbal, Chadwick, & Trower, 2000). They also showed that the depressive symptoms were associated with the psychotic symptoms in 70% of the sample over a 12-month period (Birchwood et al., 2000).

A third way to explain depression in schizophrenia is as a reaction to traumatic events following the psychotic episode. Post-psychotic depression is a short-term dysphoric condition, in which schizophrenia symptoms are also present, but not predominant (Birchwood et al., 2000). The depression could be explained as a consequence of loss of hope or an expression of despair due to a new life situation (Birchwood et al., 2000).

The above explanations show that there is a complex and close relationship between depression and schizophrenia. Studies have shown that comorbid depression is associated with psychotic relapse and readmittance, longer hospitalization and a poorer response to antipsychotic medication (Birchwood, Mason, MacMillan, & Healy, 1993; Hausmann & Fleischhacker, 2002). In addition, comorbid depression is associated with cognitive impairment, reduced social functioning and substance abuse (Hausmann & Fleischhacker, 2002). Greater depressive symptoms are also associated with an increased risk of suicide attempts (Diaz-Caneja et al., 2015).

1.5.2 Schizophrenia and anxiety

Anxiety disorder includes a variety of different disorders such as generalized anxiety, social anxiety, panic attacks and specific phobias (American Psychiatric Association, 2013). Social anxiety is considered the most prevalent in schizophrenia, and one study has shown a prevalence of 15% (Achim et al., 2011), while others have found a prevalence to vary from 14% to 39% (Bermanzohn et al., 2000; Cassano, Pini, Saettoni, & Dell'Osso, 1999; Cosoff & Hafner, 1998; Pallanti, Quercioli, & Hollander, 2004).

Social anxiety in psychotic disorders such as schizophrenia can be explained in a similar framework as depression (Birchwood, 2003). Firstly, social anxiety might be viewed as a premorbid vulnerability marker to develop psychosis, with the social withdrawal aspect of anxiety being the strongest predictor of the disorder (Johnstone, Ebmeier, Miller, Owens, & Lawrie, 2005; Owens, Miller, Lawrie, & Johnstone, 2005). However Birchwood did not find any differences in premorbid peer-relations when comparing psychosis patients with and without social anxiety (Birchwood et al., 2007). Secondly, social anxiety can be considered a predominant component of schizophrenia because anxiety is often co-occurring with paranoia and delusions (Startup, Freeman, & Garety, 2007), although this is not always the case. Pallanti and colleagues (2004) found no correlation between social anxiety and psychotic symptoms (Pallanti et al., 2004), whereas other studies have found a relationship between anxiety and negative symptoms, but not with positive symptoms (Voges & Addington, 2005). As with depression, the third way to understand social anxiety in schizophrenia is as a consequence of the psychotic episode. A psychotic episode is often followed by feelings of shame and guilt, humiliation and loss of social acceptance and eventually lack of self-esteem, which can also lead to social anxiety (Birchwood, 2003).

1.5.3 Schizophrenia and somatic complaints

As defined by the Internalizing scale of the Child Behavior Checklist (CBCL) by Achenbach (1991), somatic complaints include nine types of body aches, such as feeling dizzy, tired, aches or pains, headaches, nausea, problems with eyes, rashes or other skin problems, stomach aches or cramps, vomiting or other somatic complaints. The somatic symptoms associated with internalizing problems are believed to be based on a psychological-, rather than physical or organic origin (Whitcomb & Merrell, 2013). Somatic complaints are not identical with somatization disorder, though high scores on the somatic complaints subscale

may correspond to a diagnosis of somatization disorder (Ritsner, 2003). Somatization disorder is defined as the presentation of five or more somatic symptoms that cannot be accounted for by any detectable somatic illness (Ritsner, 2003). Much of the research on somatic conditions focuses on somatization disorder, rather than on somatic complaints. A study by Ritsner (2003) found that somatization is a prevalent problem in schizophrenia. A positive association was found between somatic complaints and emotional distress attributed to the psychopathology, side effects of medicine, insight and/or expressed emotion (Ritsner, 2003).

1.6 Why study internalizing problems in individuals with EOS?

Most of the research on internalizing problems in schizophrenia has been on adults, and the affective dimension has scarcely been studied in early-onset psychosis (Sanchez-Gistau et al., 2015). However, some research has shown that a majority of those developing schizophrenia have had emotional problems prior to the onset of psychosis, and that depressive symptoms contribute to the risk of psychosis in vulnerable subjects (Krabbendam, Hanssen, Bak, & Van Os, 2004; Verdoux & Van Os, 2002). Furthermore, a study found that 95 youths, aged 9-17 years old, experiencing a first-episode of a psychotic disorder had a high prevalence of affective symptoms during the early phases of psychosis (Sanchez-Gistau et al., 2015). As already mentioned social withdrawal has also been found to be a robust childhood risk factor and predictor of schizophrenia (Birchwood et al., 2007; Matheson et al., 2013).

The current study is part of a larger research project comparing cognitive function in 19 adolescents between 12-18 years with EOS, 20 adolescents with Attention Deficit Hyperactivity Disorder (ADHD) and 30 healthy controls (HC) (Øie & Rund, 1999; Øie, Sundet, & Rund, 2010; Øie et al., 2011). After 13 years, the research group carried out a follow-up study on the same sample group to obtain further insight into the cognitive functioning and functional outcome of the individuals. In the previous research, Øie and colleagues (2011) reported that the EOS group had a considerably higher level of internalizing problems, as measured by CBCL, than the healthy controls when they were between 12-18 years of age. The level of internalizing problems was still at a high level after 13 years; however, Øie and colleagues (2011) did not examine the factors associated with later internalizing problems. By understanding the mechanisms underlying internalizing problems better, it is easier to find ways to prevent or treat it.

The close relationship between increased suicidality and anxiety and depression in people with a psychotic disorder (Bertelsen et al., 2007; Diaz-Caneja et al., 2015; Drake, Whitaker, Gates, & Cotton, 1985; Fenton, 2000; Jarbin & Von Knorring, 2004) is an important reason for investigating emotional problems in individuals with EOS. Research suggests that post-psychotic depression is frequently connected to first-episode psychosis, as someone who has just been diagnosed with schizophrenia may experience a loss of hope, estrangement and a loss of self-esteem (Birchwood, 2003).

Between 18% and 55% of patients with schizophrenia have attempted suicide (Siris, 2001). The general lifetime risk of suicide among people with schizophrenia is generally estimated to be approximately 10% (Miles, 1977), but more recent research has indicated a lower figure (Palmer, Pankratz, & Bostwick, 2005). Among individuals with first-episode schizophrenia observed at first admission, a study found a lifetime suicide prevalence of nearly 6% (Palmer et al., 2005). Moreover, among first-admission and new-onset samples, 30.6% of the deaths were due to suicide, compared to 4.9% in samples independent of duration of illness (Palmer et al., 2005). Similarly, Jarbin and Von Knorring (2004) found that 4.5% of adolescents with early-onset psychotic disorders had died from suicide, 25% of the subjects had attempted suicide and suicide attempts were associated with depressive symptoms (Jarbin & Von Knorring, 2004). These findings underscore the importance of a better understanding of depression and other factors that might contribute to suicide ideation in individuals with EOS.

1.7 Cognitive deficits in individuals with EOS

Cognition refers to all the elements involved in acquiring, processing, retaining and retrieving information such as working memory, attention, abstract reasoning, executive functioning, verbal and visual learning and memory, and processing speed. Most cognitive functions develop gradually during childhood, but executive functions do not reach adult-like levels before mid-adolescence (Best & Miller, 2010). However, the different components of executive functions vary in their developmental course (Holmén, Juuhl-Langseth, Thormodsen, Melle, & Rund, 2009), and some parts do not fully develop and mature until early adulthood (Romine & Reynolds, 2005). Executive functions are often referred to as the director in the cognitive system, controlling many different functions (Allott, Liu, Proffitt, & Killackey, 2011).

It was originally believed that cognitive deficits occurred later on in the development of schizophrenia, and were not present in the earlier stages of the illness (Seidman et al., 2010; Woodberry, Giuliano, & Seidman, 2008). Today, we know that cognitive deficits are present early on in the course of schizophrenia, and even prior to onset in many cases (Seidman et al., 2010; Woodberry et al., 2008). Hence, the cognitive deficits are not viewed as a consequence of the disorder, but more as a predictor of the disease.

In a review of cognitive function in individuals with EOS, Frangou (2010) found that EOS patients showed impairments of medium to large effect sizes in IQ, attention, memory and executive functions (Frangou, 2010). Generally speaking, intellectual ability in individuals with EOS has been found to be 1-1.5 standard deviations below the normative mean (Bedwell et al., 1999; Fagerlund, Pagsberg, & Hemmingsen, 2006; Gochman et al., 2005; Kravariti, Morris, Rabe-Hesketh, Murray, & Frangou, 2003; Kumra et al., 2000; White, Ho, Ward, O'Leary, & Andreasen, 2006). In earlier research on the same EOS group as in the current study, Øie and colleagues (2011) also found that the level of cognitive impairment among individuals with EOS was approximately 1-2 SD below the healthy controls.

Longitudinal studies suggest that general intellectual ability in individuals with EOS remains stable after the onset of psychosis (Gochman et al., 2005). Cervellione (2007) found adolescents with schizophrenia to have a significant impairment in executive functions, which remained unchanged over a 2-year period (Cervellione, Burdick, Cottone, Rhinewine, & Kumra, 2007). However, Øie and colleagues (2011) found that there was a decline in verbal memory, attention and processing speed in EOS patients when reassessed after 13 years. Frangou and colleagues (2008) also found a decline compared to healthy controls in verbal memory and attention over a 4-year period in the Maudsley Early Onset Schizophrenia Study (Frangou et al., 2008).

1.8 Cognition and outcome research in schizophrenia

Cognition has increasingly been considered an important predictor of outcome in adult-onset schizophrenia (Lepage et al., 2014). Performance on several cognitive measures has consistently been associated with functional outcome, and to a lesser extent to clinical outcome (Green & Harvey, 2014). In the following, I will highlight some key research

documenting the association between cognition and functional outcome, and then turn to clinical outcome.

In general, impairments in working memory and executive functioning may significantly limit the ability to acquire, retain or relearn the skills necessary for everyday functioning (Lasser et al., 2007). Verbal memory, and executive functions were found important for functional competence and processing speed, attention and working memory were associated with social and functional competence in a study of schizophrenia outpatients (Bowie et al., 2008). Processing speed, verbal memory and working memory have been significantly correlated with daily problem-solving skills in patients with schizophrenia (Revheim et al., 2006). Stouten and colleagues (2014) found that cognitive deficits in patients with first-episode psychosis appeared to be more accurate longitudinal predictors of psychosocial and functional recovery in the early course of psychosis than psychotic symptoms, although symptoms also had a marked impact on psychosocial functioning at illness onset (Stouten, Veling, Laan, Van der Helm, & Van der Gaag, 2014). In a study by Simonsen and colleagues (2010), it was found that cognition explained 6% of the variance in self-reported psychosocial functioning in a sample of adult patients with schizophrenia (Simonsen et al., 2010). However, Simonsen and colleagues (2010) found current symptoms to have an even greater independent contribution to self-rated and clinician-rated psychosocial functioning, a finding which is contrary to the general belief that cognition is a stronger predictor of functioning in schizophrenia.

Although most of the studies on the association between cognition and functional outcome have been carried out on adult samples, there are some studies on EOS. These studies show results similar to research on adult patients. In the previously mentioned study by Øie and colleagues (2011), it was found that better executive functioning, visuomotor processing, motor coordination, working memory, verbal learning and visual memory at baseline were correlated with better social functioning after 13 years. The same study found that better verbal memory, visuomotor processing and visual attention at baseline were associated with better vocational/educational functioning at follow-up.

Deficits in processing speed have been found to predict poorer social functioning after 1 year in adolescent-onset schizophrenia patients (Bachman et al., 2012). Processing speed also accounted for group differences in a range of other cognitive abilities, including measures of working and verbal memory, as well as verbal fluency, which stresses the importance of

processing speed as a constraint to other more complex cognitive processes (Bachman et al., 2012).

There is little evidence on the association between cognition and clinical outcome in schizophrenia, and EOS in particular. In patients with early-onset psychosis, bivariate analyses have shown that more severe cognitive symptoms have been associated with more severe clinical outcome (Ledda, Fratta, Pintor, Zuddas, & Cianchetti, 2009), while in multivariate analyses lower IQ, lower attention scores and global cognition have all been associated with more severe clinical outcome (Pina-Camacho et al., 2015). In a review of clinical outcome research, Lepage and colleagues (2014) claim that verbal memory and social cognitive deficits appear to be the more robust markers of clinical outcome, and that other cognitive domains show little relation to clinical outcome in adults with schizophrenia (Lepage et al., 2014). Social cognition refers to the domains of cognitive functions employed in socially relevant situations (Harvey & Penn, 2010), which includes capacities such as emotion processing, theory of mind, attributional style/bias and social metacognition (Pinkham et al., 2014).

Much research has shown that symptom severity at baseline predicts clinical outcome at follow-up (Diaz-Caneja et al., 2015). Even so, the clinical outcome research focuses for the most part on positive and negative symptoms, and not on internalizing problems such as depression, anxiety and somatic complaints. Although not much research has linked cognition to clinical outcome in individuals with EOS so far, there is ample evidence that cognition is associated with depression in other populations. Impaired cognition has been estimated to occur in two-thirds of depressed patients (Abas, Sahakian, & Levy, 1990; Afridi, Hina, Qureshi, & Hussain, 2011; Butters et al., 2004). In patients with depression, cognitive impairments have been found on measures of executive functioning, sustained vigilance, visuomotor attention, ideational fluency, short-term and working memory, visuospatial processing, verbal and non-verbal learning, motor functioning and general intelligence (Jaeger, Berns, Uzelac, & Davis-Conway, 2006). Problems in these areas lead to difficulties with everyday activities, which could contribute to increased negative thought, attitudes and evaluations, and subsequently to depressive episodes. Depression is characterized by depressed mood, loss of interest and decreased energy. Furthermore, being depressed often involves reduced activity level, social isolation, poor concentration and slower processing

speed. Although the association between depression and cognition is clear, the direction of the association is less clear (Schmid & Hammar, 2013).

Of the cognitive functions, executive functions are frequently linked to depression (Snyder, 2013). Executive function is an umbrella term for a set of higher-order cognitive functions that regulate thought, feelings and behavior (Zelazo & Cunningham, 2007). Exactly which sub-processes executive functions consist of is still not agreed upon. According to Miyake´s model, executive functions often contain three central sub-processes: inhibition, working memory and cognitive flexibility (Miyake, Friedman, et al., 2000). Inhibition refers to the ability to restrain certain inappropriate responses (Miyake, Friedman, et al., 2000). Working memory is the part of memory necessary for temporary storage and processing of information (Kane, Bleckley, Conway, & Engle, 2001), whereas cognitive flexibility refers to the ability to shift between activities and mental states, sometimes also referred to as "shifting" (Miyake, Emerson, & Friedman, 2000; Miyake, Friedman, et al., 2000; Monsell, 1996).

According to Hofmann and colleagues (2012), working memory has been associated with emotion regulation, and enables the top-down control of attention and unwanted affect, the suppression of rumination and switching between adaptive cognitive strategies (Hofmann, Schmeichel, & Baddeley, 2012). An association between executive function and depression has also been found in patients with autism spectrum disorder (Cederlund, Hagberg, & Gillberg, 2010). Additionally, working memory and anxiety have been examined in multiple research studies; however, anxiety is thought to affect working memory abilities rather than the reverse (Crowe, Matthews, & Walkenhorst, 2007; Shackman et al., 2006).

An association has been found between verbal memory and self-disorder in adults with early-phase schizophrenia (Haug et al., 2012). Self-disorder is a subtle disorder in a person´s spontaneous identity feeling, the experience of him or herself as a vital subject naturally immersed in the world (Haug et al., 2012). Since the self is a dynamic structure with representations stored in memory it is possible that deficits in verbal memory may cause problems with abilities to comprehend, remember and reason one's own thoughts and self-knowledge so that the sense of self is weakened (Haug et al., 2012). Problems with self-image or self-confidence are related to the development of depression, and could be a mediator to internalizing problems (Whitcomb & Merrell, 2013).

1.9 Aims of the study

To sum up: Little research has been carried out on EOS individuals. Internalizing problems are prevalent in patients with schizophrenia, and studies on other populations have indicated that internalizing problems may predict later internalizing problems. Moreover, suicide risk is higher in the earlier stages of the illness. Clinical outcome research in schizophrenia and EOS has also focused more on positive and negative symptoms, rather than on self-reports on how patients are feeling emotionally. Cognitive deficits have been associated with clinical outcome in adults with schizophrenia, but as far as I know no studies have yet investigated the association between cognition and internalizing problems in individuals with EOS. Therefore, the aims of the present study were to examine the following in a sample of EOS patients:

- How cognition and internalizing problems were associated concurrently at baseline (T1) and at follow-up after 13 years (T2).
- How parent-rated internalizing problems at baseline (T1) were associated with self-rated internalizing problems at (T2).
- How cognitive functions at baseline (T1) were associated with self-rated internalizing problems at (T2).

1.10 Hypotheses

Hypothesis 1: Due to the significance of cognitive impairments for functional outcome in EOS schizophrenia, I hypothesized that there would be associations between cognition and internalizing problems concurrently at both T1 and T2.

Hypothesis 2: Based on research showing that the CBCL Internalizing scale is predictive of anxiety and depression in children and adolescents at risk or from the general population, I hypothesized that internalizing problems in adolescents with EOS would be associated with internalizing problems after 13 years.

Hypothesis 3: Based on earlier results from the same sample group reporting that processing speed, working memory, executive functions (flexibility) and verbal memory at baseline are associated with functional outcome measures at T2 in the EOS group, I hypothesized that deficits in these cognitive functions would also be associated with more internalizing problems at T2.

2 Methods

2.1 Participants

The current study is part of a larger research project initiated in 1992 on cognition and associations to functional outcome in individuals with EOS and ADHD, but the current study focuses on the EOS sample only. For the purpose of comparison, the healthy controls are included to show possible impairments in the EOS sample. Participants in the study were 12 subjects from a baseline (T1) sample of 19 adolescents with a *Diagnostics and Statistical Manual, Fourth Edition (DSM-IV)*-based diagnosis of schizophrenia and 30 healthy control individuals. At T2, two of the subjects in the schizophrenia group were deceased (one by suicide and one by overdose, in combination with an underlying medical disorder) and two declined to participate in the study. Furthermore, ABCL data (Internalizing scale) at T2 were missing for three individuals in the EOS group. Thus, the EOS group in the current study consists of 12 individuals. All 30 healthy control individuals were available for reassessment after 13 years. The schizophrenia diagnosis was determined at T1 by using semi-structural clinical interviews by senior clinicians and information from the patient case records. Consensus regarding diagnosis was investigated on a subsample of 13 of the 19 patients at T1. Two senior psychologists agreed on the schizophrenia diagnosis in 92% of the cases, and disagreements in diagnosis at T1 were discussed between the two psychologists to arrive at a consensus diagnosis. After 13 years, the schizophrenia diagnosis at T2 was based on the Structured Clinical Interview for DSM-IV and information from parents, psychiatrists, nurses or social workers. One psychologist and one psychiatrist reviewed the diagnosis, and agreed on it in 94% of the cases. Disagreements in diagnosis at T2 were discussed between the two to arrive at a consensus diagnosis.

Characteristics of the EOS group compared to the healthy controls are presented in Table 1, and specific schizophrenia diagnoses for the EOS group at T1 and T2 are presented in Table 2. Male subjects were more frequently represented. At follow-up, there were eight male and four female patients in the EOS group, whereas in the healthy control group there were 16 male and 14 female participants. The level of intellectual ability in the EOS group at T2 was within the normal range; 93.2 (±15.1). The level of total psychosis symptoms (Brief Psychiatric Rating Scale-BPRS) score was 42.8 (±16.0), the positive symptoms score (BPRS)

was 12.1 (±7.5) and the negative symptoms score (BPRS) was 6.5 (±3.4) at T2. Ten of the patients in the schizophrenia group had been hospitalized during the follow-up period. Five of the subjects were continuously in the hospital or in sheltered housing, and five for only a short period of time. At T2, two of the individuals in the current EOS group had recovered. Of the 12 patients at T2, six had their own apartment, four were in a psychiatric hospital or housing and two lived with their parents, all 12 were unemployed and only one of the patients had a partner. Medication use is also listed in Table 1, with two patients using a typical antipsychotic medication, four using atypical medication and three using both. One of the two recovered patients was using a small dose of antidepressant medication at T2. The patients were tested when they were judged by the examiner or by their clinician to be clinically stable.

Healthy controls were volunteers attending regular schools. They were screened for mental problems using the Child Behavior Checklist (CBCL), and individuals were excluded if they had a higher raw score than 45 (Øie & Rund, 1999). The healthy comparison group had a significantly longer education and significantly higher IQ scores at T2 than the EOS group. Øie and colleagues (2011) have previously shown that the current EOS sample group had a lower social functioning score and more internalizing problems than the healthy control group.

Table 1. *Characteristics of the EOS group compared to the healthy control group at T2*

Variable	EOS patients (*n* = 12)	Healthy controls (*n* = 30)	Group comparison
Gender (m/f)	8/4	16/14	p = .506 (Fisher)
Age (yrs)	27.6 (1.5)	27.6 (1.5)	F = .001 (.975)
Education (yrs)	10.5 (1.6)	15.4 (1.7)	F = 75.2 (.000)
FSIQ (WASI)[a]	93.2 (15.1)	112.6 (8.6)	F = 27.7 (.000)
BPRS[b]			
Positive	12.1 (7.5)	-	
Negative	6.5 (3.4)	-	
Total	42.8 (16.0)	-	
Medication			
Typical antipsychotic	*n* = 2	-	
Atypical antipsychotic	*n* = 4	-	
Both	*n* = 3	-	
DDD[c]	2.7 (1.9)	-	

[a] Full Scale IQ from Wechsler Abbreviated Scale of Intelligence
[b] Brief Psychiatric Rating Scale (Positive Scale = 7 items, Negative Scale = 3 items)
[c] Defines daily doses (Norwegian Medical Depot) (*n* = 10)

Table 2. *Diagnoses at T1 and T2 in the EOS group*

Case	T1	T2
1	Schizophrenia disorganized	Schizophrenia disorganized
2	Schizophrenia disorganized	Schizophrenia disorganized
3	Schizophrenia disorganized	Schizophrenia disorganized
4	Schizophrenia disorganized	Schizophrenia disorganized
5	Schizophrenia disorganized	Schizophrenia disorganized
6	Schizophrenia paranoid	Schizophrenia paranoid
7	Schizophrenia disorganized	Schizoaffective
8	Schizophrenia disorganized	Schizophrenia paranoid
9	Schizophrenia undifferentiated	Schizophrenia disorder
10	Schizophrenia disorganized	Schizophrenia paranoid
11	Schizophreniform disorder	Recovered
12	Schizophrenia paranoid	Recovered

2.2 Internalizing problems measure

The Child Behavior Checklist (CBCL) Internalizing scale was used as a measure of internalizing problems at T1. The CBCL is part of the Achenbach System of Empirically Based Assessment (ASEBA), which originated from Achenbach's (1966) factor-analytical derivation of syndromes of child and adolescent psychopathology (Achenbach, 1966). The CBCL version used in the current study assesses various behavioral and emotional problems in children from 4 to 18 years of age during the past six months, as rated by their parents (Achenbach, 1991). Each item measures behavior and emotional problems on a 3-point scale (0 = "Not true", 1 = "Somewhat true", or 2 = "Very true or Often true"). In total, the CBCL consists of 113 items divided into eight syndrome scale scores: Withdrawn, Somatic complaints and Anxious/depressed (Internalizing scale), Delinquent behavior and Aggressive behavior (Externalizing scale), Social problems, Thought problems and Attention problems. The CBCL is widely considered to be the gold standard of self-report child behavioral assessment (Postilnik, Eisman, Price, & Fogel, 2006), and in clinical settings, the CBCL has demonstrated excellent utility, especially in being able to distinguish between referred and non-referred populations (Achenbach, 1991; Chen, Faraone, Biederman, & Tsuang, 1994; Drotar, Stein, & Perrin, 1995). The questionnaire is frequently being used in the Child and Adolescent Mental Health Centers in Norway to determine behavioral problems, and has been

found to have good psychometric properties in general (Ivanova et al., 2007). The CBCL is a simple pen and pencil assessment form, easy to administer and cost-effective. The CBCL form was completed by the mothers of the subjects at T1. At T2, the adult version of the scale (ABCL) (Achenbach & Rescorla, 2003) was used, and the form was filled out by the individuals themselves. Longitudinal studies have demonstrated that the ABCL is tapping into the same constructs as the CBCL (Achenbach & Rescorla, 2003). In the current study, only data from the Internalizing scale was used. The Internalizing scale consists of statements such as "cries a lot" or "feels worthless or inferior" (Anxious/depressed subscale), "would rather be alone than with others" or "unhappy, sad or depressed" (Withdrawn subscale), "feels dizzy or lightheaded" or "aches or pains, not stomach or headaches" (Somatic complaints subscale). High T-scores on the Internalizing scale indicate more internalizing problems. Raw scores on the CBCL/ABCL are converted to American norm-referenced T-scores (M = 50, SD = 10). The clinical cut-off score of the CBCL/ABCL is T-score ≥ 65. There are no national CBCL/ABCL norms in Norway, but scores from Norwegian children are lower compared to American children, and Norway is a so-called low-scoring country with a population mean well below T-score = 50. Hence, borderline scores are graver than the American norm-referenced T-scores imply (Kornør & Jozefiak, 2012).

The level of internalizing problems at T1 and T2 for the EOS group and healthy controls is shown in Table 3.

2.3 Cognitive measures

The subjects were assessed using the same cognitive test battery at T2 as used at T1, with the exception of replacing the Wechsler Intelligence Scale for Children – Revised (WISC-R) with age-appropriate versions of the subtests from the Wechsler Adult Intelligence Scale – Third Edition (WAIS III) (Wechsler, 2003) and the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 2007) to screen for IQ. All subjects were tested individually, and received the tests in the same order.

In the previous study by Øie and colleagues (2011), eight cognitive domains showing adequate psychometric properties in the retest sample were used. These cognitive domains were modified according to Saykin (Saykin et al., 1991; Saykin et al., 1994). Because the number of participants in the current study has been reduced from 15 to 12 compared to the

previous study by Øie and colleagues (2011), I chose to use fewer variables in order to avoid doing too many analyses, thereby increasing the probability of finding significant results randomly and avoiding Type 1 errors. Based on the results from earlier studies in the current research project (Øie et al., 2010; Øie et al., 2011) and other studies, I regarded Auditory attention/working memory, Visuomotor processing, Executive functions (flexibility) and Verbal memory to be the most relevant for the current study. The composite scores used comprised of the same measures as in Øie and colleagues (2011). Composite scores were made by converting raw scores to standard z-scores based on the means and standard deviations of the healthy control group, and then by averaging each subject's z scores on tests for assessing the same functional domain. The formula for calculating the z-score is: (raw score - mean)/standard deviation. Where high scores indicated impairment, the direction was reversed so that high scores always indicated better cognitive function.

The variable called Executive functions (flexibility) in the study by Øie and colleagues (2011) has been labeled Cognitive flexibility in the current study, but the measure used is the same: Wisconsin Card Sorting Test (WCST) Perseverative responses. California Verbal Learning Test (CVLT) Long Free Recall was used as a measure of Verbal memory in the current study instead of CVLT Total correct words at Trials 1-5 (learning), which was used in the previous study (Øie et al., 2011). The cognitive measures used in the current study are presented in Table 3 and described in the following.

Auditory attention/working memory: A composite score was calculated of the Seashore Rhythm Test, Digit Span forward and Digit Span backwards from WISC-R and the Digit Span Distraction Test (distraction and non-distraction). For a calculation of the composite score, please see above. High composite score equals a good performance. The Seashore Rhythm Test consists of 30 pairs of non-verbal sounds. The task is to identify the same or different sounds, with a high score equaling a good performance (Reitan & Wolfson, 1993). The Digit Span Test from WISC-R equals a sequence of numbers being read out loud. For the forward condition, the task is to recall the maximum of numbers in the same order, while for the backward condition, the task is to recall the maximum of numbers in a backwards order. A high score equals a good performance (Wechsler, 1974). The Digit Span Distraction Task (DSDT) has two recall conditions: distraction and non-distraction. A voice is reading out loud the target digits, and in the distraction condition a male voice is simultaneously distracting by

reading irrelevant digits. The task is to repeat the target digits in the same order as they are presented, with a high score equaling a good performance (Oltmanns & Neale, 1975).

Visuomotor Processing: The composite score consists of Trail Making Test (version A and B) and Digit Symbol-Coding from WISC-R. For the calculation of the composite score, please see above. A high composite score equals a good performance. Trail Making Tests A and B: Test A consists of numbers on a piece of paper. The task is to connect the numbers in ascending order as rapidly as possible, and a low score equals a good performance. Test B consists of both numbers and letters, with the task being to connect the numbers and letters in ascending order, changing between a number and a letter every time. The task is timed, and should be performed as rapidly as possible. A low score equals a good performance (Reitan & Wolfson, 1993). The Digit Symbol-Coding test from WISC-R is a test in which the subject is asked to match a digit to a symbol from a given set-up. It is timed and should be done as rapidly as possible, with a high score equaling a good performance (Wechsler, 1974).

Cognitive flexibility: Wisconsin Card Sorting Test (WCST) perseverative responses (raw scores). WCST is a computer-based, problem-solving task. The subject is presented by a set of four different stimulus cards differing in color, form and number. The task is to match each card with one of the stimulus cards according to the given set of rules. The subject is being told if the response is correct or not after each trial, and has to figure out the rules by trial and error. A low score equals a good performance (Heaton, 1981).

Verbal memory: The California Verbal Learning Test (CVLT) Long Free Recall (raw scores). A list of 16 words is read out loud, and after each trial the subject is asked to recall as many as possible. This is repeated up to five times, and then another list is read with the same procedure. When the subject does not remember any more from list no. 2, he/she is asked again about list no. 1 without reading the list again. After approximately 30 minutes with non-verbal tasks, the subject is then asked to recall list no. 1 again. A high score equals a good performance (Delis, Kramer, Kaplan, & Ober, 1987).

Table 3. *Mean and SD of cognitive and internalizing measures at T1 and T2*

	T1			T2		
	EOS n= 12	HC n = 30	F/sign	EOS n = 12	HC n=30	F/sign
Cognitive domains (raw scores [a])						
Aud att/working memory	-.60 (1.16)	.0001 (.71)	4.2 (.047)	-1.17 (1.75)	-.0006 (.73)	9.6 (.004)
Visuomotor processing	-1.09 (1.42)	-.0001 (.76)	10.5 (.002)	-2.46 (2.03)	.0000 (.82)	31.9 (.000)
Cognitive flexibility (WCST)	21.7 (12.4)	15.6 (6.9)	3.8 (.059)	27.7 (23.0)	10.2 (5.1)	16.2 (.000)
Verbal memory (CVLT)	11.7 (2.7)	13.1 (2.2)	3.2 (.081)	9.7 (3.6)	13.7 (1.8)	24.2 (.000)
Internalizing problems	61.2 (12.1)	45.7 (9.6)	19.2 (.000)	59.8 (9.2)	40.2 (8.7)	41.7 (.000)
Individual tests in the cognitive composite scores (raw scores)						
<u>Aud att/working memory</u>						
Seashore Rhythm Test	25.3 (3.3)	27.1 (3.0)	3.1 (.084)	23.2 (5.6)	27.2 (2.7)	10.1 (.003)
Digit Span Forward	6.1 (1.2)	6.3 (1.2)	.36 (.552)	5.8 (1.2)	6.6 (1.2)	3.4 (.075)
Digit Span Backward	4.1 (1.9)	4.9 (1.4)	2.2 (.143)	4.0 (1.3)	4.7 (1.3)	2.2 (.150)
DSDT non-distraction	77.1 (23.1)	87.3 (10.6)	3.9 (.054)	79.8 (20.2)	88.7 (7.9)	4.4 (.043)
DSDT distraction	74.4 (24.9)	83.6 (14.2)	2.3 (.139)	78.8 (22.7)	94.0 (7.2)	11.2 (.002)
<u>Visuomotor processing</u>						
Trail Making Test A	32.7 (17.3)	24.1 (6.4)	5.6 (.023)	32.4 (12.3)	20.2 (5.2)	20.7 (.000)
Trail Making Test B	81.1 (19.0)	59.8 (19.2)	10.6 (.002)	76.7 (39.2)	46.2 (13.6)	14.3 (.001)
Digit Symbol-Coding	55.8 (13.0)	65.9 (12.2)	5.6 (.023)	53.7 (21.1)	85.6 (11.4)	40.3 (.000)

[a] For the composite scores, Aud att/working memory and Visuomotor processing, z-scores are shown.

2.4 Data Analyses

Analyses were conducted using the statistical package SPSS, version 24.0. Preliminary analyses were performed to investigate the distribution of the sample, whereas preliminary group characteristics were investigated by a Fisher exact probability test (nominal variables) and analysis of variance (ANOVA, continuous variables). Group differences between EOS individuals and healthy controls on cognitive functions and internalizing problems were analyzed by ANOVA at T1 and T2. In order to analyze changes in internalizing problems between T1 and T2, repeated measures of ANOVA were performed. Correlation analyses (Spearman's *rho*) were used to investigate concurrent associations between cognitive functions and internalizing problems at T1 and T2, internalizing problems at T1 and T2, and associations between cognition at T1 and internalizing problems at T2 in the EOS group. Spearman´s *rho* was chosen as it is considered more robust when it comes to outliers and skewed variables (Mukaka, 2012). The strength of the correlations was determined according to Cohen´s guidelines (Cohen, 1988). All tests were two-tailed and the significance level was generally set to 0.05, but due to the small sample size, a significance level of 0.1 was also accepted when the correlation was large.

Power analysis was carried out in the previous study by Øie and colleagues (2011). Based on previous published work where it was found an effect-size of $\eta 2=0.22$ for the Time X Group interaction for CVLT Delayed recall (Verbal memory), it was calculated that a sample size of 58 (including all three groups: EOS, ADHD and HC) would be enough, assuming an attrition rate of 10%. Furthermore, a post-hoc power-analysis using the program G*Power 347 estimated the power to detect an effect size of $\eta 2=0.22$ for a repeated measures ANOVA, comparing only the EOS group with the healthy controls, to be >95%, assuming 10% attrition.

2.5 Ethical perspectives

The T1 and T2 study were both approved by the Regional Committee for Medical Research Ethics in Eastern Norway (REK Øst-Norge REK 1 # 98-05-04113), and the study was conducted in accordance with the Helsinki Declaration of the World Medical Assembly. The project was also approved by the Privacy Protection Ombudsman for research at the Innlandet Hospital Trust. Patients were assessed using established and standardized instruments, and

there were no known risks associated with the examination. Ample breaks were given during testing. Feedback and results were given to support their situation, and all participants were compensated with NOK 500 (Øie et al., 2011).

3 Results

3.1 Associations between cognition and internalizing problems concurrently

The results are shown in Table 4. At T1, there is a large and negative association (*rho* = -.61) between Visuomotor processing and internalizing problems, which means that the slower the processing speed, the more the internalizing problems. The correlation is statistically significant at the 0.05 level (p = .035). The association between Auditory attention/working memory and internalizing problems is small and positive (.*rho* = .25), which means that the better the working memory, the more the internalizing problems. A moderate, positive association was found between Verbal memory and internalizing problems (*rho* = .48), while the association with Cognitive flexibility is small and negative (*rho* = -.19). The correlations for Auditory attention/working memory, Cognitive flexibility and Verbal memory with internalizing problems at T1 were not significant at the 0.05 or at the 0.1 level.

At T2, there is a large and negative correlation between Verbal memory and internalizing problems (*rho* = -.54). This means that the better the Verbal memory, the less internalizing problems. The correlation is statistically significant at the 0.1 level (p = .068), and the correlation between Visuomotor processing and internalizing problems is small and positive (*rho* = .23). Cognitive flexibility has a small correlation with internalizing problems (*rho* = .19), and the association between Auditory attention/working memory and internalizing problems is non-existent (*rho* = -.0.05). The correlations for Visuomotor processing, Cognitive flexibility and Auditory attention/working memory with internalizing problems at T2 were not significant at the 0.05 or at the 0.1 level.

Table 4. *Correlations (Spearman's rho) between internalizing problems and cognitive domains at T1 and T2*

Variable	Internalizing problems T1	Sig (two-tailed)	N
Aud att/working memory T1	.25	.435	12
Visuomotor processing T1	-.61**	.035	12
Cognitive flexibility T1	-.19	.547	12
Verbal memory T1	.48	.117	12
Variable	Internalizing problems T2	Sig (two-tailed)	N
Aud att/working memory T2	-.05	.880	12
Visuomotor processing T2	.23	.477	12
Cognitive flexibility T2	.19	.552	12
Verbal memory T2	-.54*	.068	12

** Correlation is significant at the 0.05 level (two-tailed)
* Correlation is significant at the 0.1 level (two-tailed)

3.2 Associations between internalizing problems longitudinally

The associations between internalizing problems at T1 and T2 are presented in Table 5. There was no correlation between internalizing problems at T1 and T2 in the EOS group (*rho* = -.04). Parent-reported internalizing problems at T1 did not correspond with the self-reported internalizing problems at T2.

3.3 Associations between cognition and internalizing problems longitudinally

The associations between cognitive function at T1 and internalizing problems at T2 are shown in Table 5. A large negative correlation was found between Auditory attention/working memory and internalizing problems (*rho* = -.61), and this correlation was statistically significant at the 0.05 level (p = .035). The better the working memory at T1, the less the internalizing problems at T2. For Visuomotor processing, a positive, moderate correlation with internalizing problems (*rho* = .30) was found. For Verbal memory and Cognitive flexibility, a small correlation was found with internalizing problems (*rho* = -.14 and *rho* = .15 respectively). The results for these three cognitive domains were not statistically significant at 0.05 or at the 0.1 level.

Table 5. *Correlations (Spearman's rho) between internalizing problems and cognitive domains at T1 and internalizing problems at T2*

Variable	Internalizing problems T2	Sig (two-tailed)	N
Internalizing problems T1	-.04	.896	12
Aud att/working memory T1	-.61**	.035	12
Visuomotor processing T1	.30	.347	12
Cognitive flexibility T1	.15	.636	12
Verbal memory T1	-.14	.658	12

** Correlation is significant at the 0.05 level (two-tailed)

4 Discussion

The aim of the current study was to investigate the associations between cognitive functions and internalizing problems in individuals with early-onset schizophrenia (EOS), concurrently at T1 and T2, as well as longitudinally after 13 years. The discussion is structured according to the hypotheses presented. First, associations between cognition and internalizing problems concurrently at T1 and T2 are discussed, followed by a discussion of the associations between internalizing problems at T1 and T2. Lastly, the associations between cognition at T1 and internalizing problems at T2 will be discussed. At the end, some implications for treatment, strengths and limitations of the study, and possible recommendations for future research, are discussed.

4.1 Associations between cognition and internalizing problems concurrently

Hypothesis 1 was partially supported; cognition was associated with internalizing problems concurrently, both at T1 and T2. However, different cognitive domains had large associations at T1 and T2. At T1, Visuomotor processing had a large, negative and significant association with internalizing problems. The other three cognitive domains had small to moderate associations with internalizing problems, whereas at T2, Verbal memory had a large, negative and significant association with internalizing problems. Auditory attention/working memory had an almost non-existent correlation with internalizing problems, while the other cognitive domains had small correlations with internalizing problems at T2.

4.1.1 Associations concurrently at T1

The large association between Visuomotor processing and internalizing problems at T1, indicating that a slow processing speed was associated with more internalizing problems concurrently at T1, was not surprising. In general, it seems reasonable that if thought processes are slower, it is harder to keep up with everything around you, including family and friends. This could especially be the case in adolescence, which is a vulnerable age, where the activity level is high and the need to belong is strong. Furthermore, reduced processing speed may negatively affect performance in school. If adolescents are not able to keep up with their peers academically or socially, they can easily experience frustration and may develop a poor

self-concept. As a consequence they may feel left out among their peers. Eventually, being left out could contribute to depression or a feeling of inadequacy, self-doubt and anxiety. Processing speed has been associated with functional outcome in adult-onset schizophrenia in several studies (Bowie et al., 2008; Harvey, Keefe, Patterson, Heaton, & Bowie, 2009). Similarly, in a study of clinical outcome after 1 year in adult first-episode psychosis, impairments in processing speed index were a prognostic factor for poor early outcome with respect to the development or persistence of negative symptoms (Leeson et al., 2010). Associations between processing speed and depressive symptoms as measured by Hamilton Depressive Scale were not found in their study. However, the participants in the study by Leeson and colleagues (2010) were adults and considerably older (mean age = 27) than the participants in the current study at T1. In general, there is mixed evidence on the relationship between processing speed and depression (Tsourtos, Thompson, & Stough, 2002). One study found a relationship between slower processing speed and depression in elderly (Brown, Scott, Bench, & Dolan, 1994), but another study found no such association in younger patients with depression (Purcell, Maruff, Kyrios, & Pantelis, 1997). At T1, the EOS adolescents in the current study seemed to experience more internalizing problems the slower the processing speed, which is contrary to what was found in the study by Purcell and colleagues (1997). However, the participants in the latter study (Purcell, 1997), were not adolescents (mean age = 37.5) and had a diagnosis of unipolar depression, not schizophrenia.

Correlations between the other cognitive domains and internalizing problems at T1 were not statistically significant, although small to moderate in size. Hence, in the current sample there are associations between these cognitive domains and internalizing problems, but because of the small sample size and accompanying statistical power, these results cannot be generalized to larger populations of individuals with EOS.

4.1.2 Associations concurrently at T2

At T2, Verbal memory had a large, negative and significant association with internalizing problems. The direction of the association changed from positive to negative over the 13 years. The negative correlation means that the better the verbal memory, the less the internalizing problems. At T2, the patients are more mature and have more experience, both about themselves and life in general, and it is possible that this had an impact on the results. Memory is essential for making sense of the self, the world around you, who you are and

where you come from (Conway & Pleydell-Pearce, 2000; Prebble, Addis, & Tippett, 2013; Wilson & Ross, 2003). With impairments in memory, the world around you may seem more fragmented and incoherent, which may cause a feeling of insecurity, anxiety and depression. A good verbal memory will also help in remembering your own thoughts and make it easier to express what you feel, and my assumption is that it may prevent ruminative thoughts and feelings.

Furthermore, Haug (2012) found that verbal memory was associated with self-disorder in patients with schizophrenia in a way that poor verbal memory was associated with a poor feeling of identity and a weak sense of self. With good verbal memory, a person is more likely to develop a stronger representation and memory of one's own identity and understanding of self. My speculation is that a good and strong sense of identity and self may lead to less internalizing problems, such as depression, anxiety and somatic complaints. Therefore, the results of an association between Verbal memory and internalizing problems at T2 may indicate that self-disorder is a mediating variable between verbal memory and internalizing symptoms. Nevertheless, no measures on self-disorders were included in the current study, so my interpretation must been read with caution.

4.1.3 Differences in associations at T1 and T2

Both Visuomotor processing and Verbal memory had large associations with internalizing problems (at T1 and T2 respectively), but both associations changed in strength and direction over the 13 years.

In the current EOS group, a slower processing speed was associated with *more* internalizing problems in adolescence, but when they grow into young adults, slower processing speed was associated with *less* internalizing problems. The development of the cognitive functions from adolescence to adulthood could have had an impact on the different concurrent correlations at T1 and T2. A possible explanation for the results in the current study could be that as they get older, they learn how to adapt better and compensate for the slow processing, so that it is not so much associated with internalizing problems when they come into young adulthood.

The association between Verbal memory and internalizing problems was moderate, positive and non-significant at T1, but large, negative and significant at T2. The change in direction of the association may be linked to the growing up and maturing of the cognitive functions in the

individuals from T1 to T2. At T1, the EOS patients are still very young and their cognitive functions are not completely developed, particularly higher-order functions (Best & Miller, 2010). The lack of maturation of higher-order cognitive functions at T1 could mean an underdeveloped ability in reasoning and reflecting on one's own situation, hence resulting in less self-awareness and insight. However, these explanations are only speculative, and could be explored further in future research.

4.2 Associations between internalizing problems longitudinally

Hypothesis 2 was not supported; the correlation between internalizing problems at T1 and T2, was virtually non-existent and not significant. This was contrary to what was hypothesized based on previous research on internalizing problems in children at risk, or from the general population (Mesman & Koot, 2001; Petty et al., 2008; Roza et al., 2003). Based on earlier research, I predicted that internalizing problems might be linked to inherent personality traits (Forns et al., 2011), thus suggesting a possibility of stability over time. Also, since emotional dysfunction is a common feature in patients with schizophrenia, not only at onset, but throughout the course of the illness (Birchwood, 2003), it seemed plausible that internalizing problems at T1 would be associated with internalizing problems at T2.

There could be different explanations for the non-existent correlation, with one possibly being that the EOS group had a high level of internalizing problems, both at T1 and T2, as shown in the previous study of the same sample group (Øie et al., 2011). According to Cohen's *d*, the significant differences between the EOS group and the healthy controls were large, both at T1 (Cohen's $d = 1.42$) and at T2 (Cohen's $d = 2.19$). Øie and colleagues (2011) have also previously shown that the healthy control group had a decline in internalizing problems over the 13 years, whereas the EOS group was at a stable high level over the 13 years. However, the high scores of internalizing problems at both T1 and T2 among the individuals in the EOS group implies that individuals in the EOS group had scores within a small area of the internalizing problems scale at both data collections. Thus, the lack of correlation between the T1 and T2 values might be explained by random variations within a small width of the scale in between the two data collections.

Another possible explanation could be differences in the rating of internalizing problems between parents (T1) and the self-report of the children/adolescents (T2). At T1, the parents rated their children using the CBCL, while at T2 the patients rated themselves, using ABCL. Because most of the young adults did not live with their parents at T2, it was difficult for the parents to rate their children in a valid way. There is evidence of discrepancies between adolescent- and parent rating using similar versions of questionnaires (Van Roy, Groholt, Heyerdahl, & Clench-Aas, 2010). In a sample of adolescents admitted for emotional and behavioral problems, Handwerk and colleagues (1999) found that there were discrepancies in how the parent and adolescent rated on the CBCL Internalizing scale (Handwerk, Larzelere, Soper, & Friman, 1999), and the discrepancies were larger for the older adolescents (ages 15-18) than for the younger ones (ages 11-14) (Handwerk et al., 1999). In clinical samples, it has generally been found that adults are rating behavioral and emotional problems in their children as more severe than the children are rating themselves (Handwerk et al., 1999). Internalizing problems are by nature more covert, than for example externalizing problems. Thus, the problems may not be so detectable for others than the patients themselves. Schizophrenia is also highly associated with a reduced insight (Buckley et al., 2007), which could be an explanatory factor for the difference in the rating between adolescents and parents, as the adolescents may not be aware of certain aspects of their own situation.

Lastly, previous research on the predictive value of the Internalizing scale of the CBCL has been done on younger children than in the current EOS group, and the research has been done on other clinical groups or normal controls. Individuals with EOS have a neurodevelopmental disorder, and the internalizing symptoms may develop or modify differently in this vulnerable group compared to other individuals. For this reason, the internalizing problems at T1 may not be as stable over time as in other individuals, because the schizophrenia disorder may interact with internalizing problems differently compared to other clinical groups or healthy individuals.

4.3 Associations between cognition and internalizing problems longitudinally

Hypothesis 3 was partially supported; Auditory attention/working memory at T1 had a large, negative and significant correlation with internalizing problems at T2, whereas the other cognitive domains had small to medium non-significant correlations with internalizing

problems. Visuomotor processing at T1 was moderately correlated with internalizing problems at T2, while Cognitive flexibility and Verbal memory at T1 correlated to a lesser degree with internalizing problems at T2.

In general, all the cognitive measures at T1 correlated inversely with internalizing problems reported by the individuals in the EOS group at T2. This means that the more impaired cognition in adolescent years, the more internalizing problems in the young adult years. In previous findings from the same sample group regarding functional outcome at T2, Øie and colleagues (2011) found that in general, the more impaired in cognition the EOS patients were in adolescence, the worse the functional outcome in young adulthood. Most of the EOS patients were characterized by a poor social and general functioning, they were less educated, single, lived alone and were largely unemployed at T2 (Øie et al., 2011).

In the previously mentioned study (Øie et al., 2011), all three cognitive domains: Auditory attention/working memory, Visuomotor processing and Executive function (Cognitive flexibility) were significantly correlated with social functioning longitudinally, whereas in the current study only Auditory attention/working memory at T1 had a large, negative and significant correlation with internalizing problems at T2. The significance of the results for the current sample is that the more impaired the Auditory attention/working memory in adolescence, the more the internalizing problems in young adulthood. How can these results be explained?

As previously mentioned, working memory is enabling a limited amount of information to be available for further cognitive processing. Working memory consists of an auditory and a visual component (Baddeley & Hitch, 1974), however it should be noted that only the auditory component was included in the measure of working memory in the current study. In complex cognition such as reasoning and problem solving, working memory is especially important in handling new and unknown information, as well as integrating information from multiple sources. To sequentially build on previous knowledge in a learning process may become a problem when working memory is impaired (Lepage et al., 2014). Impairments in working memory have been shown to significantly limit the ability to acquire, retain or relearn skills necessary for everyday functioning, such as forming relationships and undertaking employment (Lasser et al., 2007). If working memory is impaired, the individuals in the EOS group may have had problems with such everyday functioning. The adolescents in the current study were young, and they attended high school at T1. First and foremost,

impairments in working memory for them could lead to problems with concentration in academic settings at school. Problems in school at a young age could lead to difficulties in getting into further education and getting a job later in life. Working memory is frequently associated with struggling with academic performance (Gathercole & Alloway, 2008), so it is possible that problems in everyday life due to working memory problems might have increased internalizing problems as a consequence.

As already mentioned, poor working memory may also affect other aspects of daily living such as social functioning (McQuade, Murray-Close, Shoulberg, & Hoza, 2013). Difficulties with social relations due to problems with keeping up in a conversation or social exchange are typical examples. A study by McQuade and colleagues (2013) on fourth- and fifth-grade school children from the general population supports this. McQuade and colleagues (2013) found that poorer verbal storage working memory was significantly associated with greater peer rejection, less overall social competence, deficits in conflict resolution skills and greater physical and relational aggression. Social isolation and withdrawal might be a result of feeling inadequate in settings with peers at school and could make the situation worse. Consequently, feeling inadequate, being isolated and socially withdrawn may possibly lead to depressive symptoms, anxiety and somatic issues. The more socially isolated one gets, the harder it is to establish relationships with peers or otherwise create a social network. In the previous study by Øie and colleagues (2011), working memory was a strong predictor of social functioning at T2 in the same, but larger sample group. A possibility is that poorer working memory affects social function negatively, which may cause internalizing problems, i.e. that social function is a mediating variable.

Depression and self-concept are believed to be connected because diminished self-esteem is often prominent in depressive disorders (Kazdin, 1990). Struggling academically and socially at school, difficulties in making friendships, loneliness and being unemployed may influence self-esteem and the feeling of worthiness, which could be a mediating factor for internalizing problems. Karatzias and colleagues (2007) investigated whether lower self-esteem and negative beliefs about the illness were associated with anxiety and other affective disorders in a sample of adults diagnosed with schizophrenia (Karatzias, Gumley, Power, & O'Grady, 2007). They found a strong association between beliefs about the self and the illness, as well as the comorbidity of anxiety and affective disorders, which suggests that self-esteem may be linked to the development and maintenance of affective disorders in schizophrenia (Karatzias

et al., 2007). Whitcomb and Merrell (2013) also claim that it is logical to assume that self-esteem and internalizing problems may be negatively associated, i.e. the lower the self-esteem, the higher the level of internalizing problems (Whitcomb & Merrell, 2013). Although measures of self-esteem were not included in the current study, it is still worth mentioning the possible mediating role, even though it is only speculative and may be the subject of further research.

Working memory is connected to important processes of self-regulation (Hofmann et al., 2012), of which the directing of attention to adaptive behavior is one of the elements. The capacity to focus attention is connected to the regulation of thoughts and feelings. According to this notion, working memory is important for suppressing ruminative thoughts and feelings and to downregulate unwanted affect, which could therefore develop into depression or anxiety. Problems in this capacity can lead to increased rumination and negative affect. Other work has also shown that working memory supports multiple stages in emotion regulation (Gross, 1998; Hofmann et al., 2012). Difficulties with emotion regulation were associated with more internalizing problems in adolescence from the general public in a study by Silk and colleagues (Silk, Steinberg, & Morris, 2003). The EOS group was diagnosed with a severe illness at a vulnerable time in their life. Hence, it is possible that experiencing such a traumatic life event early on led to sadness, negative thoughts and feelings, which they have had difficulties processing at an early age. For this reason, impaired working memory might have contributed to poorer emotion-regulation and consequently led to internalizing problems.

Another explanation for the large association between impaired working memory at T1 and internalizing problems at T2 could be that when someone is having problems with keeping information for further processing, therapy may be difficult. One speculation is that it is possible that certain types of psychotherapy or psychoeducative treatment do not have the desired effect because the patient is having problems following the thought processes, or having difficulties in learning about their illness and how to best handle it. With cognitive impairments, it may also be difficult to take advantage of a possible cognitive rehabilitation process.

Cognitive flexibility at T1 had only a small non-significant correlation with internalizing problems at T2. Cognitive flexibility is another component of executive functions, and enables a shifting between mental sets (Hofmann et al., 2012). Although the executive functions are closely linked to each other, they are also distinct domains (Miyake, Friedman,

et al., 2000). Research shows that the Cognitive flexibility domain has not been linked to emotion-regulation in the way that working memory has (Hofmann et al., 2012), which might explain why there is only a small correlation with internalizing problems in the current study. The small sample size in the current study could also be an explanatory factor. As a result, there is a chance that this correlation would have been significant with a larger sample size.

In conclusion, it is important to stress that cognition in adolescent years is associated with internalizing problems in young adults with early-onset schizophrenia. Some associations have been identified as stronger than others in this study. However, the different cognitive domains may also influence each other, due to the interconnected neural networks (Fries, 2005). For example, many higher-order processes require simultaneous access to many sources of information (Butters et al., 2004). If the processing speed is too slow, the needed information will not be available to perform the task at hand. This is essentially the *cognitive speed hypothesis* (Rodríguez-Sánchez, Crespo-Facorro, Gonzalez-Blanch, Perez-Iglesias, & Vazquez-Barquero, 2007; Snyder, 2013). Similarly, working memory is not only a passive storage of information, but rather storage for ongoing processes (Butters et al., 2004). Impairments can cause many higher-order processes to fail, e.g. language tasks or reasoning (Gathercole, 1994). Although only Auditory attention/working memory, Visuomotor processing and Verbal memory had significant associations with internalizing problems, it does not mean that the other cognitive domains are not important.

4.4 Implications for treatment of individuals with EOS

Information and insight regarding individuals with EOS are needed in order to develop appropriate treatment and interventions. More information about the factors associated with internalizing problems in individuals with EOS could eventually contribute to better outcomes. As mentioned previously, two of the participants in the EOS group were deceased at T2, one had committed suicide and the other died from an overdose following a medical complication. The fact that 10% of the sample group had died in such circumstances after 13 years shows the importance of studying this group to acquire more insight into what is associated with internalizing problems in individuals with EOS.

It is important to map the possible cognitive impairments early, and to offer supplementary services in order to compensate for any cognitive limitations. Extensive assistance in school is essential in order to facilitate the learning processes and the social interaction with peers, and choosing the right career or adapting to a job situation would also be advantageous. Offering psychoeducation and support to the patients and their families is vital. Cognitive training in adolescence and adulthood should be considered in addition to other treatment programs with the intention of reducing cognitive impairments and learning how to compensate for them by using other strategies. Cognitive training involves different techniques and exercises depending on the impairments (Ueland & Rund, 2004). Recent research has focused on how the cognitive training can be applied to everyday daily function; thus, it is important to make the training relevant for the patient and maybe incorporate it into immersed rehabilitation. A study on the effects of a cognitive remediation program on adolescents with early-onset psychosis indicated that the remediation program may have beneficial effects for some aspects of cognition, and possibly an indirect effect on functional outcome (Ueland & Rund, 2004).

4.5 Strengths and limitations of the study

The longitudinal and prospective design, an assessment of patients early in the illness and a high retention rate are clear strengths of the current study. Only bivariate correlations were included, since multivariate analyses would be difficult with the small *n*. However, large and significant correlations were found between some of the variables in this study, which must be considered a strength taking into account the small sample size. In a review by Díaz-

Caneja (2015), the importance of bivariate studies is highlighted because of the general scarcity of available EOS research (Diaz-Caneja et al., 2015). Including a healthy control group is another strength, as it enables a comparison of scores between the two groups from the same country to establish what is impaired in the EOS group.

However, there are also certain limitations of the current study. The main limitation is the small sample size, which reduces the statistical power of the tests. Only data from 12 patients in the EOS group was available for analysis at follow-up, and differences in correlations are difficult to detect when the sample is so small. A small sample is a common problem in longitudinal studies of adolescents with schizophrenia, due to the rarity of the illness and of the repeat design (Cervellione et al., 2007). In this study, significant correlations were found between a few of the cognitive domains and internalizing problems at T1 and T2, and from T1 to T2. Nonetheless, there might be correlations that are not reaching a significance level due to the small sample size. Also, although strong associations have been found between cognition and internalizing problems, the direction is less clear. It could be that cognitive impairments are influencing the level of internalizing problems or the other way around.

Some patients were assessed without medication at baseline, and with medication at follow-up. The patients have also received different types of treatment, which could have affected the results in general. It has been documented that antipsychotic medication has a minimal effect on cognition (Keefe, Bilder, et al., 2007; Keefe, Sweeney, et al., 2007), although one cannot completely rule out the possibility of confounding medication effects.

The CBCL has been proven to have good psychometric properties, and is widely used to measure emotional/behavior problems. However, the Internalizing scale is a composite scale including the subscales of depression, anxiety and somatic complaints, which may cause imprecision, particularly when comparing to other studies where only depression or anxiety has been studied (Whitcomb & Merrell, 2013).

Finally, it should be noted that IQ has not been controlled for in this study because using IQ as a covariate may reduce some of the variation in cognition since lower IQ may be considered an attribute of having schizophrenia (Dennis et al., 2009)

4.6 Recommendations for further research

In the current study, some clear associations have been identified. Even so, there might be associations that have not been identified due to a lack of statistical power. Therefore, it is recommended to replicate this study in a longitudinal design and with a larger sample size. Moreover, the small *n* made it difficult to run regression analyses controlling for several variables. Hence, mediating variables such as social function, difficulties in school, relational problems or self-esteem have so far not been identified in this context, and could be explored. Further research is needed to investigate how these variables might relate to each other.

The special interest in internalizing problems in the current study was due to the interaction effects on the Internalizing scale in the previous study by Øie and colleagues (2011), showing that subjects with EOS had the same high level of internalizing problems at both times. Yet, studies of other populations have shown that there is an association between externalizing problems and later internalizing problems (Keiley et al., 2003). Therefore, exploring the significance of externalizing problems could be a topic for future research.

Recent research has shown that social cognition also has a strong correlation to functional outcome (Fett, Viechtbauer, Penn, van Os, & Krabbendam, 2011). The social cognition domain was not included at baseline in the current study because there was little focus on social cognition at that point. However, the significance of it should not be left out, and it is possible that social cognition is a mediating variable in the current study that needs to be further investigated.

Primarily due to the limited scope, positive and negative symptoms were not included in the current study. Although there is already quite a bit of research on psychosis symptoms and clinical outcome in adult-onset schizophrenia, little research still exists on individuals with EOS. Especially since negative symptoms and depression sometimes are confused, it would be advantageous to have more research in this field.

5 Conclusion

The goal of the current study was to investigate the association between cognition and internalizing problems in young individuals with EOS. Even though there is increasing interest in research on outcome in schizophrenia, few studies exist on early-onset schizophrenia. To the best of my knowledge, this is the first study to investigate the relation between cognition and clinical outcome by using the CBCL Internalizing scale. The results showed that there is an association between cognition and internalizing problems, both concurrently at baseline, concurrently at follow-up after 13 years and between cognition at T1 and internalizing problems at T2. There was a large, negative and significant correlation between Visuomotor processing and internalizing problems concurrently at T1. At T2, there was a large, negative and significant correlation between Verbal memory and internalizing problems, but no association between internalizing problems at T1 and T2. Furthermore, a large, negative and significant correlation was found in the EOS group between Auditory attention/working memory at T1 and internalizing problems at T2.

The associations between different cognitive domains at different times in the life-cycle could be connected to a difference in maturity in cognitive functions between adolescence and adulthood. The findings are strong and significant in a small sample group, and the results also have implications for the treatment of individuals with EOS. A focus on facilitation, understanding and training of cognitive impairments at an early age should be intensified in order to prevent internalizing problems from developing.

References

Abas, M. A., Sahakian, B. J., & Levy, R. (1990). Neuropsychological deficits and CT scan changes in elderly depressives. *Psychological Medicine, 20*(03), 507-520.

Achenbach, T. M. (1966). The classification of children's psychiatric symptoms: A factor-analytic study. *Psychological Monographs: General and Applied, 80*(7), 1-37.

Achenbach, T. M. (1991). *Manual for the Child Behavior Checklist / 4-18 and 1991 Profile*. Burlington: University of Vermont.

Achenbach, T. M., & Rescorla, L. A. (2003). *Manual for the ASEBA Adult Forms & Profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Achim, A. M., Maziade, M., Raymond, É., Olivier, D., Mérette, C., & Roy, M.-A. (2011). How prevalent are anxiety disorders in schizophrenia? A meta-analysis and critical review on a significant association. *Schizophrenia Bulletin, 37*(4), 811-821.

Ackerson, L. (1942). *Children's behavior problems. Vol. II: Relative importance and interrelations among traits*. Chicago: University of Chicago Press.

Afridi, M. I., Hina, M., Qureshi, I. S., & Hussain, M. (2011). Cognitive disturbance comparison among drug-naïve depressed cases and healthy controls. *Journal of the College of Physicians and Surgeons–Pakistan, 21*, 351-355.

Allott, K., Liu, P., Proffitt, T.-M., & Killackey, E. (2011). Cognition at illness onset as a predictor of later functional outcome in early psychosis: Systematic review and methodological critique. *Schizophrenia Research, 125*(2), 221-235.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.): American Psychiatric Association.

Amminger, G. P., Henry, L. P., Harrigan, S. M., Harris, M. G., Alvarez-Jimenez, M., Herrman, H., . . . McGorry, P. D. (2011). Outcome in early-onset schizophrenia revisited: Findings from the Early Psychosis Prevention and Intervention Centre long-term follow-up study. *Schizophrenia Research, 131*(1), 112-119.

Bachman, P., Niendam, T. A., Jalbrzikowkski, M., Park, C. Y., Daley, M., Cannon, T. D., & Bearden, C. E. (2012). Processing speed and neurodevelopment in adolescent-onset psychosis: Cognitive slowing predicts social function. *Journal of Abnormal Child Psychology, 40*(4), 645-654.

Baddeley, A. D., & Hitch, G. (1974). Working memory. *Psychology of Learning and Motivation, 8*, 47-89.

Bedwell, J. S., Keller, B., Smith, A. K., Hamburger, S., Kumra, S., & Rapoport, J. L. (1999). Why does postpsychotic IQ decline in childhood-onset schizophrenia? *American Journal of Psychiatry, 156*(12), 1996-1997.

Bermanzohn, P. C., Porto, L., Arlow, P. B., Pollack, S., Stronger, R., & Siris, S. G. (2000). Hierarchical diagnosis in chronic schizophrenia: A clinical study of co-occurring syndromes. *Schizophrenia Bulletin, 26*(3), 517-525.

Bertelsen, M., Jeppesen, P., Petersen, L., Thorup, A., Øhlenschlaeger, J., Le Quach, P., . . . Nordentoft, M. (2007). Suicidal behaviour and mortality in first-episode psychosis: The OPUS trial. *The British Journal of Psychiatry, 191*(51), 140-146.

Best, J. R., & Miller, P. H. (2010). A developmental perspective on executive function. *Child Development, 81*(6), 1641-1660.

Birchwood, M. (2003). Pathways to emotional dysfunction in first-episode psychosis. *The British Journal of Psychiatry, 182*(5), 373-375. doi: 10.1192/bjp.182.5.373

Birchwood, M., Iqbal, Z., Chadwick, P., & Trower, P. (2000). Cognitive approach to depression and suicidal thinking in psychosis. *I. Ontogeny of post-psychotic depression, 177*(6), 516-528. doi: 10.1192/bjp.177.6.516

Birchwood, M., Mason, R., MacMillan, F., & Healy, J. (1993). Depression, demoralization and control over psychotic illness: A comparison of depressed and non-depressed patients with a chronic psychosis. *Psychological Medicine, 23*(02), 387-395.

Birchwood, M., Trower, P., Brunet, K., Gilbert, P., Iqbal, Z., & Jackson, C. (2007). Social anxiety and the shame of psychosis: A study in first-episode psychosis. *Behaviour Research and Therapy, 45*(5), 1025-1037. doi: http://dx.doi.org/10.1016/j.brat.2006.07.011

Bleuler, E. (1911). *Dementia praecox or the group of schizophrenias*. New York: International University Press.

Bowie, C. R., Leung, W. W., Reichenberg, A., McClure, M. M., Patterson, T. L., Heaton, R. K., & Harvey, P. D. (2008). Predicting schizophrenia patients' real-world behavior with specific neuropsychological and functional capacity measures. *Biological Psychiatry, 63*(5), 505-511.

Brown, R., Scott, L., Bench, C., & Dolan, R. (1994). Cognitive function in depression: Its relationship to the presence and severity of intellectual decline. *Psychological Medicine, 24*(04), 829-847.

Buckley, P. F., Wirshing, D. A., Bhushan, P., Pierre, J. M., Resnick, S. A., & Wirshing, W. C. (2007). Lack of insight in schizophrenia. *CNS Drugs, 21*(2), 129-141. doi: 10.2165/00023210-200721020-00004

Butters, M. A., Whyte, E. M., Nebes, R. D., Begley, A. E., Dew, M. A., Mulsant, B. H., . . . Pollock, B. G. (2004). The nature and determinants of neuropsychological functioning in late-life depression. *Archives of General Psychiatry, 61*(6), 587-595.

Cassano, G. B., Pini, S., Saettoni, M., & Dell'Osso, L. (1999). Multiple anxiety disorder comorbidity in patients with mood spectrum disorders with psychotic features. *American Journal of Psychiatry, 156*(3), 474-476.

Castle, D., & Bosanac, P. (2012). Depression and schizophrenia. *Advances in Psychiatric Treatment, 18*(4), 280-288. doi: 10.1192/apt.bp.111.008961

Cederlund, M., Hagberg, B., & Gillberg, C. (2010). Asperger syndrome in adolescent and young adult males. Interview, self-and parent assessment of social, emotional, and cognitive problems. *Research in Developmental Disabilities, 31*(2), 287-298.

Cervellione, K. L., Burdick, K. E., Cottone, J. G., Rhinewine, J. P., & Kumra, S. (2007). Neurocognitive deficits in adolescents with schizophrenia: Longitudinal stability and predictive utility for short-term functional outcome. *Journal of the American Academy of Child & Adolescent Psychiatry, 46*(7), 867-878.

Chen, W. J., Faraone, S. V., Biederman, J., & Tsuang, M. T. (1994). Diagnostic accuracy of the Child Behavior Checklist scales for attention-deficit hyperactivity disorder: A receiver-operating characteristic analysis. *Journal of Consulting and Clinical Psychology, 62*(5), 1017-1025.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed. ed.). Hillsdale, N. J: Laurence Erlbaum.

Conway, M. A., & Pleydell-Pearce, C. W. (2000). The construction of autobiographical memories in the self-memory system. *Psychological Review, 107*(2), 261-288.

Cosoff, S. J., & Hafner, R. J. (1998). The prevalence of comorbid anxiety in schizophrenia, schizoaffective disorder and bipolar disorder. *Australian & New Zealand Journal of Psychiatry, 32*(1), 67-72. doi: 10.3109/00048679809062708

Crowe, S. F., Matthews, C., & Walkenhorst, E. (2007). Relationship between worry, anxiety and thought suppression and the components of working memory in a non-clinical sample. *Australian Psychologist, 42*(3), 170-177.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (1987). *The California Verbal Learning Test (CVLT) manual*. New York: Psychological Corporation.

Dennis, M., Francis, D. J., Cirino, P. T., Schachar, R., Barnes, M. A., & Fletcher, J. M. (2009). Why IQ is not a covariate in cognitive studies of neurodevelopmental disorders. *Journal of the International Neuropsychological Society, 15*(03), 331-343.

Diaz-Caneja, C. M., Pina-Camacho, L., Rodriguez-Quiroga, A., Fraguas, D., Parellada, M., & Arango, C. (2015). Predictors of outcome in early-onset psychosis: A systematic review. *npj Schizophrenia, 1*, 14005. doi: 10.1038/npjschz.2014.5

Drake, R., Whitaker, A., Gates, C., & Cotton, P. (1985). Suicide among schizophrenics: A review. *Comprehensive Psychiatry, 26*(1), 90-100.

Drotar, D., Stein, R. E., & Perrin, E. C. (1995). Methodological issues in using the Child Behavior Checklist and its related instruments in clinical child psychology research. *Journal of Clinical Child Psychology, 24*(2), 184-192.

Evensen, S., Wisløff, T., Lystad, J. U., Bull, H., Ueland, T., & Falkum, E. (2016). Prevalence, employment rate, and cost of schizophrenia in a high-income welfare society: A population-based study using comprehensive health and welfare registers. *Schizophrenia Bulletin, 42*(2), 476-483. doi: 10.1093/schbul/sbv141

Fagerlund, B., Pagsberg, A. K., & Hemmingsen, R. P. (2006). Cognitive deficits and levels of IQ in adolescent onset schizophrenia and other psychotic disorders. *Schizophrenia Research, 85*(1), 30-39.

Fatemi, S. H., & Folsom, T. D. (2009). The neurodevelopmental hypothesis of schizophrenia, revisited. *Schizophrenia Bulletin, 35*(3), 528-548. doi: 10.1093/schbul/sbn187

Fenton, W. S. (2000). Depression, suicide, and suicide prevention in schizophrenia. *Suicide and Life-Threatening Behavior, 30*(1), 34-49.

Fett, A.-K. J., Viechtbauer, W., Penn, D. L., van Os, J., & Krabbendam, L. (2011). The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: A meta-analysis. *Neuroscience & Biobehavioral Reviews, 35*(3), 573-588.

Fish, B., & Shapiro, T. (1964). A descriptive typology of children´s psychiatric disorders. II. A behavioral classification. In R. L. Jenkins & J. O. Cole (Eds.), *American Psyciatric*

Association Psychiatric Research Reports 18 (pp. 75-90). Washington DC: American Psyciatric Association.

Fombonne, E., Wostear, G., Cooper, V., Harrington, R., & Rutter, M. (2001). The Maudsley long-term follow-up of child and adolescent depression. *The British Journal of Psychiatry, 179*(3), 210-217.

Forbes, E. E., & Dahl, R. E. (2010). Pubertal development and behavior: Hormonal activation of social and motivational tendencies. *Brain and Cognition, 72*(1), 66-72.

Forns, M., Abad, J., & Kirschner, T. (2011). Internalizing and externalizing problems. In R. J. R. Leveque (Ed.), *Enzyclopedia of Adolescence*. New York: Springer.

Frangou, S. (2006). Early onset schizophrenia: Cognitive and clinical characteristics. In P. D. Harvey & T. Sharma (Eds.), *The early course of schizophrenia* (pp. 60-69). New York: Oxford University Press.

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

Frangou, S., Hadjulis, M., & Vourdas, A. (2008). The Maudsley early onset schizophrenia study: Cognitive function over a 4-year follow-up period. *Schizophrenia Bulletin, 34*(1), 52-59.

Fries, P. (2005). A mechanism for cognitive dynamics: Neuronal communication through neuronal coherence. *Trends in Cognitive Sciences, 9*(10), 474-480. doi: http://doi.org/10.1016/j.tics.2005.08.011

Gathercole, S. E. (1994). Neuropsychology and working memory: A review. *Neuropsychology, 8*(4), 494-505.

Gathercole, S. E., & Alloway, T. P. (2008). *Working memory and learning : A practical guide for teachers*. Los Angeles: SAGE.

Gochman, P. A., Greenstein, D., Sporn, A., Gogtay, N., Keller, B., Shaw, P., & Rapoport, J. L. (2005). IQ stabilization in childhood-onset schizophrenia. *Schizophrenia Research, 77*(2), 271-277.

Graber, J. A. (2004). Internalizing problems during adolescence *Handbook of Adolescent Psychology* New York: John Wiley & Sons, Inc.

Green, M. F., & Harvey, P. D. (2014). Cognition in schizophrenia: Past, present, and future. *Schizophrenia Research. Cognition, 1*(1), e1-e9. doi: 10.1016/j.scog.2014.02.001

Gross, J. J. (1998). The emerging field of emotion regulation: An integrative review. *Review of General Psychology, 2*(3), 271-299.

Häfner, H., Löffler, W., Maurer, K., Hambrecht, M., & Heiden, W. (1999). Depression, negative symptoms, social stagnation and social decline in the early course of schizophrenia. *Acta Psychiatrica Scandinavica, 100*(2), 105-118.

Häfner, H., Maurer, K., Trendler, G., An Der Heiden, W., & Schmidt, M. (2005). The early course of schizophrenia and depression. *European Archives of Psychiatry and Clinical Neurosciences, 255*(3), 167-173. doi: 10.1007/s00406-005-0584-8

Häfner, H., Riecher-Rössler, A., Hambrecht, M., Maurer, K., Meissner, S., Schmidtke, A., . . . van der Heiden, W. (1992). IRAOS: An instrument for the assessment of onset and early course of schizophrenia. *Schizophrenia Research, 6*(3), 209-223.

Handwerk, M. L., Larzelere, R. E., Soper, S. H., & Friman, P. C. (1999). Parent and child discrepancies in reporting severity of problem behaviors in three out-of-home settings. *Psychological Assessment, 11*(1), 14-23.

Harvey, P. D., Keefe, R. S., Patterson, T. L., Heaton, R. K., & Bowie, C. R. (2009). Abbreviated neuropsychological assessment in schizophrenia: Prediction of different aspects of outcome. *Journal of Clinical and Experimental Neuropsychology, 31*(4), 462-471.

Harvey, P. D., & Penn, D. (2010). Social cognition: The key factor predicting social outcome in people with schizophrenia? *Psychiatry (Edgmont), 7*(2), 41-44.

Haug, E., Melle, I., Andreassen, O. A., Raballo, A., Bratlien, U., Lien, L., & Møller, P. (2012). The association between self-disorders and neurocognitive dysfunction in schizophrenia. *Schizophrenia Research, 135*(1), 79-83.

Hausmann, A., & Fleischhacker, W. (2002). Differential diagnosis of depressed mood in patients with schizophrenia: A diagnostic algorithm based on a review. *Acta Psychiatrica Scandinavica, 106*(2), 83-96.

Heald, A., Morris, J., & Soni, S. D. (2008). Characterisation of depression in patients with schizophrenia. *Indian Journal of Medical Research, 127*(6), 544-550.

Heaton, R. K. (1981). *Wisconsin Card Sorting Test, Manual*. Odessa, FL: Psychological Assessment Resources.

Hofmann, W., Schmeichel, B. J., & Baddeley, A. D. (2012). Executive functions and self-regulation. *Trends in Cognitive Sciences, 16*(3), 174-180.

Holmén, A., Juuhl-Langseth, M., Thormodsen, R., Melle, I., & Rund, B. R. (2009). Neuropsychological profile in early-onset schizophrenia-spectrum disorders:

Measured with the MATRICS battery. *Schizophrenia Bulletin, 36*(4), 852-859. doi: 10.1093/schbul/sbn174

Ivanova, M. Y., Achenbach, T. M., Dumenci, L., Rescorla, L. A., Almqvist, F., Weintraub, S., . . . Dobrean, A. (2007). Testing the 8-syndrome structure of the Child Behavior Checklist in 30 societies. *Journal of Clinical Child and Adolescent Psychology, 36*(3), 405-417.

Jaeger, J., Berns, S., Uzelac, S., & Davis-Conway, S. (2006). Neurocognitive deficits and disability in major depressive disorder. *Psychiatry Research, 145*(1), 39-48.

Jarbin, H., & Von Knorring, A.-L. (2004). Suicide and suicide attempts in adolescent-onset psychotic disorders. *Nordic Journal of Psychiatry, 58*(2), 115-123.

Johannessen, J. O. (2002). Schizofreni - omfang og betydning. *Tidsskrift - Norske Laegeforening, 122*(20), 2011-2014.

Johnstone, E. C., Ebmeier, K. P., Miller, P., Owens, D. G., & Lawrie, S. M. (2005). Predicting schizophrenia: Findings from the Edinburgh high-risk study. *The British Journal of Psychiatry, 186*(1), 18-25.

Kane, M. J., Bleckley, M. K., Conway, A. R., & Engle, R. W. (2001). A controlled-attention view of working-memory capacity. *Journal of Experimental Psychology: General, 130*(2), 169-183.

Karatzias, T., Gumley, A., Power, K., & O'Grady, M. (2007). Illness appraisals and self-esteem as correlates of anxiety and affective comorbid disorders in schizophrenia. *Comprehensive Psychiatry, 48*(4), 371-375. doi: http://dx.doi.org/10.1016/j.comppsych.2007.02.005

Kazdin, A. E. (1990). Childhood Depression. *Journal of Child Psychology and Psychiatry, 31*(1), 121-160. doi: 10.1111/j.1469-7610.1990.tb02276.x

Keefe, R. S., Bilder, R. M., Davis, S. M., Harvey, P. D., Palmer, B. W., Gold, J. M., . . . Stroup, T. S. (2007). Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Archives of General Psychiatry, 64*(6), 633-647.

Keefe, R. S., Sweeney, J. A., Gu, H., Hamer, R. M., Perkins, D. O., McEvoy, J. P., & Lieberman, J. A. (2007). Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: A randomized, double-blind 52-week comparison. *American Journal of Psychiatry, 164*(7), 1061-1071.

Keiley, M. K., Lofthouse, N., Bates, J. E., Dodge, K. A., & Pettit, G. S. (2003). Differential risks of covarying and pure components in mother and teacher reports of externalizing and internalizing behavior across ages 5 to 14. *Journal of Abnormal Child Psychology, 31*(3), 267-283.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., . . . Wang, P. S. (2003). The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). *Jama, 289*(23), 3095-3105.

Kornør, H., & Jozefiak, T. (2012). Måleegenskaper ved den norske versjonen av Child Behavior Checklist (CBCL). *PsykTestBarn.* 1:3. Retrieved March 29th 2017, Retrieved from www.psyktestbarn.no

Krabbendam, L., Hanssen, M., Bak, M., & Van Os, J. (2004). Psychotic features in the general population. Risk factors for what? In W. F. Gattaz & H. Häfner (Eds.), *Search for the Causes of Schizophrenia: Volume V* (pp. 54-78). Heidelberg: Steinkopff.

Kravariti, E., Morris, R. G., Rabe-Hesketh, S., Murray, R. M., & Frangou, S. (2003). The Maudsley early onset schizophrenia study: Cognitive function in adolescents with recent onset schizophrenia. *Schizophrenia Research, 61*(2), 137-148.

Kroes, M., Kalff, A. C., Steyaert, J., Kessels, A. G. H., Feron, F. J. M., Hendriksen, J. G. M., . . . Vles, J. S. H. (2002). A longitudinal community study: Do psychosocial risk factors and Child Behavior Checklist Scores at 5 years of age predict psychiatric diagnoses at a later age? *Journal of the American Academy of Child & Adolescent Psychiatry, 41*(8), 955-963. doi: http://dx.doi.org/10.1097/00004583-200208000-00014

Kumra, S., Wiggs, E., Bedwell, J., Smith, A. K., Arling, E., Albus, K., . . . Rapoport, J. L. (2000). Neuropsychological deficits in pediatric patients with childhood-onset schizophrenia and psychotic disorder not otherwise specified. *Schizophrenia Research, 42*(2), 135-144.

Lasser, R. A., Nasrallah, H., Helldin, L., Peuskens, J., Kane, J., Docherty, J., & Tronco, A. T. (2007). Remission in schizophrenia: Applying recent consensus criteria to refine the concept. *Schizophrenia Research, 96*(1), 223-231.

Ledda, M. G., Fratta, A. L., Pintor, M., Zuddas, A., & Cianchetti, C. (2009). Early-onset psychoses: Comparison of clinical features and adult outcome in 3 diagnostic groups. *Child Psychiatry and Human Development, 40*(3), 421-437.

Leeson, V. C., Barnes, T. R., Harrison, M., Matheson, E., Harrison, I., Mutsatsa, S. H., . . . Joyce, E. M. (2010). The relationship between IQ, memory, executive function, and

processing speed in recent-onset psychosis: 1-year stability and clinical outcome. *Schizophrenia Bulletin, 36*(2), 400-409.

Lepage, M., Bodnar, M., & Bowie, C. R. (2014). Neurocognition: Clinical and functional outcomes in schizophrenia. *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie, 59*(1), 5-12.

Levesque, R. J. R., Levesque, R. J. R., & SpringerLink. (2011). *Encyclopedia of Adolescence*

Matheson, S. L., Vijayan, H., Dickson, H., Shepherd, A. M., Carr, V. J., & Laurens, K. R. (2013). Systematic meta-analysis of childhood social withdrawal in schizophrenia, and comparison with data from at-risk children aged 9–14 years. *Journal of Psychiatric Research, 47*(8), 1061-1068.

McQuade, J. D., Murray-Close, D., Shoulberg, E. K., & Hoza, B. (2013). Working memory and social functioning in children. *Journal of Experimental Child Psychology, 115*(3), 422-435.

Merrell, K. W. (2008). *Helping students overcome depression and anxiety: A practical guide.* (2nd ed.). New York: Guilford.

Mesman, J., & Koot, H. M. (2001). Early preschool predictors of preadolescent internalizing and externalizing DSM-IV diagnoses. *Journal of the American Academy of Child & Adolescent Psychiatry, 40*(9), 1029-1036. doi: http://dx.doi.org/10.1097/00004583-200109000-00011

Miles, C. P. (1977). Conditions predisposing to suicide: A review. *The Journal of Nervous and Mental Disease, 164*(4), 231-246.

Miyake, A., Emerson, M. J., & Friedman, N. P. (2000). *Assessment of executive functions in clinical settings: Problems and recommendations.* Paper presented at the Seminars in speech and language.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cognitive Psychology, 41*(1), 49-100.

Monsell, S. (1996). Control of mental processes. *Unsolved mysteries of the mind: Tutorial essays in cognition*, 93-148.

Moritz, S., Woodward, T., Krausz, M., Naber, D., & Group, P. S. (2002). Relationship between neuroleptic dosage and subjective cognitive dysfunction in schizophrenic

patients treated with either conventional or atypical neuroleptic medication. *International Clinical Psychopharmacology, 17*(1), 41-44.

Mukaka, M. M. (2012). A guide to appropriate use of correlation coefficient in medical research. *Malawi Medical Journal : The Journal of Medical Association of Malawi, 24*(3), 69-71.

Murphy, J. M., Laird, N. M., Monson, R. R., Sobol, A. M., & Leighton, A. H. (2000). A 40-year perspective on the prevalence of depression: The Stirling County Study. *Archives of General Psychiatry, 57*(3), 209-215.

Ochoa, S., Usall, J., Cobo, J., Labad, X., & Kulkarni, J. (2012). Gender differences in schizophrenia and first-episode psychosis: A comprehensive literature review. *Schizophrenia Research and Treatment, 2012*.

Oltmanns, T. F., & Neale, J. M. (1975). Schizophrenic performance when distractors are present: Attention deficit or differential task difficulty? *Journal of Abnormal Psychology, 84*(3), 205-209.

Ordonez, A. E., Loeb, F. F., Zhou, X., Shora, L., Berman, R. A., Broadnax, D. D., . . . Rapoport, J. L. (2016). Lack of gender-related differences in childhood-onset schizophrenia. *Journal of American Academy Child and Adolescent Psychiatry, 55*(9), 792-799. doi: 10.1016/j.jaac.2016.05.022

Owens, D. C., Miller, P., Lawrie, S. M., & Johnstone, E. C. (2005). Pathogenesis of schizophrenia: A psychopathological perspective. *The British Journal of Psychiatry, 186*(5), 386-393.

Pallanti, S., Quercioli, L., & Hollander, E. (2004). Social anxiety in outpatients with schizophrenia: A relevant cause of disability. *American Journal of Psychiatry, 161*(1), 53-58.

Palmer, B. A., Pankratz, V. S., & Bostwick, J. M. (2005). The lifetime risk of suicide in schizophrenia: A reexamination. *Archives of General Psychiatry, 62*(3), 247-253.

Perala, J., Suvisaari, J., Saarni, S. I., Kuoppasalmi, K., Isometsa, E., Pirkola, S., . . . Lonnqvist, J. (2007). Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Archives of General Psychiatry, 64*(1), 19-28. doi: 10.1001/archpsyc.64.1.19

Petty, C. R., Rosenbaum, J. F., Hirshfeld-Becker, D. R., Henin, A., Hubley, S., LaCasse, S., . . . Biederman, J. (2008). The Child Behavior Checklist broad-band scales predict

subsequent psychopathology: A five-year follow-up. *Journal of Anxiety Disorders, 22*(3), 532-539. doi: 10.1016/j.janxdis.2007.04.003

Pina-Camacho, L., Garcia-Prieto, J., Parellada, M., Castro-Fornieles, J., Gonzalez-Pinto, A. M., Bombin, I., . . . Janssen, J. (2015). Predictors of schizophrenia spectrum disorders in early-onset first episodes of psychosis: A support vector machine model. *European Child & Adolescent Psychiatry, 24*(4), 427-440.

Pinkham, A. E., Penn, D. L., Green, M. F., Buck, B., Healey, K., & Harvey, P. D. (2014). The social cognition psychometric evaluation study: Results of the expert survey and RAND panel. *Schizophrenia Bulletin, 40*(4), 813-823.

Postilnik, I., Eisman, H. D., Price, R., & Fogel, J. (2006). An algorithm for defining somatization in children. *Journal of the Canadian Academy of Child Adolescent Psychiatry, 15*(2), 64-74.

Poulton, R., Caspi, A., Moffitt, T. E., Cannon, M., Murray, R., & Harrington, H. (2000). Children's self-reported psychotic symptoms and adult schizophreniform disorder: A 15-year longitudinal study. *Archives of General Psychiatry, 57*(11), 1053-1058.

Prebble, S. C., Addis, D. R., & Tippett, L. J. (2013). Autobiographical memory and sense of self. *Psychological Bulletin, 139*(4), 815-840. doi: 10.1037/a0030146

Purcell, R., Maruff, P., Kyrios, M., & Pantelis, C. (1997). Neuropsychological function in young patients with unipolar major depression. *Psychological Medicine, 27*(06), 1277-1285.

Rajji, T., Ismail, Z., & Mulsant, B. (2009). Age at onset and cognition in schizophrenia: Meta-analysis. *The British Journal of Psychiatry, 195*(4), 286-293.

Reitan, R. M., & Wolfson, D. (1993). *The Halstead-Reitan Neuropsychological Test Battery: Theory and clinical interpretation* (2nd ed.). Tucson, AZ: Neuropsychology Press.

Remschmidt, H. (1993). Childhood and adolescent schizophrenia. *Current Opinion in Psychiatry, 6*(4), 470-479.

Revheim, N., Schechter, I., Kim, D., Silipo, G., Allingham, B., Butler, P., & Javitt, D. C. (2006). Neurocognitive and symptom correlates of daily problem-solving skills in schizophrenia. *Schizophrenia Research, 83*(2), 237-245.

Ritsner, M. (2003). The attribution of somatization in schizophrenia patients: A naturalistic follow-up study. *The Journal of Clinical Psychiatry, 64*(11), 1370-1378.

Rodríguez-Sánchez, J. M., Crespo-Facorro, B., Gonzalez-Blanch, C., Perez-Iglesias, R., & Vazquez-Barquero, J. L. (2007). Cognitive dysfunction in first-episode psychosis: The processing speed hypothesis. *The British Journal of Psychiatry, 191*(51), 107-110.

Romine, C. B., & Reynolds, C. R. (2005). A model of the development of frontal lobe functioning: Findings from a meta-analysis. *Applied Neuropsychology, 12*(4), 190-201. doi: 10.1207/s15324826an1204_2

Roza, S. J., Hofstra, M. B., Van der Ende, J., & Verhulst, F. C. (2003). Stable prediction of mood and anxiety disorders based on behavioral and emotional problems in childhood: A 14-year follow-up during childhood, adolescence, and young adulthood. *American Journal of Psychiatry, 160*(12), 2116-2121.

Rutter, M., & Rutter, M. (1993). *Developing minds : Challenge and continuity across the life span*. New York: BasicBooks.

Rutter, M., & Sroufe, L. A. (2000). Developmental psychopathology: Concepts and challenges. *Development and psychopathology, 12*(3), 265-296.

Sanchez-Gistau, V., Baeza, I., Arango, C., González-Pinto, A., Serna, E., Parellada, M., . . . Castro-Fornieles, J. (2015). The affective dimension of early-onset psychosis and its relationship with suicide. *Journal of Child Psychology and Psychiatry, 56*(7), 747-755.

Saykin, A. J., Gur, R. C., Gur, R. E., Mozley, P. D., Mozley, L. H., Resnick, S. M., . . . Stafiniak, P. (1991). Neuropsychological function in schizophrenia: Selective impairment in memory and learning. *Archives of General Psychiatry, 48*(7), 618-624.

Saykin, A. J., Shtasel, D. L., Gur, R. E., Kester, D. B., Mozley, L. H., Stafiniak, P., & Gur, R. C. (1994). Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. *Archives of General Psychiatry, 51*(2), 124-131.

Schmid, M. T., & Hammar, Å. (2013). A follow-up study of first-episode major depressive disorder. Impairment in inhibition and semantic fluency—potential predictors for relapse? *Frontiers in Psychology, 4*, 1-13. doi: 10.3389/fpsyg.2013.00633

Seidman, L. J., Giuliano, A. J., Meyer, E. C., Addington, J., Cadenhead, K. S., Cannon, T. D., . . . Walker, E. F. (2010). Neuropsychology of the prodrome to psychosis in the NAPLS consortium: Relationship to family history and conversion to psychosis. *Archives of General Psychiatry, 67*(6), 578-588.

Shackman, A. J., Sarinopoulos, I., Maxwell, J. S., Pizzagalli, D. A., Lavric, A., & Davidson, R. J. (2006). Anxiety selectively disrupts visuospatial working memory. *Emotion, 6*(1), 40-61.

Silk, J. S., Steinberg, L., & Morris, A. S. (2003). Adolescents' emotion regulation in daily life: Links to depressive symptoms and problem behavior. *Child Development, 74*(6), 1869-1880. doi: 10.1046/j.1467-8624.2003.00643.x

Simonsen, C., Sundet, K., Vaskinn, A., Ueland, T., Romm, K. L., Hellvin, T., . . . Andreassen, O. A. (2010). Psychosocial function in schizophrenia and bipolar disorder: relationship to neurocognition and clinical symptoms. *Journal of the International Neuropsychological Society, 16*(05), 771-783.

Siris, S. G. (2001). Suicide and schizophrenia. *Journal of Psychopharmacology, 15*(2), 127-135.

Siris, S. G., Addington, D., Azorin, J.-M., Falloon, I. R. H., Gerlach, J., & Hirsch, S. R. (2001). Depression in schizophrenia: Recognition and management in the USA. *Schizophrenia Research, 47*(2–3), 185-197. doi: http://dx.doi.org/10.1016/S0920-9964(00)00135-3

Siris, S. G., & Bench, C. (2003). Depression and schizophrenia. In S. R. Hirsch & D. R. Weinberger (Eds.), *Schizophrenia* (pp. 142-167). Oxford: Blackwell.

Snyder, H. R. (2013). Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: A meta-analysis and review. *Psychological Bulletin, 139*(1), 81-139.

Startup, H., Freeman, D., & Garety, P. A. (2007). Persecutory delusions and catastrophic worry in psychosis: Developing the understanding of delusion distress and persistence. *Behaviour Research and Therapy, 45*(3), 523-537.

Stouten, L. H., Veling, W., Laan, W., Van der Helm, M., & Van der Gaag, M. (2014). Psychotic symptoms, cognition and affect as predictors of psychosocial problems and functional change in first-episode psychosis. *Schizophrenia Research, 158*(1), 113-119.

Terzian, M., Hamilton, K., & Ericson, S. (2011). What works to prevent or reduce internalizing problems or socio-emotional difficulties in adolescents: Lessons from experimental evaluations of social interventions. Retrieved March 29th 2017, Retrieved from https://www.childtrends.org/wp-content/uploads/2013/06/2011-34DUPWhatWorksSocio-Emotional.pdf

Test, M. A., Burke, S. S., & Wallisch, L. S. (1990). Gender differences of young adults with schizophrenic disorders in community care. *Schizophrenia Bulletin, 16*(2), 331-334.

Tsourtos, G., Thompson, J., & Stough, C. (2002). Evidence of an early information processing speed deficit in unipolar major depression. *Psychological Medicine, 32*(02), 259-265.

Ueland, T., & Rund, B. (2004). A controlled randomized treatment study: The effects of a cognitive remediation program on adolescents with early onset psychosis. *Acta Psychiatrica Scandinavica, 109*(1), 70-74.

Van Roy, B., Groholt, B., Heyerdahl, S., & Clench-Aas, J. (2010). Understanding discrepancies in parent-child reporting of emotional and behavioural problems: Effects of relational and socio-demographic factors. *BMC Psychiatry, 10*(1), 56. doi: 10.1186/1471-244x-10-56

Verdoux, H., & Van Os, J. (2002). Psychotic symptoms in non-clinical populations and the continuum of psychosis. *Schizophrenia Research, 54*(1), 59-65.

Voges, M., & Addington, J. (2005). The association between social anxiety and social functioning in first-episode psychosis. *Schizophrenia Research, 76*(2), 287-292.

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

Wechsler, D. (2003). *Wechsler Adult Intelligence Scale-Third ed. (WAIS-III). Norwegian manual*. Stockholm: Pearson Assessment.

Wechsler, D. (2007). *Wechsler Abbreviated Scale of Intelligence (WASI). Norwegian manual supplement*. Stockholm: Pearson Assessment.

Whitcomb, S. A., & Merrell, K. W. (2013). *Behavioral, social, and emotional assessment of children and adolescents* (4th ed.). New York: Routledge.

White, T., Ho, B.-C., Ward, J., O'Leary, D., & Andreasen, N. C. (2006). Neuropsychological performance in first-episode adolescents with schizophrenia: A comparison with first-episode adults and adolescent control subjects. *Biological Psychiatry, 60*(5), 463-471.

Wilson, A., & Ross, M. (2003). The identity function of autobiographical memory: Time is on our side. *Memory, 11*(2), 137-149. doi: 10.1080/741938210

Woodberry, K. A., Giuliano, A. J., & Seidman, L. J. (2008). Premorbid IQ in schizophrenia: A meta-analytic review. *American Journal of Psychiatry, 165*(5), 579-587.

World Health Organization. (2016). Schizophrenia. Retrieved March 6th 2017, Retrieved from http://www.who.int/mediacentre/factsheets/fs397/en/

Zelazo, P. D., & Cunningham, W. A. (2007). Executive Function: Mechanisms underlying emotion regulation *Handbook of emotion regulation* (pp. 135-158). New York, NY, US: Guilford Press.

Øie, M., & Rund, B. R. (1999). Neuropsychological deficits in adolescent-onset schizophrenia compared with attention deficit hyperactivity disorder. *The American Journal of Psychiatry, 156*(8), 1216-1222. doi: 10.1176/ajp.156.8.1216

Øie, M., Sundet, K., & Rund, B. R. (2010). Neurocognitive decline in early-onset schizophrenia compared with ADHD and normal controls: Evidence from a 13-year follow-up study. *Schizophrenia Bulletin, 36*(3), 557-565. doi: 10.1093/schbul/sbn127

Øie, M., Sundet, K., & Ueland, T. (2011). Neurocognition and functional outcome in early-onset schizophrenia and attention-deficit/hyperactivity disorder: A 13-year follow-up. *Neuropsychology, 25*(1), 25-35. doi: 10.1037/a0020855