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

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ABSTRACT

The present follow-up study examines the associations between cognition and parent-rated internalizing problems among adolescents with early-onset schizophrenia (EOS) at baseline (T1) and self-rated internalizing problems 13 years later (T2). Twelve individuals (8 male/4 female) with EOS and 30 healthy controls (16 male/14 female) were included in the study. All were between 12 and 18 years of age at T1. Internalizing problems were measured with the Achenbach System of Empirically Based Assessment Internalizing Scale. Cognition was examined with a neuropsychological test battery measuring auditory attention/working memory, visuomotor processing, cognitive flexibility and verbal memory. Compared to healthy controls, the EOS group had significant cognitive deficits and more internalizing problems both at T1 and T2. There was no correlation between parent-rated internalizing problems at T1 and self-rated internalizing problems at T2 in the EOS group. However, deficits in auditory attention/working memory at T1 were significantly associated with internalizing problems at T2. A focus on improving the treatment of cognitive impairments may be important in preventing the development of internalizing problems in young patients with schizophrenia. The small sample size of the study is a limitation and further research is recommended.

1. Introduction

Depressive symptoms are common among patients with first-episode psychosis (Coentre et al., 2017). Results indicate that depressive symptoms in schizophrenia are a discrete symptom domain with only partial overlap with positive or negative symptoms (Schennach et al., 2015). There are only few studies examining the course and development of depressive symptoms in patients with a first episode psychosis. In one 12-month follow-up study it was found that depression early in the emergence of a psychosis was fundamental to the development of future depression and suicidal thinking (Upthegrove et al., 2010). Another study found that poor childhood social functioning, long duration of untreated psychosis and depressive symptoms at baseline predicted depression at 12-month follow-up in patients with first episode psychosis (Sönmez et al., 2013). In a ten-year follow-up study of first-episode psychosis patients, it was found that patients with poor social functioning in childhood and alcohol use at baseline were more prone to have depressive symptoms at 10-year follow-up (Sönmez et al., 2016). Longitudinal studies on depressive symptoms in adult first episode patients have consistently found that the depressive symptoms decreased during the follow-up period (Sönmez et al., 2013).

Research indicates that between 30% and 62% of patients with schizophrenia present with co-morbid anxiety disorders (Howells et al., 2017), with the most frequent co-morbid anxiety disorder being social phobia (Achim et al., 2011). Pallanti et al. (2004) showed that social phobia was not related to the positive or negative symptoms of schizophrenia. According to Birchwood et al. (2007), comorbid social phobia can develop from the expectation of a devastating loss of social status in patients with schizophrenia. There is a close relationship between anxiety and depression and increased suicidality in people with a psychotic disorder (Bertelsen et al., 2007; Diaz-Caneja et al., 2015; Fenton, 2000; Jarbin and Von Knorring, 2004). Thus, knowledge about variables associated with development of depressive and anxiety symptoms in people with a psychotic disorder may facilitate earlier identification of patients who are prone to develop a severe course.

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Most of the research on depression and anxiety in schizophrenia has been on adults, and the affective dimension has scarcely been studied in early-onset schizophrenia (EOS) (Sanchez-Gistau et al., 2015). EOS is defined as an occurrence of schizophrenia before the age of 18 (Frangou, 2006). Partly because neurobiological and psychosocial development is not yet complete at this age, 50–60% of individuals with EOS have a poor prognosis (Clemmensen et al., 2012). It is therefore important to acquire more insight into the causes of internalizing problems in this particularly vulnerable group of young individuals for prevention and treatment purposes.

A child or adolescent who has depressive symptoms and anxiety frequently experiences other internalizing symptoms such as social withdrawal and physical concerns (Merrell, 2008). Thus, it makes sense to examine internalizing problems as a group of symptoms in research on adolescents with EOS, as opposed to only focusing on depression or anxiety. In this regard, the Children Behavior Check List (CBCL) provides a reliable and valid measurement with high stability over time in children with ADHD (Biederman et al., 2001; Mattison and Spitznagel, 1999; Bingham et al., 2003). Petty et al. (2008) 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 a longitudinal study by Roza et al. (2003) of children and adolescents from the general population, both the CBCL Internalizing and Externalizing Scales proved to be significant independent predictors of mood disorders (Roza et al., 2003). One study found that internalizing problems, as measured by the CBCL, are common among children who later develop EOS (Muratori et al., 2005). Øie et al. (2011) reported that individuals with EOS between 12–18 years of age had a considerably higher level of internalizing problems measured by the CBCL than healthy controls. The level of internalizing problems was still elevated relative to controls after 13 years. However, Øie et al. (2011) did not examine possible baseline factors that may be associated with later internalizing problems. Therefore, in this study, we intend to gain more knowledge about early predictors (i.e., internalizing problems or cognitive deficits during adolescence) of later internalizing problems during young adulthood among individuals with EOS.

Cognitive deficits have been well documented in both adult onset schizophrenia and in EOS. In a review of cognitive function in individuals with EOS, Frangou (2010) found that EOS patients showed impairments with medium to large effect sizes in IQ, attention, memory and executive functions (Frangou, 2010). Both in first episode schizophrenia and in chronic schizophrenia, cognitive deficits are strongly related to poorer functional outcome (Fett et al., 2011; Stouten et al., 2014). In a study of youth with EOS, Øie et al. (2011) found that poorer cognition at baseline was correlated with worse social functioning and vocational/educational functioning at 13-year follow-up. Cognitive deficits occur early in the course of psychosis and generally tend to improve marginally or remain stable over time in adult onset schizophrenia (Szöke et al., 2008). In contrast, Øie et al. (2011) found a decline in verbal memory, attention and processing speed in EOS patients when reassessed after 13 years. Given that chronic and first-episode samples and EOS samples vary in the longitudinal course of cognitive functions, research documenting associations between cognition and outcomes in adult onset samples cannot be generalized to patients with EOS. Further, compared to older patients with schizophrenia, individuals with EOS are about to enter adulthood, attending school, deciding on further education, and establishing important social networks. If cognitive impairments in individuals with EOS halt their development in social and academic areas (Øie et al., 2011), they may also mediate the development of internalizing symptoms.

The current study is part of a larger 13-year follow-up study of 19 adolescents with EOS between 12–18 years of age, 20 adolescents with Attention Deficit Hyperactivity Disorder (ADHD) and 30 healthy controls (Øie et al., 2010, 2011). The aim of the present study was to investigate possible 13-year longitudinal predictors of self-rated internalizing symptoms in the EOS patient sample. Cognition and parent-rated internalizing symptoms were assessed at baseline and self-rated internalizing symptoms were the outcome measure assessed at follow-up. By identifying early predictors of later internalizing problems, treatment can start early and possibly influence the course, morbidity and mortality.

With this background, we wished to test in a sample of EOS individuals whether a) baseline parent-rated internalizing symptoms and b) baseline cognitive deficits, could predict self-rated internalizing symptoms at 13-year follow-up.

2. Methods

2.1. Participants

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, data from the Internalizing scale at T2 were missing for three individuals in the EOS group. All 30 healthy control individuals were available for reassessment after 13 years. 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). We used the expanded Brief Psychiatric Rating Scale (BPRS) (Lukoff et al., 1986) to assess symptoms of psychosis at T2. The BPRS covers a 2-week period and intends to indicate general severity of psychotic symptoms. It consists of 24 items that rate severity of psychiatric symptoms on a scale from 1 (not present) to 7 (extremely severe). A positive and a negative symptoms score were based on a factor analysis conducted by Ventura et al. (1995), with seven and three items, respectively. The total psychosis symptoms score was 42.8 (±16.0), the positive symptoms score was 12.1 (±7.5) and the negative symptoms score was 6.5 (±3.4). Ten of the patients in the EOS group had been hospitalized during the follow-up period. Five of the individuals had been 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 EOS group had recovered. They were living independently, had a partner and were employed. Among the group that was still symptomatic, half were living on their own, all were unemployed and only one of the patients had a partner. Eleven of the individuals in the EOS group had not yet started neuroleptic treatment at the time of testing at T1 and one was still drug naive at T2. Healthy controls were volunteers attending regular schools. They were screened for mental problems using the CBCL, and individuals were excluded if they had a raw score higher than 45 (Øie and Rund, 1999). The healthy comparison group had significantly more education and significantly higher IQ scores at T2 than the EOS group. Øie et al. (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 at T2. Characteristics of the EOS group compared to the healthy controls at T2 are presented in Table 1.

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	Fisher's $p = 0.506$
Age (yrs)	27.6 (1.5)	27.6 (1.5)	$F = 0.001$, $p = 0.975$
Education (yrs)	10.5 (1.6)	15.4 (1.7)	$F = 75.2$, $p < 0.001$
FSIQ (WASI)[a]	93.2 (15.1)	112.6 (8.6)	$F = 27.7$, $p < 0.001$
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] Defined daily doses (Norwegian Medical Depot).

2.2. Procedure

The schizophrenia diagnosis was determined at T1 using semi-structured clinical interviews by senior clinicians and information from the patient case records. 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. The patients were tested when they were judged by the examiner or by their clinician to be clinically stable.

2.3. Internalizing problems measure

The Child Behavior Checklist (CBCL) Internalizing scale was used as a measure of internalizing problems at T1. 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). In total, the CBCL consists of 113 items divided into eight syndrome scale scores, three of which (the Social Withdrawal, Somatic Complaints, and Anxiety/Depression scales) are summed to yield the Internalizing scale. Data for each subscale were not available for analysis. The CBCL questionnaire has been found to have good psychometric properties in general (Ivanova et al., 2007). The form was completed by the mothers of the subjects at T1. At T2, the adult version of the scale (ABCL) (Achenbach and Rescorla, 2003) was used, and the form was filled out by the individuals themselves. Longitudinal studies have demonstrated that the ABCL assesses the same constructs as the CBCL (Achenbach and Rescorla, 2003). High T-scores on the Internalizing scale indicate more internalizing problems. The clinical cut-off score of the CBCL/ABCL is a T-score ≥65.

2.4. 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.

Based on the results from earlier studies in the current research project (Øie et al., 2010,2011) and other studies, auditory attention/working memory (Seashore Rhythm Test, WISC-R Digit Span forward and backward, Digit Span Distraction Test), visuomotor processing (Trail Making Test, WISC-R Digit Symbol-Coding), cognitive flexibility (Wisconsin Card Sorting Test perseverative responses) and verbal memory (California Verbal Learning Test – Long-Delay Free Recall) were determined to be the most relevant variables for the current study. 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. Where high scores indicated impairment, the direction was reversed so that high scores always indicated better cognitive function.

2.5. Data analyses

Analyses were conducted using the statistical package SPSS, version 24.0. Group differences between EOS individuals and healthy controls (HC) on cognitive functions and internalizing problems were analyzed by ANOVA at both T1 and T2. Due to the small sample size, correlations were used instead of partial correlations and regression analyses controlling for third variables. Correlation analyses (Spearman's rho) were used to investigate associations between both internalizing problems and cognitive functions at T1 and internalizing problems at T2 in the EOS group. Spearman´s rho was chosen as it is considered more robust than Pearson's correlation when it comes to outliers and skewed variables (Mukaka, 2012). All tests were two-tailed and the significance level was set to 0.05.

3. Results

As shown in Table 2, at both T1 and T2, the EOS group had significantly impaired scores compared to the HC group on measures of auditory attention/working memory, visuomotor processing, and internalizing problems, and at T2, they had impaired scores on cognitive flexibility and verbal memory, as well.

As shown in Table 3, there was no correlation between parent-reported internalizing problems at T1 and self-reported internalizing problems at T2 in the EOS group (rho = −0.04).

However, a significant negative correlation was found between auditory attention/working memory and internalizing problems at T2 (rho = −0.61; $p = 0.035$), indicating that better working memory at T1 is associated with fewer internalizing problems at T2 (Table 3).

4. Discussion

The aim of the present study was to investigate whether parent-rated internalizing problems and cognitive functions in individuals with EOS at baseline (T1) were associated with self-rated internalizing problems 13 years later (T2). Our results indicated no correlation between internalizing problems at T1 and T2. This was contrary to what

Table 2
Mean and SD of cognitive and internalizing measures at T1 and T2.

Measure	EOS $n = 12$	HC $n = 30$	F (p-value)
Auditory attention/working memory[a]			
T1	−0.60 (1.16)	0.00 (0.71)	4.2 (0.047)
T2	−1.17 (1.75)	0.00 (0.73)	9.6 (0.004)
Visuomotor processing[a]			
T1	−1.09 (1.42)	0.00 (0.76)	10.5 (0.002)
T2	−2.46 (2.03)	0.00 (0.82)	31.9(< 0.001)
Cognitive flexibility[b]			
T1	21.7 (12.4)	15.6 (6.9)	3.8 (0.059)
T2	27.7 (23.0)	10.2 (5.1)	16.2(< 0.001)
Verbal memory[b]			
T1	11.7 (2.7)	13.1 (2.2)	3.2 (0.081)
T2	9.7 (3.6)	13.7 (1.8)	24.2(< 0.001)
Internalizing problems[c]			
T1 (parent-reported)	61.2 (12.1)	45.7 (9.6)	19.2(< 0.001)
T2 (self-reported)	59.8 (9.2)	40.2 (8.7)	41.7(< 0.001)

[a] For the auditory attention/working memory and visuomotor processing composite scores, z-scores are shown.

[b] For the cognitive flexibility and verbal memory composite scores, raw-scores are shown. For cognitive flexibility raw scores of the WCST perseverative responses are shown. High scores indicate less cognitive flexibility.

[c] For Internalizing problems, T-scores are shown.

Table 3
Correlations (Spearman's rho) between internalizing problems and cognitive domains at T1 and internalizing problems at T2 in the EOS group.

Variable	Internalizing problems T2	p-value	n
Internalizing problems T1	−0.04	0.896	12
Auditory attention/working memory T1	−0.61*	0.035	12
Visuomotor processing T1	0.30	0.347	12
Cognitive flexibility T1	0.15	0.636	12
Verbal memory T1	−0.14	0.658	12

was hypothesized based on earlier research (Biederman et al., 2001; Petty et al., 2008; Roza et al., 2003; Sönmez et al., 2013; Upthegrove et al., 2010). There are several possible explanations for this lack of correlation. Because 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 has been done in other clinical groups or normal controls, these prior findings may not generalize to the population of adolescents with EOS. In an additional analysis we found as expected from others research (Roza et al., 2003) a significant correlation between parent-rated internalizing problems at T1 and self-reported internalizing problems at T2 among healthy controls (rho = 0.46; $p = 0.01$). One explanation of the different result between the groups, may be that internalizing symptoms develop differently in the individuals with EOS because they have a neurodevelopmental disorder. For this reason, the internalizing problems at T1 in the EOS group may not be as stable over time as in other children and adolescents. In addition, there could be differences in the rating of internalizing problems between parents (T1) and the self-report of individuals (T2) in the two groups. Self-report was used at follow up because most of the young adults did not live with their parents, and consequently, it may have been difficult for the parents of the EOS group to provide valid ratings of their adult children. There is evidence of discrepancies between adolescent and parent ratings using similar versions of questionnaires (Handwerk et al., 1999; Van Roy et al., 2010). Further, research on adult patients with first episode psychosis has shown that depressive symptoms decreased during the follow-up period (Sönmez et al., 2013). However, in our EOS group, the level of internalizing problems was still elevated at the follow-up assessment 13 years later (Øie et al., 2011).

The high level of internalizing problems in our EOS sample at both T1 and T2 may have several causes. Three possible pathways have previously been described to explain the development of emotional dysfunction (including anxiety and depression) in psychotic disorders: (1) emotional dysfunction as a pre-morbid developmental disorder and a vulnerability marker for schizophrenia, (2) as a core component of the psychotic syndrome, and (3) emerging as a psychological reaction to the psychotic episode (Birchwood et al., 2003). Among individuals with EOS, these three explanations are all plausible in the short term. However, after a long period of 13 years, with maturation during adolescence and intervening treatment, it is improbable that internalizing problems are associated with events at baseline. Thus, it is possible that internalizing problems follow another trajectory in individuals with EOS compared to older individuals with psychosis.

In accordance with our hypotheses, reduced cognitive function at T1 was associated with internalizing problems at T2. Our results showed that the more impaired auditory attention/working memory was during the adolescent years in the EOS group, the more internalizing problems they had in their young adult years. Working memory enables a limited amount of information to be available for further cognitive processing. 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. 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). In previous findings from the same EOS sample, Øie et al. (2011) found that impaired cognition during adolescence was associated with being less educated, being single, living alone and being unemployed at T2. The adolescents in the current study were young and attending high school at T1. It is possible that impairments in auditory attention/working memory could lead to problems with concentration in academic settings. Problems in school at a young age could also lead to difficulties pursuing further education and obtaining a job later in life. This in turn may lead to frustration, reduced self-esteem and internalizing problems, and, thus reduced function at school may serve as a mediating variable for internalizing problems.

As already mentioned, poor working memory may also affect other aspects of daily living such as social functioning (McQuade et al., 2013). Difficulties with social relations due to problems with keeping up in a conversation or social exchange are typical examples (McQuade et al., 2013). In a previous study by Øie et al. (2011), auditory attention/working memory, visuomotor processing and cognitive flexibility were strong predictors of social functioning at T2 in a similar, but larger sample of individuals with EOS. One possibility is that poorer auditory attention/working memory affects social function negatively, which may in turn cause internalizing problems, i.e. social function may be a mediating variable.

Working memory is connected to important processes related to the self-regulation of emotions, thoughts and behavior (Hofmann et al., 2012). Working memory is important for suppressing ruminative thoughts and feelings and to downregulate unwanted effect, which could develop into depression or anxiety. Other work has also shown that working memory supports multiple stages in emotion regulation (Gross, 1998; Hofmann et al., 2012). It is possible that experiencing a serious mental disorder, like schizophrenia, during adolescence can lead to sadness, negative thoughts and feelings, which the adolescent may have difficulty processing. For this reason, impaired working memory might have contributed to poorer emotional regulation and consequently led to internalizing problems. Another explanation for the

strong association between impaired auditory attention/working memory at T1 and internalizing problems at T2 could be that when someone is having problems retaining information for further processing, therapy may be difficult. One possibility is that certain types of psychotherapy or psychoeducation treatment may 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.

4.2. Strengths and limitations

The longitudinal and prospective design, the assessment of patients early in their illness and the high retention rate are clear strengths of the current study. Including a healthy control group is another strength, as it enables a comparison of scores between the two groups from the same country to determine the levels of relative impairment in the EOS group.

The main limitation is the small sample size, which reduces the statistical power of the tests, and made it difficult to run regression analyses controlling for several variables. Only bivariate correlations were included, since multivariate analyses would be difficult with such a small sample size. However, in a review by Díaz-Caneja et al. (2015), the importance of bivariate studies is highlighted because of the general scarcity of available EOS research (Diaz-Caneja et al., 2015). A small sample is a common problem in longitudinal studies of adolescents with schizophrenia, due to the rarity of the illness and the challenges of long-term follow-up of this population (Cervellione et al., 2007). However, the sample size does not undermine the statistically significant and meaningful correlation between baseline attention/working memory and later internalizing problems. Rather it means that only strong relationships will be detectable at statistically reliable levels in this sample.

Some patients were assessed without medication at baseline, and with medication at follow-up. The patients also received different types of treatment, which could have affected the results in general. Although antipsychotic medication has been shown to have minimal effect on cognition (Keefe et al., 2007a,2007b), the possibility of confounding medication effects cannot be completely ruled out.

The Internalizing scale is a composite scale including the Withdrawn, Anxious/Depressed and Somatic Complaints syndrome scales, which may cause imprecision, particularly when comparing to other studies where only depression or anxiety has been studied (Whitcomb and Merrell, 2013).

The results of the present study may 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 and may prevent internalizing problems from developing. 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 social interaction with peers, and assistance in choosing the right career and adapting to a job situation would also be advantageous. 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.

Conflict of interest

All authors declare that they have no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.04.033.

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