Original article

Do clinical characteristics predict the cognitive course in early-onset schizophrenia-spectrum disorders?

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Abstract

Background: Being in a period with extensive brain maturation, adolescents with early-onset schizophrenia-spectrum disorders (EOS) provide unique neurodevelopmental data that may contribute to a better understanding of schizophrenia at all ages. Cognitive dysfunction is a central feature of schizophrenia and is more pronounced in EOS than in later onset illness. However, there is limited research on both the long-term course of global cognition in EOS, and how cognition over time is influenced by clinical characteristics during the early illness period.

Methods: Thirty-one EOS patients and 73 controls (age 12-18) were assessed on clinical variables at baseline (PANSS, duration of untreated psychosis [DUP], hospitalizations, suicide attempts and remission). Neuropsychological assessments with the MATRICS Consensus Cognitive Battery (MCCB) were conducted at baseline, after both one and two years, and composite scores of total performance were calculated. The analyses were performed with a linear mixed model.

Results: The present study suggested that global cognition followed a stable course over the first years of the disease in EOS, though at a significantly lower level in EOS compared to the controls. We did not detect a relationship between DUP, remission, positive/negative symptoms and hospitalizations on the one hand, and long-term cognition on the other, but PANSS-general and suicide attempt history at baseline were identified as risk factors of longitudinal cognitive function.

Conclusions: Though at different levels, the EOS group and the controls had a similar cognitive course over two years. Some baseline characteristics (psychotic symptoms, DUP, remission and hospitalization) had no influence on cognition within the first two years of

illness. In contrast, general symptoms and a history of suicide attempts at baseline were more potent risk factors of the cognitive course than the psychotic-specific symptoms, and should therefore be subject to specific attention in the evaluation and treatment of patients with early onset psychosis.

Keywords: cognition, early-onset schizophrenia, suicide attempts, general symptoms

Introduction

A major objective in schizophrenia research is to find reliable prognostic factors that may help identify therapeutic targets and allocate resources to those with the greatest needs. Approximately 5% of the schizophrenia population has an illness onset before 18 years of age, which is often referred to as early-onset schizophrenia-spectrum disorders (EOS) (Cannon et al., 1999). Research suggests that EOS reflects increased disease severity, with a worse clinical course and outcome (Remschmidt et al., 2007; Schimmelmann, Conus, Cotton, McGorry, & Lambert, 2007). The cognitive profile in EOS seems to be similar to adult-onset schizophrenia (AOS) (Holmen, Juuhl-Langseth, Thormodsen, Melle, & Rund, 2010; Kravariti, Morris, Rabe-Hesketh, Murray, & Frangou, 2007; Oie, Sundet, & Ueland, 2011), but more impaired (Jepsen et al., 2013; Nieto & Castellanos, 2011; Rajji, Ismail, & Mulsant, 2009), and with a more pronounced developmental and premorbid anomaly (Frangou, 2013; Kumra & Charles Schulz, 2008; Teigset, Mohn, & Rund, 2016). EOS patients develop symptoms in a period with extensive brain maturation and alterations in cognitive structures and functions (Juuhl-Langseth, Holmen, Thormodsen, Oie, & Rund, 2014); thus, they provide unique neurodevelopmental data that may contribute to a better understanding of schizophrenia at all ages (Bombin et al., 2013; Rapoport, Giedd, & Gogtay, 2012; Remschmidt, 2002).

Although cognitive deficits do not appear in all cases (Rund, Zeiner, Sundet, Oie, & Bryhn, 1998), they are considered to be a core feature of schizophrenia (Palmer, Dawes, & Heaton, 2009; Rund et al., 2006; Torgalsboen, Mohn, & Rishovd Rund, 2014; Townsend & Norman, 2004), and are more pronounced in schizophrenia than in bipolar disorders (Landro, Orbeck, & Rund, 1993; Seidman et al., 2013) . While some studies argue for specific deficits, others suggest deficiencies across the cognitive domains (Christensen et al., 2014; Jepsen et

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al., 2013; Kravariti, Morris, Rabe-Hesketh, Murray, & Frangou, 2003b; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009; Nieto & Castellanos, 2011; Rajji et al., 2009). A number of comprehensive meta-analyses from both chronic and first-episode schizophrenia suggest that essentially all cognitive domain are affected, with most effect sizes ranging from moderate to large (Heinrichs & Zakzanis, 1998; Mesholam-Gately et al., 2009), and that the deficiencies are consistent over decades and across cultures (Schaefer, Giangrande, Weinberger, & Dickinson, 2013). A natural consequence of this has been a more frequent use of composite scores in cognitive studies of schizophrenia (Meyer et al., 2014; Rund et al., 2015).

The trajectories of cognitive deficits over the course of the disease are being debated, and one question has been whether schizophrenia involves neurodegeneration (Rund, 2009). To date, most longitudinal studies indicate a stable cognitive course in AOS (Bora, 2015; Rund et al., 2015), with a growing body of research suggesting a similar stability in EOS (Bombin et al., 2013; Frangou, Hadjulis, & Vourdas, 2008; Jepsen, Fagerlund, Pagsberg, Christensen, Nordentoft, et al., 2010; Juuhl-Langseth et al., 2014; Mayoral et al., 2008; Oie, Sundet, & Rund, 2010). However, the course of global cognition over the first years, as measured in composite scores, has yet to be reported in EOS. A further objective is to identify factors affecting the cognitive course. While both cognition and clinical variables have been subject to comprehensive research in schizophrenia, the interaction between the two has gained less attention, especially in EOS. An essential question is to what extent the longitudinal course of cognition is influenced by clinical characteristics in the early illness period.

Previous research from AOS diverges on the association between psychotic symptoms and cognition, both at baseline (Harvey, Green, Bowie, & Loebel, 2006; Rund et

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al., 2004; Ventura, Thames, Wood, Guzik, & Hellemann, 2010) and longitudinally (Bagney et al., 2015; Barder et al., 2013; Fervaha, Foussias, Agid, & Remington, 2014; Hoff et al., 1999; Mayer, 2002; Meier et al., 2014; Rund et al., 2015). Research that examines baseline correlations suggests that negative symptoms interact with cognition to a greater extent than positive symptoms (Bora, Yucel, & Pantelis, 2009; Kravariti et al., 2012; O'Connor et al., 2013), with one long-term study reporting that negative symptoms may help mediate the relationship between cognition and functioning (Meyer et al., 2014). Other longitudinal findings report associations between a reduction in positive symptoms and cognitive improvement (Hoff et al., 1999), or a small to no relationship between positive/negative symptoms and cognition (Rund et al., 2004).

Research on youths with bipolar disorder indicates increased cognitive deficits due to symptom severity and psychotic features (Arango, Fraguas, & Parellada, 2014; Fitzgerald et al., 2004; McCarthy, Weiss, Segovich, & Barbot, 2016; Udal et al., 2013). In youths with schizophrenia-spectrum disorders, we find only one study that has investigated the long-term interaction between psychotic symptoms and cognition (Wozniak, Block, White, Jensen, & Schulz, 2008). They found no association between cognition and psychotic symptoms, with the exception of a lower IQ predicting more negative symptoms after one year. However, their study had a short follow-up period and other clinical characteristics were not examined, thereby raising questions about the relationship between a wider range of symptoms and cognition, in addition to whether the deterioration endures over time. Furthermore, the disappearance of psychotic symptoms may also affect long-term cognition, although the relationship between remission and cognition has yet to be investigated in EOS. Nevertheless, in an adult sample, Rund et al. (2015) found that a stable remission without relapse in the first year seemed to predict a better cognitive course.

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Another relevant clinical variable is illness duration. The "neurotoxicity-hypothesis" suggests that a longer duration of untreated psychosis (DUP) accelerates cognitive deterioration (Wyatt, 1991). In adult samples, some longitudinal studies report that a shorter DUP leads to a better overall cognitive functioning (Cuesta et al., 2012; Dominguez et al., 2013; Yamazawa et al., 2008), but the majority of studies report no such association (Goldberg et al., 2009; Melle et al., 2008; Rund, 2014; Rund et al., 2015; Rund et al., 2007). Research on the interaction between DUP and cognition in EOS is rare. One baseline study found no immediate effect of illness duration on cognitive performance in EOS (Kravariti, Morris, Rabe-Hesketh, Murray, & Frangou, 2003a), while another longitudinal study found that a shorter illness duration was associated with a greater improvement in executive functions after two years (Fraguas et al., 2014). Whereas the majority of AOS studies reported no association between DUP and cognitive course (Goldberg et al., 2009; Melle et al., 2008; Rund et al., 2015; Rund et al., 2007), the findings of Fraguas et al. (2014) suggest a possibly worse impact of DUP on cognition in EOS compared with AOS.

A final research question concerns the relationship between non-psychotic symptoms and cognition. About half of all schizophrenia patients attempt suicide, and 9–13% ultimately do commit suicide (Potkin, Anand, Alphs, & Fleming, 2003), as depression and insight seem to be important predictors (Hor & Taylor, 2010). Even so, little is known about the relationship between suicidality and cognition in EOS, and results are inconsistent in AOS; some indicate an association between a higher cognitive function and a history of suicide attempts, while others find no such association (Delaney et al., 2012; Kim, Jayathilake, & Meltzer, 2003; Potkin et al., 2003; Zoghbi et al., 2014).

If clinical characteristics at baseline can predict the cognitive course in EOS, this is essential for prognosis and therapy. In the present study, we first report how the cognitive

composite score develops over time in EOS, compared to healthy controls. However, the primary aim of this paper is to investigate to what extent the cognitive course in EOS is influenced by clinical characteristics during the early illness period, such as symptoms of schizophrenia, DUP, remission, suicide attempts and number and duration of hospitalizations caused by psychosis.

Method

Some assessments of the longitudinal trajectory in the current EOS group have already been reported (Juuhl-Langseth et al., 2014), and revealed stable deficits in all cognitive domains, with the exception of working memory and processing speed. Because of drop-outs, only 65% of the patients were included in the analyses at the last time point. In the present study, we analyzed cognitive composite scores and used statistical analyses (linear mixed model) that allow the inclusion of all participants with at least one neurocognitive evaluation.

Subjects

The current paper is part of the Early-onset Study, a longitudinal study carried out at the University of Oslo. Patients were consecutively recruited between 2005 and 2009, and were tested three times; at baseline, after one year and after two years (Holmen et al., 2010; Juuhl-Langseth et al., 2014; Thormodsen, Juuhl-Langseth, Holmen, & Rishovd Rund, 2012). The patients were recruited from various inpatient and outpatient units in Eastern Norway, and inclusion criteria were age (12-18 years) and the diagnosis of schizophrenia spectrum disorder according to DSM-IV. Exclusion criteria were central nervous system pathology, head injury (loss of consciousness for more than 30 minutes and/or any neurological sequelae), or an estimated IQ of less than 70.

A total of 31 patients were included at baseline (T1), and schizophrenia-spectrum disorders describe the whole sample, with a diagnosis of schizophrenia: n=17 (54.9%) (including paranoid schizophrenia, catatonic schizophrenia, schizophrenia undifferentiated and residual schizophrenia), schizophreniform psychosis: n=1 (3.2%), schizoaffective disorders: n=3 (9.7%) and psychosis not otherwise specified (NOS): n=10 (32.3%). The percentage distribution of diagnoses stayed relatively stable; after one year (T2), 55% (n=12) were diagnosed with schizophrenia), 14% (n=3) with schizoaffective disorders and 18% (n=4) with psychosis NOS. After two years (T3), 55% (n=11) of the EOS patients were diagnosed with schizophrenia, 20% (n=4) with schizoaffective disorders and 10% (n=2) with psychosis NOS. Three patients had no diagnoses at T3, two of whom had psychosis NOS, and one residual schizophrenia at baseline. At T1, 74% of the patients received antipsychotic medication, 41% of them were medicated at T2 and 50% at T3. At T1, all received second-generation antipsychotic medication (Quetiapine (n=5), Risperdone (n=3), Ziprasidone (n=3), Aripiprazole (n=4), Olanzapine (n=7) and Clozapine (n=1)), three in combination with first-generation anti-psychotics, four in combination with anti-depressants, two in combination with benzodiazepines and one in combination with mood stabilizers. Calculated daily doses (CDD) (WHO, 2010) in mean at T1 was 1.2, at T2 1.5 and at T3 1.4 for antipsychotic medication. CDD of medication were based on the international daily dose of medication technical measurement system (WHO, 2010), where the CDD is the outcome of the prescribed daily dose divided by the average recommended daily dose of medication. The results were previously reported by Juuhl-Langseth et al. (2014), who found no significant change in CDD over time, and no relationship between medication and cognitive performance. The mean age of the EOS group was 15.6 years at baseline. No deaths occurred in our sample in the timeframe measured.

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The healthy controls (HC) were randomly selected from the Norwegian population register and contacted by letter, or they were contacted through advertisements at four schools in Eastern Norway. They were all matched to patients on gender, age and length of education. All patients and HC attended regular school classes at normal grade levels. The HC was screened for mental problems using the Mini-International Neuropsychiatric Interview (M.I.N.I.) screening module (Sheehan et al., 1998), and were excluded from the study when disqualified by the screening criteria.

A total of 31 patients and 73 healthy controls were included at baseline and were followed longitudinally. The number of participants who attended the study at T2/T3 was: EOS 22/20, and controls 41/40, and the participants who completed all the tests included in the composite score were 29 patients at T1, 18 at T2 and 18 at T3 in the EOS group, in the control group there were 67 participants at T1, 39 at T2 and 40 at T3.

Table 1 Demographic and clinical characteristics for EOS patients and healthy controls at baseline

	EOS ($N = 31$)	HC ($N = 73$)	Test statistics
Age in years (SD)	15.8 (2.0)	15.8 (2.0)	ns
Gender, male/female, N (%)	16/15 (52/48)	35/38 (48/52)	ns
Handedness, r/l, N (%)	27/4 (87/13)	67/6 (92/8)	ns
IQ* (SD)	97.1 (14.6)	108.5 (14.1)	$t(102) = -3.72$***
Mean length of mothers education in years (SD)	13.3 (2.9)	15.2 (2.8)	$t(101) = -3.20$**
Mean length of fathers education in years (SD)	13.6 (3.0)	14.8 (2.8)	ns
Mean duration of illness in years (SD)	1.7 (1.4)		
Mean DUP in weeks	35.0 (1-208)		

(range)	
Patients who have attempted to commit suicide (1-5 times), *N* (%)	7 (22.6)
Number of times in hospital, median (range)	1.0 (0-10)
Patients with remission, *N* (%)	10 (34.5)

*Wechslers Abbreviated Scale of Intelligence, full scale IQ. *** p<.001. **p<.01

All participants were given a complete description of the study, and written informed consent was obtained from both the patients and their parents, if the participant was younger than 16. The study was also approved by the Regional Committee for Medical Research Ethics (REK Sør-Øst) and the Norwegian Data Inspectorate.

Clinical assessments

The clinical and cognitive assessments were carried out by trained clinical psychologists. All baseline tests were performed within eight weeks after inclusion in the study. Diagnostic evaluations were based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), modules A-D. The interviewers participated in regular diagnostic consensus meetings led by well-experienced clinical researchers, and completed the training course in SCID assessment arranged by the University of California, Los Angeles (UCLA). The mean overall kappa as assessed in the UCLA training course was 0.77 (Holmen et al., 2010).

For the assessment of psychotic symptoms and functioning, the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987) was used, and we calculated the PANSS baseline scores for the positive, negative and general component. The age of onset was defined by a PANSS score of 4 or more on the Positive or General Scale (see DUP), and

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the mean age of onset in the group was 14 years (range 10-17). Moreover, only baseline scores were used in the analyses. However, Juuhl-Langseth et al. (2014) previously reported stability in symptom levels over the three time points and found no significant changes over time in positive, negative or general symptoms, thereby securing that the baseline group did not differ significantly from those who participated at T2 and T3. Global functioning was measured at baseline with the Global Assessment of Functioning-Split version (Split-GAF) (Pedersen, Hagtvet, & Karterud, 2007). As in the symptom scales, there were no significant changes in split-GAF (symptoms or function) from T1 to T3 (mean at T1/T2/T3; symptoms 47.5/54.3/58.4, function 47.8/58.1/58.2).

DUP was measured by the time interval from the first onset of psychotic symptoms; defined as the first week with a PANSS score of 4 or more on one of the Positive Scale items 1 (delusions), 3 (hallucinatory behavior), 5 (grandiosity), 6 (suspiciousness/persecution), or General Scale item 9 (unusual thought content) to the start of the first adequate treatment of psychosis (defined as the start of adequate antipsychotic medication or admission to the hospital for treatment).

Suicide attempts were assessed in the clinical interviews by asking the youths if they had ever attempted to kill themselves, and if yes, how many times. As reported by the patients, the total number of suicide attempts before baseline was recorded. In the group of 31 patients, 6.7% reported one suicide attempt, 10% had two attempts, 3.3% had three attempts and 3.3% had five attempts.

Hospitalization was measured by the number of times a patient was admitted to psychiatric inpatient treatment due to psychotic symptoms before baseline assessment. The total length of inpatient treatment was measured in weeks, while the mean length of hospitalization in the group was 28.7 weeks (range 0-138).

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Remission was defined by the disappearance of psychotic symptoms for at least seven days before baseline, as defined by the same PANSS symptoms as defined in DUP (see above). Of those in remission, 20% were in remission for seven days, 10% for 14 days, whereas 70% were in remission for 8-17 weeks.

All the clinical characteristics were measured only once (T1). Among the potential risk factors (PANSS, DUP, number of times on hospital, remission, suicidality), PANSS had three missing values, suicidality had one missing value, and remission had two missing values.

Neuropsychological assessments

All participants were tested with the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB) [see previous results on the same participants for the longitudinal domain-scores (Juuhl-Langseth et al., 2014)]. The MCCB (Green & Nuechterlein, 2004; Green et al., 2004; K. H. Nuechterlein et al., 2008) has been widely used in AOS samples and is found to have good test-retest reliability and a limited practice-effect (Keefe et al., 2011; Rajji et al., 2013).

The MCCB covers the following seven domains (K. H Nuechterlein & Green, 2006): *1) Speed of Processing* [Trail Making Test A (TMT-A; (War Department, 1944)], Symbol Coding (Brief Assessment of Cognition in Schizophrenia, BACS; (R. S. E. Keefe, 1999)), and Fluency (Category Fluency; (Blair, 1989)]; *2) Attention* [The Continuous Performance Test-Identical Pairs (CPT-IP); (Cornblatt, Risch, Faris, Friedman, & Erlenmeyer-Kimling, 1988)]; *3) Working Memory* [Spatial Span (The Wechsler Memory Scale, SS-WMS; (Wechsler, 1997)) and Letter Number Span (The University of Maryland Letter Number Span test, LNS; (Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997))]; *4) Verbal Learning* [The revised Hopkins Verbal Learning Test (HVLT-R, immediate recall;(Brandt, 2001))]; *5) Visual*

Learning [The revised Brief Visuospatial Memory Test (BVMT-R; (Benedict, 1997)]; *6)*

Reasoning/Problem Solving [The Mazes Test (Neuropsychological Assessment Battery,

NAB; (White, 2003))]; and *7) Social Cognition* [The Managing Emotions part of the Mayer-

Salovey-Caruso Emotional Intelligence Test (MSCEIT; (Mayer, 2002)]. In addition, a

composite sum score was calculated using the arithmetic average of the first six domains (the

average T-score across domains). At the time of neurocognitive assessments of patients in this

study (2005-2008), the psychometric properties for the MSCEIT for this age group were

unknown, and this test was not used.

Because there are no norms for the MCCB scores of tests respondents below the age

of 20, we calculated our own T-scores with a mean of 50 and an SD of 10. General

intellectual function (IQ) was assessed according to norms using the four sub-tests of the

Wechsler Abbreviated Scale of Intelligence (WASI) (Vocabulary, Similarities, Block

Design and Matrix Reasoning) (Wechsler, 2007).

Statistical analyses

All analyses were performed using SPSS Statistics (version 20) or STATA 14.0 software. For

technical reasons a few participants (two patients at T1, four at T2 and two at T3, and six

healthy controls at T1, two at T2 and none at T3) were unable to perform every test of the

battery included in the composite score. Thus, there were some randomly missing data points.

To account for missing data and confounding variables, all analyses were performed with a

linear mixed model that has been recommended for repeated measures (Gueorguieva &

Krystal, 2004). The method has been found to preserve sample size in small longitudinal

psychological studies despite missing data, an advantage over ANOVA, and provide similar

measures of significance (Muth et al., 2016).

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To estimate differences between the groups over the entire follow-up period (i.e. baseline, T2 and T3) for cognitive composite scores as outcome and control for repeated measurements, we used linear mixed models with an unstructured covariance matrix. Time (measured in years after inclusion), group and time-by-group interaction were fixed effects in all models. All models included random intercept and a random effect for time. Based on the linear mixed model, we estimated mean values with 95% confidence intervals (CI) for the three time points (baseline, T2 and T3) for each group. We also estimated the mean group changes from baseline to two years (Figure 1).

To identify risk factors of change in cognitive composite scores over time in the patient group, linear mixed models analyses were performed. All models included fixed effects for time as a continuous variable. The following clinical variables at baseline were considered for inclusion: in DUP, in the PANSS (positive, negative and general) baseline scores, in suicide attempts, in Split-GAF (symptoms and function), in remission and in hospitalizations (number of times and total weeks). Any variable with a $p<.15$ from the univariable analysis were included as fixed factors in the multivariable model. A manual backward stepwise elimination procedure using a multivariable regression model was performed to identify independent risk factors. In all models a random intercept and random effect for time was included, and an unstructured covariance matrix were used. Multivariate analyses were preceded by estimation of correlation between risk factors.

Results

Our findings for the cognitive composite score in the EOS group and the HC group over the three assessments, from baseline to the two-year follow-up, are illustrated in Figure 1 and Table 2. Analyses with a linear mixed model showed a stable significant effect of group on

the longitudinal composite scores (regression coeff. for group -9.76 95% CI (-12.1 to -7.4), p<.001)), indicating that the mean difference between the groups were far apart at all time points (figure 1). After two years, no statistically significant reduction in the composite score was found within or between the two groups (mean between group change: -0.20 95% CI (-2.00 to 1.59), p= 0.826). IQ measured at baseline was identified as the only confounding factor. When adjusting for the confounding effect of IQ, the effect between the two groups changed in direction (adjusted mean between group change: 0.09 95% CI (-1.67 to 1.87)), meaning that the controls experienced a larger change in the composite score compared to patients. The difference was still not statistically significant.
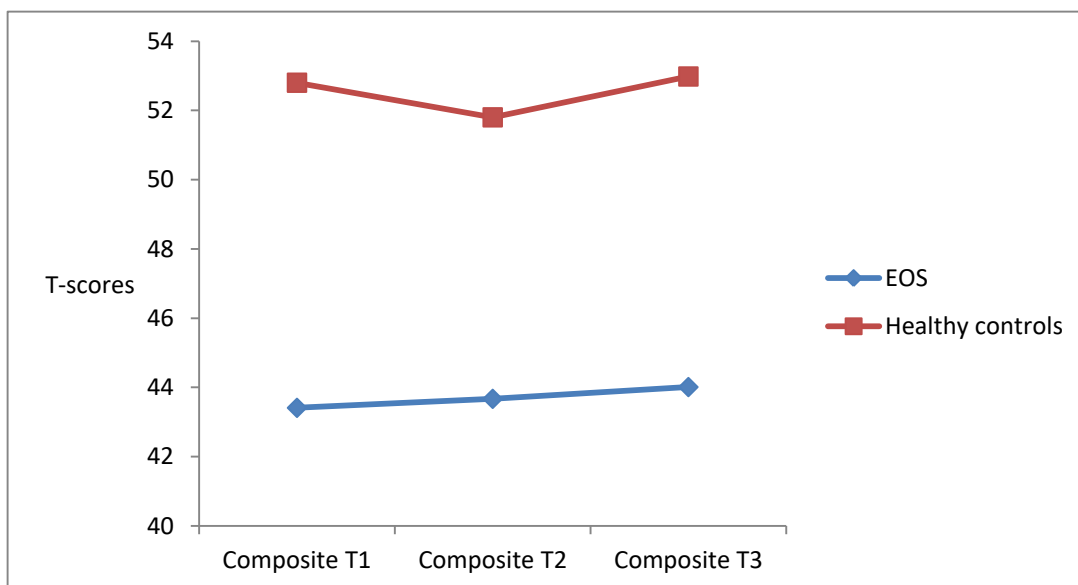
Figure 1

Table 2 Observed values at baseline and estimated values at follow up for the Composite scores

	n	Mean	n	Mean	n	Mean	Mean	Mean

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		value at baseline (SD)		value at year 1 (95% CI)		value at year 2 (95% CI)	change: Year 2 minus baseline (95% CI)	between group change (95% CI); p-value
Patients	29	43.4 (5.9)	18	42.5 (40.6 to 44.5)	18	42.1 (39.9 to 44.4)	-0.86 (-2.35 to 0.64)	-0.20 (-2.00 to 1.59); 0.826
Healthy controls	67	52.8 (5.2)	41	52.4 (51.1 to 53.7)	40	52.1 (50.6 to 53.5)	-0.66 (-1.65 to 0.33)	

To identify possible risk factors of the longitudinal composite score, linear mixed model analyses were performed. The univariable analyses did not detect a relationship between Split-GAF, remission or hospitalizations (times or length) and the composite score, and were thus not included in the multiple regression analysis.

From the univariable analysis DUP, all the PANSS variables (positive, negative and general), and the number of suicide attempts were identified as possible risk factors of the longitudinal composite score (p<.15). However, since the PANSS (positive, negative, and general) baseline scores were strongly correlated, only PANSS general baseline score were included in multivariable analysis, as it was identified as the strongest risk factor. Multiple regression analysis showed that PANSS general and suicide attempt history at baseline were the only risk factors that significantly predicted the longitudinal cognitive course. The results are shown in Table 3.

Table 3 Estimated risk factors of change in Cognitive Composite Score over time in EOS patients using multiple linear mixed models

Parameter	Estimate	SE	df	t	95% CI Lower	95% CI Upper
Intercept	53.16	3.16	53.0	16.80	46.82	59.51
PANSS general	-0.26	0.09	48.8	-2.92**	-0.44	-0.08
Suicide attempts	-2.16	1.01	26.6	-2.15*	-4.23	-0.09
Time	-0.99	0.52	15.9	-1.89	-2.09	0.12

**p<.01,*p<.05

When comparing the dropouts (attended solely at T1) with the ones who continued to T2 and/or T3, the EOS dropouts were more compromised with regard to baseline cognitive functioning (composite scores) than the patients who remained in the study (t(27)=3.3, p<.01). These differences did not appear in the control group.

Discussion

The mixed model supported what is previously reported in the Early-onset Study (Juuhl-Langseth et al., 2014), as well as other longitudinal studies (Frangou et al., 2008; Jepsen, Fagerlund, Pagsberg, Christensen, Hilker, et al., 2010), namely that there seems to be a deficit in the cognitive function in EOS compared to controls, and that the course is relatively stable over a period of two years. Since the control group functioned above average in IQ, this might have affected the results. When adjusting for IQ in the analyses, the controls did experience a larger cognitive change compared to patients. However, the difference was not significant. Furthermore, the EOS dropouts had larger cognitive deficits at baseline than the ones that stayed in the study, which could imply a different cognitive course for these patients. Nevertheless, a stable global cognitive course indicates that degeneration, defined as a

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progressive neurodegenerative process after illness onset, does not occur in EOS within the few first years of diagnosis, a finding which is consistent with most previous studies (Frangou et al., 2008; Jepsen, Fagerlund, Pagsberg, Christensen, Hilker, et al., 2010), but not all (Oie et al., 2010).

We found that a higher amount of general symptoms (PANSS) at baseline significantly predicted a deteriorated longitudinal composite score in EOS. In the separate univariate analyses, both positive symptoms (PANSS) and negative symptoms (PANSS) predicted the cognitive course. However, they both lost their predictive value in the multiple regression analyses. Our findings are in line with previous research from AOS that detects no significant long-term relationship between positive/negative symptoms and cognition (Harvey et al., 2006; Rund et al., 2015; Rund et al., 2004), thus indicating a continuity between EOS and schizophrenia with later onset. Like us, Wozniak et al. (2008) found no significant relationship between psychotic symptoms and cognition in adolescent schizophrenia. Yet, their study did not report an evaluation of general symptoms (Wozniak et al., 2008). The general psychopathology scale of the PANSS measures the severity of the schizophrenic illness (Kay et al., 1987). While the positive and negative scales measure the amount of typical psychotic symptoms, the general scale includes 16 non-specific psychiatric symptoms, i.e. depression, anxiety, guilt feeling and social avoidance. In our study, we examined the total score and not the symptoms separately. Our study therefore gives no indication of the relative effect of specific symptoms included in the scale. However, our findings suggest that general symptoms are a more potent predictor of the neurocognitive course in EOS than the psychotic symptoms. This may imply that cognitive deterioration is influenced by a strong affective response to the illness, rather than a result of irrational or psychotic symptoms in and of themselves.

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As with later onset schizophrenia, the youths with schizophrenia-spectrum disorders have an increased risk of suicide within a year after the onset of psychosis (Sanchez-Gistau et al., 2013), particularly if they have a history of depression and previous suicide attempts (Melle, 2013). Our results indicated that a history of suicide attempts was related to cognitive deterioration. An association between suicidality and neurocognitive functioning in AOS has also been reported in some studies, suggesting a relationship between hopelessness, a greater insight into one's own illness and a higher cognitive functioning on the one side, and a higher risk of suicidality on the other (Delaney et al., 2012; Kim et al., 2003), while other studies report no such associations (Potkin et al., 2003; Zoghbi et al., 2014). To the best of our knowledge, no previous research has investigated the relationship between suicide attempts and long-term cognition in EOS. Hence, our study is the first to demonstrate that a history of suicide attempts at baseline predict a worsened neurocognitive course in EOS. This relationship should be understood in the context of general symptoms, because both suicidal ideation and suicide attempts most likely interact with several symptoms on the general scale, i.e. depression and social avoidance. As suggested by Fialko et al. (2006), suicide attempts in psychosis appear to be caused by an entire range of general symptoms, rather than by the psychotic symptoms alone. Those who suffer from psychosis are often met with stigma, pessimism and exclusion in society (van Os & Kapur, 2009), consequently adding an extra burden to the illness that may affect both general symptoms and suicidality. Furthermore, suicide attempts have been associated with impulsivity as measured by neurocognitive tests (Wang et al., 2014; Wu et al., 2009). Impulsivity is often also connected to cognitive deterioration (Arce & Santisteban, 2006), and both suicide attempts and impulsivity may indicate a higher level of general symptoms. Our findings of a relationship between a history of suicide attempts at baseline and a deteriorated global cognition in EOS after two years

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should be replicated in studies with longer follow-up periods, to examine whether the cognitive worsening endures. Still, the high rate of suicidality in schizophrenia strongly suggests that suicidal ideation and history need to be determined, and protective measures have to be taken while planning the inpatient and outpatient treatment of these patients.

Our study indicated a stable longitudinal cognitive course in EOS, but also that high PANNS general symptoms and number of suicide attempts at baseline predicted cognitive deterioration, which may indicate heterogeneity within the EOS group. Thus, there may be a subgroup of patients who deteriorates over time due to higher levels of general symptoms and suicidality. However, our sample size is too small to isolate such a subgroup, but the hypothesis should be subject to investigation in future research with larger sample sizes.

Like a majority of studies from AOS (Rapp et al., 2013; Rund, 2014; Rund et al., 2015), we found no significant influence of DUP on long-term cognition in EOS, thus there were no signs of neurotoxicity at least in the timeframe measured. In adolescence, the brain matures extensively, and one could assume that a longer DUP would have a more severe impact on cognition in this time period. Nonetheless, we detected no indication of DUP being more critical in adolescent psychosis than in adult psychosis. In line with our findings, Kravariti et al. (2003a) found no significant effect of illness duration on baseline cognitive performance in EOS. Nevertheless, the results of Fraguas et al. (2014) indicated that DUP predicts reduced long-term executive functioning in EOS. A possibility is that DUP affects executive functions more severely than other cognitive domains, and by evaluating composite scores in our study the impact was diffused.

Furthermore, our study did not reveal a significant relationship between Split-GAF and cognition, or between remission before baseline and the longitudinal composite score. In an adult sample, Rund et al. (2015) found that stable remission without relapse in the first

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year predicted a better cognitive course, implying that patients with a stable remission respond better to treatment, and have good prognosis and cognitive trajectories. A possible cause for the divergent results is that remission in a younger population is more unstable, and therefore not a good predictor of cognitive development in EOS. In our study, we defined remission by the disappearance of psychotic symptoms for at least seven days, which is short. It has previously been suggested that six months is an indication of clinical remission via the PANSS (Andreasen et al., 2005; Opler, Yang, Caleo, & Alberti, 2007). Even though 70% of the patients in our EOS group were in remission over a period of 8-17 weeks, none of the patients were symptom free for more than five months before baseline. As a result, remission in our group seemed quite unstable, and would have been nonexistent with a stricter definition of remission (six months).

The present study found no significant relationship among the number of hospitalizations, length of stay in institutions and longitudinal cognition. Even though long-term institutional stays have decreased markedly, hospitalizations occur, often caused by severe psychosis. A recent review concludes that there are minimal indications of cognitive changes due to institutionalizations; whether long or short (Harvey, Loewenstein, & Czaja, 2013), which is supported by our findings.

A limitation of our study is the modest sample size, hence opening for the possibility that a larger sample might reveal more significant associations between clinical variables and long-term cognition. However, our sample size is not particularly smaller than those of other EOS studies with a similar attrition rate (Fraguas et al., 2014; Kravariti et al., 2003a, 2003b; Wozniak et al., 2008). Also, the drop-out of patients and missing data represents a limitation. In longitudinal studies, the ideal is to have a complete set of data and no drop-outs, but this has been difficult to achieve. The mixed model has been recommended over repeated

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measures ANOVA in longitudinal psychological studies with small sample sizes, because of its ability to accommodate missing data points (Krueger & Tian, 2004; Muth et al., 2016). Still, results based on missing data should always be interpreted with caution. As already mentioned, the dropouts in the EOS group had more profound cognitive deficits than the ones who continued, which raises questions about the generalizability of the results. However, in relation to the risk factors measured at T1, the EOS patients at baseline were clinically very similar to those who participated at T2 and T3, both in diagnoses, symptoms and global functioning. Moreover, only one of the patients who had attempted to commit suicide before baseline left the study, thereby indicating that our findings were minimally influenced by drop-outs.

A further limitation concerns medication effect. Approximately 70% of the patients received second-generation anti-psychotics, and we had limited control over medication effects in relation to cognitive achievements. In one study, longer exposure to medication has been reported to predict a lower level of performance in aspects of attention, psychomotor processing speed and spatial working memory (Kravariti et al., 2003a). However, previous analyses of the current material did not detect a relationship between medication and cognitive performance (Juuhl-Langseth et al., 2014).

A final limitation concerns the measurement of clinical variables, especially the unreliable assessment of suicide attempts that was solely based on the patient's self-reports. It is difficult to obtain reliable measures concerning suicide attempts. However, the clinical psychologists involved in the assessments attended regular diagnostic consensus meetings led by well-experienced clinical researchers throughout the entire assessment process, to help ensure inter-rater reliability.

The strengths of the present study are the use of a standardized comprehensive neurocognitive test battery, the MCCB, which facilitate comparisons in future research. Because of the low frequency of EOS, the patient group provides valuable information about baseline cognitive functioning, in combination with a minimized effect of confounding variables associated with chronicity. Furthermore, the longitudinal follow-up studies are of great importance in detecting neurocognitive trajectories in schizophrenia (Bora, Yucel, & Pantelis, 2010; Gur et al., 2014; Rund, 1998).

Conclusions

The EOS patients followed much the same stable cognitive course as found in schizophrenia patients with a later onset, thus confirming continuity between early-onset and adult-onset schizophrenia. Despite the small sample size, clinical characteristics in the early illness period, such as DUP, remission and hospitalization, did not seem to influence the neurocognitive course. Our findings indicate that higher scores of general symptoms, as well as suicide attempt history, predict a deteriorated cognitive course, and should be subject to specific attention in the evaluation and treatment of patients with early-onset psychosis.

the collection, analysis and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

Conflict of interest

No conflicts declared.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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