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ORIGINAL CONTRIBUTION

Course of intelligence deficits in early onset, first episode schizophrenia: a controlled, 5-year longitudinal study

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Abstract Only few prospective longitudinal studies have assessed the course of intelligence deficits in early onset schizophrenia (EOS), and these have used different age appropriate versions of Wechsler Intelligence Scales and age appropriate norms. The post-psychotic development of intelligence in EOS has predominantly been characterized as relatively stable in these studies. However, comparisons of IQs from different test versions based on the different norms may not permit unequivocal interpretations. The objective of the current study was to compare the development of intelligence in EOS patients ($N = 10$) from their first psychotic episode to 5 years of post onset with that of healthy controls ($N = 35$) and patients who at baseline had been diagnosed with other non-affective psychoses ($N = 8$). The same version of a Wechsler Intelligence Scale was administered at both baseline and follow-up assessments, and the same norms were used to derive IQs at baseline and follow-up. Significantly smaller change in mean full scale intelligence quotient (FSIQ) was found in diagnostically stable EOS patients compared with healthy controls during the follow-up period. However, no statistically significant difference in mean FSIQ change was observed between patients with EOS and patients with other non-affective psychoses, although this result must be interpreted with caution due to the small sample sizes. The results suggest abnormally slow acquisition of new intellectual information and skills in EOS patients during the first 5 years after full clinical presentation.

Keywords Intelligence · IQ · Longitudinal · Adolescent · Schizophrenia · Early onset psychosis

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Introduction

Very few prospective longitudinal studies have examined the course of intelligence deficits in early onset schizophrenia (EOS; onset before age 18). Early onset schizophrenia is associated with premorbid impairments in intelligence [16], speech development, social functioning, and academic performance [1, 51]. In addition, more substantially restricted premorbid affect, odd beliefs, and odd speech (schizoid and schizotypal traits) have been found in EOS than in adult-onset schizophrenia [51]. Substantial percentages of patients with EOS have been found to have a chronic form of the illness [33, 44] with a poor long-term psychosocial outcome [15, 44] and with more severe social and educational impairments than non-schizophrenic psychoses [25].

Deficits in attention, working memory, and verbal learning and memory, but not in intelligence, have been found to be associated with short-term functional outcome in EOS [9]. Nevertheless, intelligence is an important aspect of cognitive functioning in EOS and early onset

schizophrenia spectrum disorders because intelligence deficits may explain deficits in planning [34] and working memory [49] that are associated with the disorder. Intelligence deficits, as reflected in significantly lower full scale intelligence quotient (FSIQ), verbal intelligence quotient (VIQ), and performance intelligence quotient (PIQ) have been observed in patients with EOS at the time of their first episode [12, 54]. Significant deficits in FSIQ and PIQ have also been found in patients with recent-onset EOS [34]. Using prorated IQ estimates based on a subset of an IQ test battery, marginally [32] or significantly lower intellectual performance has been observed in patients with EOS [40, 43] as well as in patients with early onset schizophrenia spectrum disorders [20, 49]. In addition, a study reports the mean FSIQ in EOS to be 1.6 SD below the population mean [38]. However, the intelligence deficits in EOS are not significantly different from samples of other psychotic patients [12, 35, 38]. When compared with non-psychotic psychiatric disorders, significantly lower PIQ were observed in a sample of adolescent patients with schizophrenia or other psychoses [19]. Based on the information from studies that include healthy controls and exclude patients with mental retardation, we calculated effect sizes for intelligence deficits in EOS. With regard to FSIQ, Cohen's *d* was in the order of 1.77 [54], 1.61 [12], to 0.90 [34]; and with regard to brief IQ estimates, Cohen's *d* varied from 2.18 [43], 1.37 [20], 1.18 [40], to 0.56 [32]. Despite the differences in exclusion criteria and IQ measures, these findings point to substantial intelligence deficits in young patients with EOS.

A recently published controlled longitudinal study found a significant increase in a composite measure of global cognitive function over a 2-year follow-up period in a mixed group of patients with EOS or other psychosis and the control group [37]. Regarding development of intelligence, premorbid intellectual performance deficits aggravate around the time of onset of very early onset schizophrenia also referred to as childhood onset schizophrenia (COS; onset by age 12), and a mean loss of 9.96 FSIQ points has been observed in the period from 2 years before illness onset to 1.7 years after [16]. The first prospective longitudinal study [7] of the course of intelligence impairment in patients with COS found a significant decline in post-psychotic FSIQ from baseline testing at 12.3 years of age over a mean retest interval of 2.9 years. In contrast, a later study of a larger cohort of patients with COS, including the previous sample of patients, found no decline in mean FSIQ across multiple follow-up assessments, with approximately 2-year intervals across the 2–8+ years follow-up period. This seems to reflect long-term stabilization of FSIQ starting about 2 years after illness onset and continuing during adolescent and early adult years up to 13+ years after illness onset [16]. A recent longitudinal study used a case–control design to assess the development of deficits in several domains of cognitive functioning, including intelligence, in adolescent patients with EOS using two time points of assessments with a mean interval of 4 years. A statistically significant, but relatively small improvement in mean FSIQ was found in patients and controls with no significant between-group difference in amount of change [14]. These longitudinal studies used age appropriate versions of Wechsler Intelligence Scales and age appropriate norms that make assessments of IQ from childhood and well into adulthood possible. However, comparisons of IQs from different test versions based on different norms may not permit unequivocal interpretations.

The objective of the current study was to compare the development of intelligence in EOS patients from their first psychotic episode to 5 years post onset with healthy controls and patients who at baseline had been diagnosed with other psychoses. In effort to avoid some of the interpretative problems, we administered the same version of the Wechsler Intelligence Scale at baseline and follow-up assessments and used the same norms to derive IQs at baseline and follow-up.

Methods

Sample

At baseline, 48 patients with first episode, non-organic, psychosis fulfilling the ICD-10 [55] diagnostic criteria for one of the following diagnoses were recruited: schizophrenia; persistent delusional disorders; acute and transient psychotic disorders; schizoaffective disorders; other non-organic psychotic disorders; mania with psychotic symptoms; bipolar affective disorder (current episode manic or current episode severe depression with psychotic symptoms); severe depressive episode with psychotic symptoms; and schizotypal disorder. Patients were between 10 and 17 years of age at the time of their first contact with one of the three child- and adolescent psychiatric departments in the Copenhagen and Northern Sjaelland, Denmark. The patient exclusion criteria were a premorbid lifetime history of mental retardation [35, 43], the presence of any chronic somatic disease, neurological illness, severe head injury, compulsory hospitalization, antipsychotic treatment for more than 6 months, or fulfillment of the ICD-10 diagnostic criteria for psychotic disorder (F1x.5) due to psychoactive substance use. One patient withdrew during the baseline assessment and one subject was excluded because of hydrocephalus, leaving 46 patients in the sample. At baseline, participants and parents were informed about the follow-up study and gave

informed consent to be contacted for a follow-up assessment. The baseline assessment included age of onset of psychotic symptoms, severity of psychotic and other psychiatric symptoms, severity of neurocognitive deficits [12] (significant IQ, memory, attention, and executive function deficits, but no IQ differential factor profile were found in EOS patients), and structural brain abnormalities [41] (significantly larger volumes in the body of right lateral ventricle was observed in EOS patients).

As the present analysis focus on EOS in the context of non-affective psychoses, patients diagnosed with schizotypal disorder or affective psychoses at baseline were excluded (see Fig. 1). Some patients were unable to complete the baseline assessment of intelligence due to severe anxiety, psychotic symptoms, lack of motivation, or they had not been administered the Wechsler Intelligence Scale for Children, Third Edition version (WISC-III) [52] or declined participation in the follow-up study. These and other sources of attrition resulted in ten patients with a baseline diagnosis of EOS and eight patients with other non-organic, non-affective psychoses (EOP) (delusional disorder ($N = 1$); acute and transient psychotic disorders ($N = 2$); other non-organic psychotic disorders ($N = 5$)) with complete WISC-III data from baseline and follow-up in the current patient groups. For a detailed description of the demographic characteristics see Table 1. At baseline assessment, one patient with EOS was antipsychotic naïve while the remaining nine patients (90.0%) were treated with various types of typical (4 patients) and atypical antipsychotic medications (5 patients) with a mean treatment duration of 9.6 weeks (SD = 5.7) (see Table 1). At that time, five of the eight patients with EOP (62.5%) were treated with various types of typical (1 patient) and atypical antipsychotic medications (3 patients) (1 patient received both typical and atypical antipsychotic medications), with a mean treatment duration of 4.7 weeks (SD = 5.5).

At baseline, healthy controls matched with the 46 patients on gender and age (within 6 months) were recruited from schools and institutions in Copenhagen. Exclusion criteria for controls were a history of psychiatric disorders, mental retardation, learning disability, chronic somatic or neurological disease, head injuries, abuse of psychoactive substances, or a psychotic disorder in any first-degree relatives. Figure 1 shows the number of controls lost to the different sources of attrition including the youngest healthy control subject (age 15 at follow-up) excluded (as an outlier) due to extreme improvement in performance at follow-up compared with baseline. For a detailed description of the demographic characteristics, see Table 1.

After complete written and oral description of the follow-up study, written informed consent was obtained from all subjects and from a parent, if the subject was younger than 18 years of age. The follow-up study was approved by the local Ethics Committees and carried out in accordance with the Helsinki declaration. Follow-up assessments were carried out on an average 5.5 (SD = 0.4) years after the baseline study. Patients and controls received a small financial incentive for their participation.

Assessment of psychopathology

ICD-10 [55] diagnoses at baseline and follow-up were reached by consensus using the Schedules for Clinical Assessment in Neuropsychiatry Version 2.1 (SCAN 2.1) [56] based on the video-monitored interviews. As described, two clinical subgroups were created based on the baseline diagnoses, consisting of EOS ($N = 10$) and EOP ($N = 8$). The severity of psychotic symptoms was assessed using the Scale for the Assessment of Positive Symptoms (SAPS) [3] and the Scale for the Assessment of Negative Symptoms (SANS) [2]. Other psychiatric symptoms were also assessed, the results of which are beyond the scope of the current paper and will be presented elsewhere. As shown in Table 1, psychotic symptoms for all patients were grouped into the psychoticism, disorganized, and negative symptom dimensions [4]. The age of onset of fully developed psychotic symptoms was assessed at baseline based on the information derived from the Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS) [21, 36] administered to patients and parents, as well as information from other sources. Control subjects were also interviewed using SCAN 2.1 at follow-up, to rule out the onset of a psychiatric disorder during the follow-up period.

Assessment of socioeconomic status

Parental education and occupation at baseline were rated into six social classes according to criteria described by Hansen [22]. These classes were organized in three groups (see Table 1). In addition, parental household income at baseline was rated into one of three economic status groups (low, middle, or high).

Assessment of intelligence

Cognitive deficits at baseline were assessed with a comprehensive neuropsychological test battery including, measures of intelligence, attention, executive functions, verbal memory, as well as cognitive and motor reaction times. At baseline, the neuropsychological test battery was administered by BF and has been described in detail elsewhere [11, 12]. For the purpose of a valid comparison of cognitive performance over time, the baseline neuropsychological test battery including WISC-III was re-administered to all subjects at the follow-up assessment. With one exception, the

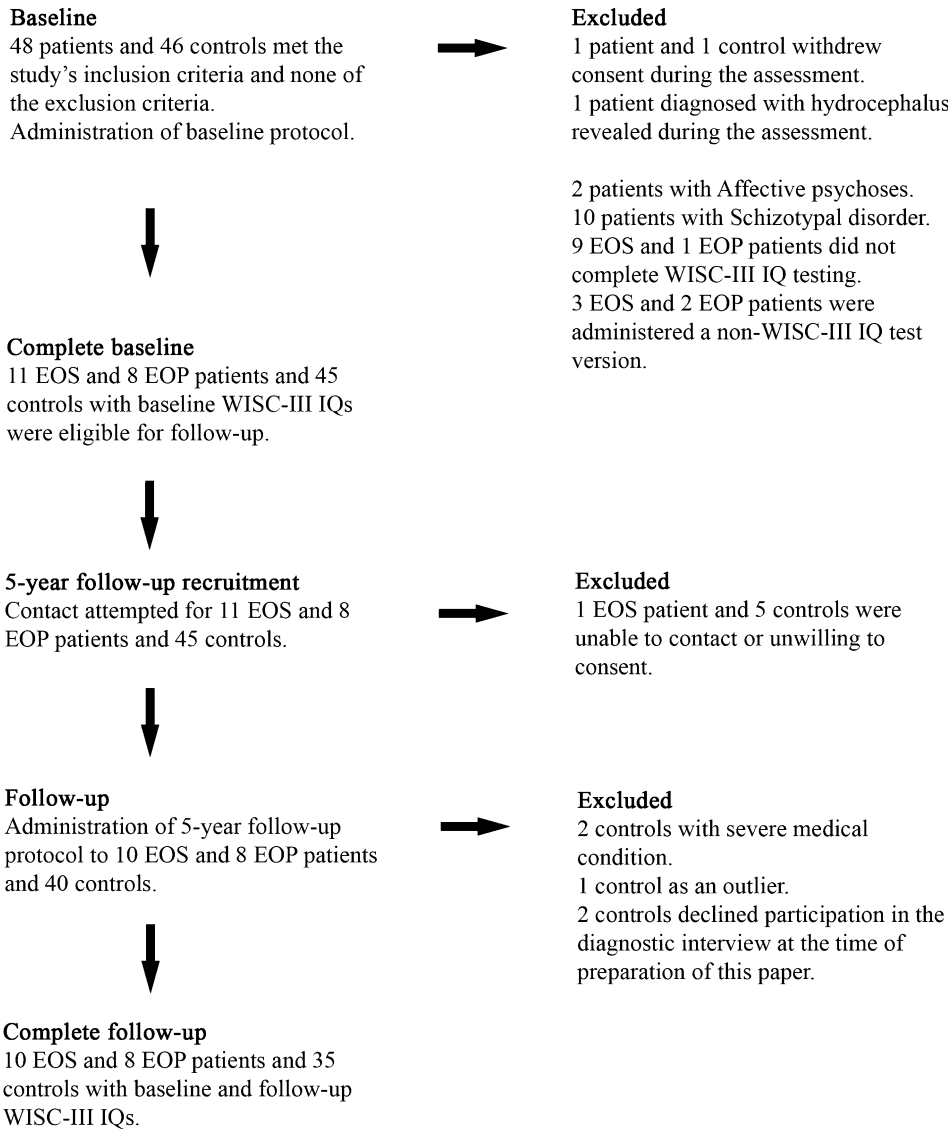

Fig. 1 Retention of EOS and EOP patients and healthy controls from baseline to follow-up assessment

neuropsychological tests were administered in the same fixed order at follow-up as at the baseline assessment. Additional neuropsychological tests were also administered at follow-up. To compare the change in IQ from baseline to follow-up, follow-up WISC-III FSIQ, VIQ, and PIQ were derived using the baseline norms. Changes in IQ were calculated by subtracting each baseline IQ from the corresponding follow-up IQ. Thus, change in FSIQ, PIQ and VIQ was used as the unit of measurement of intelligence development.

The study included one EOS patient who at baseline obtained an IQ below 70 and, therefore, was co-morbid with mental retardation and mental or behavioral disorders due to multiple drug use and use of other psychoactive substances at baseline and due to the use of alcohol at follow-up. In addition, the study included one patient with EOP and co-morbid mental or behavioral disorders due to the use of cannabinoids at follow-up and one EOS patient, who at follow-up was treated with anticholinergic medication, which may impair cognition [45]. Based on the clinical assessment of JRJ (the interviewer) and self-reported alcohol and drug use on selected SCAN 2.1 items [56] at the beginning of every test session, none were judged intoxicated at the time of neuropsychological testing. The neuropsychological assessment at follow-up was administered by JRJ (neuropsychologist), who was blind with regard to the neuropsychological test scores at baseline.

Table 1 Demographic and clinical characteristics for patients with EOS or EOP and controls

	EOS ($N = 10$)	EOP ($N = 8$)	Controls ($N = 35$)	p[a]
Mean age at baseline[b] (SD) (years)	15.5 (1.9)	15.3 (1.4)	15.7 (1.5)	0.693/0.815
Mean age at follow-up[c] (SD) (years)	21.1 (1.9)	20.6 (1.6)	21.3 (1.6)	0.666/0.579
Mean follow-up interval (SD) (years)	5.6 (0.6)	5.3 (0.3)	5.6 (0.3)	0.898/0.288
Gender (female/male)	6/4	4/4	20/15	0.872/0.671
Education at baseline[d] (SD) (years)	8.2 (1.9)	8.5 (1.1)	9.3 (1.7)	0.095/0.723
Antipsychotic treatment				
Baseline (medicated/drug naïve)[e]	9/1	5/3		
Follow-up (medicated/not medicated)[f]	5/5	1/7		
Parental education/occupation[g]				
Academic/bachelor	20.0%	62.5%	54.3%	
Expert/skilled	50.0%	37.5%	45.7%	
Unskilled/unemployed	30.0%	0.0%	0.0%	0.002/0.099
Parental income (household)[g]				
High income	40.0%	37.5%	82.9%	
Middle income	40.0%	37.5%	11.4%	
Low income	20.0%	25.0%	5.7%	0.026/0.968
Mean age at onset of psychotic symptoms (years) (SD)	11.9 (3.6)	13.0 (4.0)		/0.544
				p[h]
Mean psychoticism dimension[i,l] (SD)				
Baseline	3.8 (1.0)	2.9 (0.7)		
Follow-up	2.3 (1.3)	0.8 (0.9)		0.014/0.001
Mean disorganization dimension[j,l] (SD)				
Baseline	1.1 (1.0)	1.2 (1.3)		
Follow-up	1.2 (1.3)	0.3 (0.6)		0.757/0.036
Mean negative symptom dimension[k,l] (SD)				
Baseline	2.6 (0.9)	2.1 (0.6)		
Follow-up	2.0 (1.3)	1.5 (0.8)		0.180/0.157

[a] EOS group versus control group/EOS group versus EOP group

[b] Age range at the time of neuropsychological testing at baseline, EOS: 11–17 years, EOP: 13–17 years, and controls: 12–18 years

[c] Age range at the time of neuropsychological testing at follow-up, EOS: 17–23 years, EOP: 18–22 years, and controls: 17–23 years

[d] I.e. the number years of school attendance, ranges: EOS ($N = 9$): 4–10 years, EOP: 7–10 years, controls: 6–12 years

[e] EOS: 1 patient zuclopenthixol daily dose (dd) 8 mg; 1 patient pimozide dd 4 mg and chlorprothixene dd 15 mg; 1 patient risperidone dd 1 mg and olanzapine dd 5 mg; 2 patients risperidone dd 2 mg; 1 patient risperidone dd 3 mg; 1 patient perphenazine dd 12 mg; 1 patient perphenazine dd 16 mg; 1 patient olanzapine dd 20 mg. EOP: 1 patient zuclopenthixol dd 4 mg and olanzapine dd 17.5 mg; 1 patient risperidone dd 2 mg; 1 patient risperidone dd 3 mg; 1 patient olanzapine dd 7.5 mg; 1 patient chlorprothixene dd unknown

[f] EOS: 1 patient flupenthixole decanoate dose unknown (every 2 weeks) and haloperidole daily dose (dd) 4 mg; 1 patient levomepromazine dd 100 mg and quetiapine dd 400 mg and risperidone (Risperdal Consta®) 50 mg (every 2 weeks); 1 patient risperidone dd 1 mg; 1 patient quetiapine dd 450 mg; 1 patient perphenazine decanoate 108 mg (every 2 weeks). EOP: 1 patient clozapine dd 250 mg

[g] Frequency within patient- and control group at baseline

[h] EOS baseline rating versus follow-up rating/EOP baseline rating versus follow-up rating

[i] ($\sum$ global rating of severity of hallucinations score; global rating of severity of delusions score)/2

[j] ($\sum$ global rating of severity of bizarre behavior score; global rating of positive formal thought disorder score; inappropriate affect item rating score)/3

[k] ($\sum$ global rating of affective flattening score; global rating of alogia score; global rating of avolition–apathy score; global rating of anhedonia–asociality score)/4

[l] 0 = none; 1 = questionable; 2 = mild; 3 = moderate; 4 = marked; 5 = severe

Statistical analyses

Univariate analyses were conducted using SPSS 11.0. The χ^2 test was used for comparison of nominal data between independent groups. The normality of distributions of IQs and change in IQs was confirmed using Shapiro–Wilk tests. Independent samples *t* tests were used to compare data from independent groups, whereas paired sample *t* tests were used to compare within-group data between baseline and follow-up. The analysis of covariance (ANCOVA) with FSIQ at baseline as the covariate was used to compare IQ change between EOS patients and healthy controls. ANCOVA with FSIQ, negative, and disorganization symptom severity ratings at baseline as covariates was also used to compare change in IQ between EOS and EOP patients. Pearson correlation was calculated to evaluate possible relations between symptom severity at baseline and change in IQs over time in EOS patients as well as to evaluate cross-sectional relations between symptom severity and IQs at baseline and follow-up. Finally, Pearson correlation was calculated to assess the degree of stability of FSIQ over time in EOS and healthy controls. Most symptom variables had skewed distributions and for these variables, all analyses were repeated using relevant rank tests (Mann–Whitney, Wilcoxon and Spearman correlations).

Owing to the small sample sizes and increased risk for type II errors, we did not correct for multiple comparisons. Significance level was set at the 0.05 level.

Results

Psychopathology and sociodemographics

At follow-up, the baseline diagnosis of schizophrenia was confirmed in all cases in the EOS group. In contrast, diagnostic instability was highly prevalent in the EOP group where the baseline diagnoses were changed in 87.5% of the cases. Five of the 8 EOP patients [62.5%) were diagnosed with a non-psychotic disorder or no psychiatric disorder at follow-up (schizophrenia ($N = 1$); delusional disorder ($N = 1$); other non-organic psychotic disorders ($N = 1$); moderate depressive episode ($N = 1$); recurrent depressive disorder, current episode moderate ($N = 1$); panic disorder ($N = 1$); disturbance of activity and attention ($N = 1$); examination and observation for other reason ($N = 1$)]. Demographic and clinical characteristics of the follow-up samples are described in Table 1. In the EOS group, the average age of the first psychotic symptoms was 11.9 (SD = 3.6) years. Table 1 also shows that the psychoticism dimension severity ratings improved significantly in the EOS group from baseline to follow-up, whereas no significant differences were observed regarding disorganization and negative symptom dimension severity ratings over that time period (Wilcoxon tests confirmed these results). Fifty percent of EOS patients and 12.5% of EOP patients reported being treated with antipsychotic medications (2 EOS patients with typical antipsychotic medications; 2 EOS patients and 1 EOP patient with atypical antipsychotic medications; 1 EOS patient with both types of antipsychotic medications) at the time of the follow-up assessment (see Table 1). Since the baseline assessment, 20% of EOS patients and 12.5% of EOP patients reported having been continuously treated with antipsychotic medications. One EOS patient also received anticholinergic treatment at follow-up.

No significant differences in background characteristics were found between the EOS and EOP groups (see Table 1). No significant differences were found between these groups regarding negative and disorganization symptom severity at baseline, while a trend was observed for psychoticism symptom severity (significant for the Mann–Whitney *U* test).

Patients with EOS and healthy controls did not differ regarding age and gender distribution, but parental income and education/occupation differed significantly between the groups.

Intelligence scores

IQs were significantly lower in EOS than in the controls at both baseline and follow-up assessments (see Table 2). For the EOS group paired *t* tests revealed no significant difference between baseline and follow-up for any of the three IQs. For the controls, statistically significant increases in FSIQ ($t = 12.26$, $df = 34$, $p < 0.001$), VIQ ($t = 6.98$, $df = 34$, $p < 0.001$), and PIQ score ($t = 11.67$, $df = 34$, $p < 0.001$) were seen during the follow-up interval.

Table 3 shows a significant difference between the EOS and the control group in mean change in FSIQ, whereas the between-group difference in mean change in VIQ and PIQ were only marginally significant. Preliminary analyses did not reveal any significant or substantial correlations between baseline FSIQ and change in any IQ in the EOS or the healthy control group, but because of the highly significant between-group difference in mean FSIQ at baseline, ANCOVA was conducted with baseline FSIQ as covariate. This analysis revealed a significant difference between EOS and the healthy controls with respect to mean change in FSIQ and VIQ, but not regarding mean change in PIQ. The adjusted mean change in IQ, 95% confidence intervals, and *p* values are shown in Table 3. Separate exclusion of the EOS patient with co-morbid mental retardation and a substance use disorder and the EOS patient treated with anticholinergic medication at follow-up, did

Table 2 Mean FSIQ, VIQ, and PIQ at baseline for the EOS, EOP, and control group and equivalent 'FSIQ', 'VIQ', and 'PIQ' based on the same baseline norms at follow-up

	EOS ($N = 10$) Mean (SD)	EOP ($N = 8$) Mean (SD)	Controls ($N = 35$) Mean (SD)	p[a]
Baseline				
FSIQ	87.4 (14.5)	89.0 (13.1)	110.1 (12.0)	<0.001/0.812
VIQ	87.0 (15.8)	90.4 (15.6)	108.3 (13.9)	<0.001/0.657
PIQ	91.0 (15.7)	89.9 (15.0)	110.0 (11.8)	<0.001/0.880
Follow-up				
'FSIQ'	93.1 (20.5)	101.8 (13.8)	124.9 (13.3)	<0.001/0.324
'VIQ'	91.4 (18.1)	97.0 (18.7)	118.5 (13.6)	<0.001/0.529
'PIQ'	97.1 (24.0)	107.3 (8.0)	126.5 (13.2)	0.004/0.235

[a] Independent samples t test of EOS group versus control group/EOS group versus EOP group

not change the statistical significance of the unadjusted or baseline FSIQ adjusted comparisons of mean FSIQ change between the remaining nine EOS patients and controls. Parental baseline education/occupation and household income did not significantly predict mean change in any IQ and they were consequently not included as covariates in the statistical models.

Regarding the stability of FSIQ over the time interval, Pearson $r = 0.87$ ($p = 0.001$) in EOS patients and $r = 0.85$ ($p < 0.001$) in healthy controls.

No significant differences in IQs at baseline or follow-up were observed between EOS and EOP groups (see Table 2). In contrast to the EOS group, significant increase at follow-up was shown in the EOP group regarding FSIQ ($t = 5.12$, $df = 7, p = 0.001$), VIQ ($t = 2.99, df = 7, p = 0.020$), and PIQ ($t = 4.36$, $df = 7$, $p = 0.003$). T tests showed no significant difference in any IQ change score between the EOS and EOP groups (see Table 4). Adjusting for FSIQ, negative, and disorganized symptom severity at baseline, the between-group difference in mean change in FSIQ, VIQ, and PIQ remained non-significant (see Table 4). The adjusted mean changes in IQs are also shown in Table 4. After exclusion of one EOS and one EOP patient with substance use disorders, the difference in mean change in FSIQ between the remaining EOS and EOP patients was still non-significant ($t = -1.10$, $df = 14$, $p = 0.290$) and confirmed after adjusting for baseline FSIQ, negative, and disorganized symptom severity ($F_{(1,11)} = 0.78$, $p = 0.396$). After exclusion of the EOS patient treated with an anticholinergic medication, the difference in mean change in FSIQ between the remaining EOS and EOP patients was still non-significant ($t = -1.51$, $df = 15$, $p = 0.152$) and confirmed after adjusting for baseline FSIQ, negative, and disorganized symptom severity ($F_{(1,12)} = 1.77$, $p = 0.208$).

Correlations between IQ and psychopathology ratings

In the EOS sample, only modest and non-significant correlations were observed between change in FSIQ, VIQ, and PIQ over time and severity of negative and disorganization symptoms at baseline (these results were confirmed using Spearman's rho).

At baseline, no cross-sectional correlation coefficients between the three IQs and the three symptom dimension severity ratings obtained statistically significance. These correlation coefficients were of modest size and five of the nine were even positive (similar results were found when using Spearman's rho). At follow-up, all cross-sectional correlation coefficients between the three IQs and the three symptom dimension severity were statistically non-significant and negative. The correlation coefficients between negative symptom severity and IQs were in the medium to large range. The correlation coefficients between IQs and psychoticism symptom severity were small, whereas they were in the small to large ranges regarding disorganization symptom severity and IQs. Somewhat similar results were found when using the non-parametric Spearman's rho, although the correlation between the follow-up negative symptom severity and FSIQ attained statistical significance (Spearman's rho $= -0.65$, $p = 0.043$). In addition, the follow-up disorganization symptom severity and PIQ was statistically significant (Spearman's rho $= -0.66$, $p = 0.038$), whereas no significant correlations between follow-up psychoticism symptom severity and IQs were found, similarly to the parametric correlations.

Table 3 Unadjusted and adjusted comparisons of mean change in FSIQ, VIQ, and PIQ between EOS patients and controls

	EOS ($N = 10$)		Controls ($N = 35$)		p[a]	p[b]
	Mean (SD)	Adjusted mean[c]	Mean (SD)	Adjusted mean[c]		
FSIQ	5.7 (10.8)	5.9 (−0.3–12.2)	14.8 (7.1)	14.7 (11.8–17.7)	0.003	0.021
VIQ	4.4 (7.5)	2.3 (−4.1–8.8)	10.1 (8.6)	10.7 (7.7–13.8)	0.063	0.031
PIQ	6.1 (17.4)	8.8 (0.4–17.2)	16.5 (8.4)	15.7 (11.8–19.7)	0.096	0.163

[a] Independent samples t tests; unadjusted

[b] Analyses of covariance; adjusted for baseline FSIQ

[c] 95% confidence interval

Table 4 Unadjusted and adjusted comparisons of mean change in FSIQ, VIQ, and PIQ between EOS and EOP patients

	EOS ($N = 10$)		EOP ($N = 8$)		p^a	p^b
	Mean (SD)	Adjusted mean[c]	Mean (SD)	Adjusted mean[c]		
FSIQ	5.7 (10.8)	5.7 (−1.4–12.9)	12.8 (7.0)	12.7 (4.7–20.8)	0.131	0.191
VIQ	4.4 (7.5)	4.8 (−0.5–10.1)	6.6 (6.3)	6.1 (0.2–12.1)	0.513	0.730
PIQ	6.1 (17.4)	5.7 (−5.7–17.1)	17.4 (11.3)	17.8 (5.1–30.6)	0.133	0.159

[a] Independent samples *t* test

[b] Analyses of covariance; adjusted for baseline FSIQ, negative and disorganization symptom severity

[c] 95% confidence interval

Discussion

To our knowledge, this is the first study in which identical Wechsler IQ test version and baseline norms were used at both baseline and follow-up assessments in early onset schizophrenia patients. This strategy attempts to avoid possible confounding associated with comparison of IQs derived from different IQ test versions and norms. Using this approach, we compared the IQ changes in EOS patients from first episode to 5 years post onset with healthy controls and patients who at baseline had been diagnosed with other psychoses. All patients had received standard treatment in the 5 years since illness onset, and the EOS patients were all diagnostically stable (i.e., still diagnosed with schizophrenia) at 5 year follow-up. In comparison, diagnoses in the EOP group were much less stable. The average change in FSIQ was significantly smaller in the EOS group than in the healthy control group, while the results were only marginally significant for mean change in VIQ. When adjusting for FSIQ at baseline, statistically significant between-group differences were observed for mean change in both FSIQ and VIQ. With regard to change in PIQ, both unadjusted and baseline FSIQ adjusted analyses revealed non-significant differences between EOS and the control group. Given the small sample size, statistical power is an obvious problem, and the results for change in PIQ are ambiguous. The lack of statistical significance in mean change in PIQ may reflect a type II error given the relatively large observed differences in mean PIQ increase (cf. Table 3), but the pattern of IQ changes suggests that when compared with healthy controls, EOS patients show less serious developmental deficits with the 'non-verbal' performance subtests than with the verbal subtests. We interpret this pattern of results as suggesting an abnormally small average growth in general and verbal intelligence during the first 5 years after full clinical presentation in EOS patients. If perfectly equivalent age-relevant IQ test versions and norms had been used, the observed subnormal mean gain in test scores in EOS patients during this illness phase would most likely have led to a decline in mean FSIQ at follow-up. This mean FSIQ decline would not reflect deterioration of acquired intellectual knowledge and skills, but subnormal learning of new information and skills given the improvement, albeit non-significant, in mean intellectual performance observed in our EOS patient group. Thus, our results did not support post-onset deterioration in intelligence, and we interpret our results as in accordance with the neurodevelopmental model of schizophrenia [53].

The abnormally low increase in mean FSIQ and VIQ in our sample of EOS patients seems to contrast with the earlier findings of relative stability in age-corrected FSIQ persisting up to 13+ years after the onset of psychosis [16]. This finding of long-term stability in FSIQ is corroborated by similar, minor and statistical significant improvements in age-corrected FSIQ in EOS patients and controls over a mean interval of 4 years [14]. A possible explanation for the different findings may be methodological since previous longitudinal studies of intelligence in EOS and COS administered age appropriate childhood and adult IQ test versions. In contrast, we administered the same childhood IQ test at both assessments and used the baseline norms at follow-up to avoid possible differences between assessment methods and norms. Ceiling effects may be a potential problem associated with re-administration of a childhood IQ test version to young adults, but none of the patients with EOS or EOP obtained maximum scores in any WISC-III subtest at follow-up. However, 11.4% and 31.4% of the healthy controls obtained maximum scores in at least one verbal subtest and one non-verbal subtest, respectively, and this uneven distribution of ceiling effects may have created a bias toward underestimating the magnitude of the between-group differences in change of intellectual performance.

In contrast to Gochman et al. [16] and Frangou et al. [14], we included one EOS patient with both mental retardation and mental or behavioral disorders due to multiple drug use and use of other psychoactive substances at baseline and due to use of alcohol at follow-up. However, previous studies found that approximately 30% of early onset schizophrenic patients are mentally retarded [26], and consequently mentally retarded patients should be included in representative samples of early onset, first presentation schizophrenia patients.

The significant increase in IQs observed in healthy controls cannot be explained by practice effects given the 5-year time interval between the two assessments, as non-significant and negligible differences in mean WISC-III FSIQ and PIQ have previously been demonstrated over a shorter interval [8]. The small increases in IQs in EOS patients may to some extent reflect test performance factors rather than the amount of growth in intelligence. Possible negative influences on IQ test performance from attention- and verbal memory deficits associated with EOS may have worsened during the follow-up interval, as significant declines in immediate verbal memory [14] and attention have been observed after the onset of EOS [14, 39]. Also, using a cross-sectional design, attention deficits in EOS have been shown to worsen with increasing age [46]. Thus, deterioration of specific cognitive functions may have introduced bias toward low IQ test performance at follow-up and consequently led to an underestimation of the true gain in intelligence in EOS patients over time. However, decline in these cognitive functions may also interfere with the ability of EOS patients to acquire new information and skills and thus cause real reduction in intelligence growth.

Evaluating the validity of IQs in the context of psychopathological symptom severity at the time of test administration, we interpret the baseline pattern of non-significant and predominantly small correlations between severity of symptom dimensions and IQs as reflecting small effects of psychopathological symptom severity on intellectual performance. At the 5-year follow-up assessment, significant correlations between IQs and negative and disorganization symptom severity were found, whereas IQs appear to be relatively independent of psychotic symptom severity. Given the questionable and mild mean negative and disorganization symptom severity at follow-up, we conclude that the IQs obtained in the chronic phase of this EOS sample are essentially unbiased by schizophrenia symptoms.

Another possible influential factor in relation to the development of intelligence in EOS is antipsychotic medication, which was not investigated in this naturalistic study, as it was impossible to control the medication administered over a 5-year period. The influence from antipsychotic medications on intellectual performance may be of minor importance, as the improvements in overall cognitive function associated with atypical antipsychotic treatment are of relatively small magnitude [31, 59], and some of the cognitive improvements found in other studies have been suggested to be caused by practice effects [18] and/or expectation biases [31]. In addition, a meta-analysis found no relationship between neuroleptic dose and IQ effect sizes in adults [23]. The treatment in our EOS sample at follow-up included various first-generation antipsychotic medications including perphenazine that has been found to have only small effects on overall cognitive function, similar to the effects of atypical antipsychotic medications [31]. However, as 90% of the EOS sample was treated with antipsychotic medication at baseline and only 50% at follow-up assessment, we cannot exclude the possibility that the difference in mean FSIQ and VIQ change between EOS patients and healthy controls may have been influenced by the cessation of antipsychotic medication. However, the high FSIQ retest coefficient observed in our EOS patients indicates IQ stability similar to the stability in healthy controls, and this finding also suggest that FSIQ is relatively unbiased in both the early and chronic EOS phase.

A significant IQ decline has been reported around the time of onset of COS [16] and adult schizophrenia [58]. As the baseline assessment in our study took place at the time of the first psychotic episode, it is possible that onset-related decline in intelligence continued in some patients after baseline assessment. However, considering the mean age of 11.9 years at onset of psychotic symptoms in the EOS patients and the mean age of 15.5 years at the baseline assessment (a mean interval of 3.6 years), the effects of onset-related IQ decline is likely to be negligible.

One of the limitations of the study is the lack of administration of urine drug detection tests that are preferable to clinical assessment and self-reported information on alcohol and drug use. The small patient sample sizes clearly limit the generalizability of our results and reduce the statistical power to detect changes in intellectual performance. Statistical significant differences were found between patients and controls despite the small sample sizes, but the lack of statistically significant differences in mean FSIQ and PIQ changes between EOS and EOP groups must be interpreted with caution due to the small sample sizes, as the results likely may reflect a type II error given the relatively large observed differences in mean FSIQ and PIQ increases (cf. Table 4). Comparing change in IQs between EOS and EOP groups, baseline negative and disorganization symptom severity ratings were thought to be appropriate covariates in addition to FSIQ because they have been found to be associated with intellectual performance deficits [6, 10, 27]. In addition, negative but not positive symptomatology is associated with cognitive performance in EOS [5].

The observed positive predictive value of 100% for early onset schizophrenia in our EOS subgroup points to high diagnostic stability. High long-term stability for early onset schizophrenia has also been found in both studies with follow-up assessment blind to initial diagnoses [24, 25] and studies without blind re-assessment [30]. Nevertheless, substantially lower long-term diagnostic stability for early onset schizophrenia has also been reported [48]. The stability of Other nonorganic psychotic disorders (F28) is low, as indicated by a positive-predictive value of 20%. This estimate appears in line with the low long-term positive predictive value of 0% for early onset atypical psychosis

[25], 33% for early onset psychosis not otherwise specified (NOS) [30], and 17% for early onset psychosis NOS in a study that probably did not include blind re-assessment [13]. Our results suggest that the diagnostic distinction between schizophrenia and other non-organic psychotic disorders (F28) at illness onset is of long-term clinical significance in early onset patients.

In healthy children and adolescents, FSIQ is associated with whole-brain gray matter volume [42, 57] and with left and right parietal, frontal, temporal lobe, and cingulate gray matter volumes [57]. In COS patients, an abnormal total, frontal, temporal, and parietal gray matter reduction has been demonstrated during adolescence without significant change in mean FSIQ [17]. Larger gray matter loss rates have also been found in superior medial frontal cortices and left cingulate cortex in COS patients compared with controls and FSIQ was unrelated to the gray matter volumes at baseline and follow-up [50]. Larger gray matter loss rates in parietal, temporal, and frontal cortices have also been found in COS patients when compared with controls and the overall tissue deficit correlated with FSIQ at follow-up [47]. Regarding adolescent-onset schizophrenia, brain volume abnormalities have been demonstrated, but no significant volume changes were found during late adolescence [28, 29]. These studies have not explored the possible associations between cognitive performance and brain structure volume, and whether subnormal growth in intelligence in the current EOS sample is related to structural brain volume changes will be the subject of further analyses.

Conclusion

Using an identical Wechsler IQ test version and the same norms at both baseline and follow-up assessments in this controlled longitudinal study, we demonstrated abnormally small growth in general and verbal intelligence in EOS patients during the 5 years after their first psychotic episode. These results suggest abnormally slow acquisition of new intellectual information and skills in early onset schizophrenia rather than deterioration of intelligence, and they support a neurodevelopmental model of early onset schizophrenia. In contrast, development in non-verbal intelligence in EOS was not significantly different from that of healthy controls, but this finding as well as the lack of significant difference in growth in intelligence between EOS and EOP patients must be interpreted with caution due to limited sample sizes.

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