

Executive functioning improves after remission of psychosis and may not deteriorate at short follow-up in early-onset schizophrenia

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Submitted: 2015-01-19 *Accepted:* 2015-02-11 *Published online:* 2015-05-18

Key words: **cognitive impairment; early onset schizophrenia; executive function; negative symptoms; positive symptoms**

Neuroendocrinol Lett 2015; **36**(2):153–160 PMID: 26071585 NEL360215A05 © 2015 Neuroendocrinology Letters • www.nel.edu

Abstract

OBJECTIVE: Cognitive functions are important determinants of outcome in schizophrenia. Psychiatric hospitalization and intensive treatment in the early-onset psychosis may reduce the severity of psychotic symptoms and improve cognitive functions. It is not clear if after discharge improvement or further deterioration of cognition is observed. The aim of the current study is the evaluation of executive functioning in early onset schizophrenia (EOS) across stages of illness.

METHOD: Two groups of EOS patients: hospitalized subjects with first episode (FES, n=16) at the introduction of pharmacotherapy (T1) and after mean 7 weeks (T2) and stable outpatients group (SO, n=24) were assessed with the Wisconsin Card Sorting Test (WCST) the Positive and Negative Syndrome Scale. Matched healthy (n=32) controls were assessed with WCST.

RESULTS: All patients performed significantly worse in WCST than healthy controls. Subjects in acute psychotic episode (FES T1) presented more pronounced executive impairment and psychopathological symptoms than after the resolution of psychotic symptoms (FES T2). No differences in executive function between FES T2 and SO group were observed. In all assessments perseverative errors correlated with negative symptoms.

CONCLUSION: Cognitive impairment is present at the onset of EOS and persists in attenuated but stable form after the resolution of psychotic symptoms.

INTRODUCTION

Schizophrenia is a devastating disorder, with typical onset in late adolescence and early adulthood. Early onset schizophrenia (EOS) – before age 18 – is considered to be the most severe form of the disease (Rabinowitz *et al.* 2006; Vyas *et al.* 2011).

EOS is characterized by more pronounced genetic burden, large number of subclinical abnormalities in psychomotor, social and intellectual development before illness onset and often insidious development of psychotic symptoms. This form of the disorder is believed to have a substantial neurodevelopmental component (Renschmidt &

Theisen 2012). The neurodevelopmental hypothesis of schizophrenia summing up biological and environmental risk factors that influence brain development is discussed in recent review by Rapoport *et al.* (2012). The outcome in EOS is often unfavorable (Clemmensen *et al.* 2012) even in patients who are compliant with medications and other forms of therapy.

One of the proposed factors mediating the outcome in schizophrenia is cognitive impairment (Allot *et al.* 2011). It is considered to be the core feature of schizophrenia, present in both adult-onset (Szoke *et al.* 2008) and early-onset psychosis (e.g. Kravariti *et al.* 2003; McClellan *et al.* 2004; Ueland *et al.* 2004; Holmen *et al.* 2010). General intellectual ability in EOS is 0.7 to 1.3 standard deviation below the normative mean. Memory, attention and executive functions are also impaired (Vyas *et al.* 2011). Profile of cognitive impairment in EOS seems to be at least as broad as in adult population and possibly earlier onset of the disorder is associated with more pronounced deficits (Rajji *et al.* 2009).

In the population studies including adult-onset schizophrenia subjects cognitive impairment seem to be present before illness onset (Reichenberg *et al.* 2010) and after the development of psychosis probably cognition deteriorates (Hoff *et al.* 2005). The life-span course of cognitive functioning in schizophrenia remain unclear. Long-term population studies suggest cognitive decline, however the exact period when the cognitive deterioration occurs is discussed (Meier *et al.* 2014). First short-term studies of atypical antipsychotics cognitive efficacy suggested the possibility of cognitive improvement during antipsychotic treatment (Weiss *et al.* 2002). Some methodological issues, including the impact of practice effect on observed improvement are recently suggested (Goldberg *et al.* 2007). Recent studies are less optimistic (Ayasa-Arriola *et al.* 2013). Especially in the early-onset schizophrenia cognitive efficacy of antipsychotics is doubtful (Robles *et al.* 2011; Remberk *et al.* 2012).

Medium-term studies with EOS samples are also inconclusive. In child and adolescent samples improvement of raw tests' results is expected as a result of normal intellectual development. Cognitive development with persisting stable deficit in comparison to healthy controls in two years follow-up was observed by Juuhl-Langseth *et al.* (2014). Similar results were obtained by Bombin *et al.* (2013). Frangou *et al.* (2008) during 4 years follow-up observed relatively stable impairment with improvement in speed of information processing and deterioration in verbal memory and attention. Other studies (Cervellione *et al.* 2007; Wozniak *et al.* 2008) suggest stable level of executive deficits after the illness onset.

Traditionally EOS patients are considered to have worse outcome than adults with schizophrenia. In adolescents not only the severity of symptoms but also the negative effect of the disorder on educational and personal achievements disturb the ability to function independently (Vyas *et al.* 2011; Remschmidt *et*

al. 2012). Some aspects of schizophrenia, which show relative autonomy from psychopathological symptoms, i.e. neurocognition (Green 1996; Nuechterlein *et al.* 2011), social cognition (Green *et al.* 2012; Horan *et al.* 2012) and communication abilities (Bowie *et al.* 2008, Bearden *et al.* 2011) may also strongly affect functional outcome of psychosis in adult, and possibly adolescent patients as it has been recently proposed. Results of cognitive studies across illness stages are also often used as arguments in the discussion concerning neurodevelopmental versus neurodegenerative nature of schizophrenia (Bora 2014; Kobayashi *et al.* 2014).

In EOS also negative symptoms can be significant predictor of the functional outcome (Cervellione *et al.* 2007; Vyas *et al.* 2007; Grant & Beck 2009) that is related to a poorer prognosis for future social functioning (Green *et al.* 2000; Nieuwenstein *et al.* 2001; Ventura *et al.* 2011). In some studies, severity of negative and disorganization symptoms correlate with cognitive impairment (Nieuwenstein *et al.* 2001; Schuepbach *et al.* 2002) also in adolescent subjects (Rhinewine *et al.* 2005) however correlations are usually modest. Results are not univocal and in some studies, especially in EOS population this link is not observed (Banaschewski *et al.* 2000).

Aim of the current study was assessment of pattern of executive dysfunction across illness stages in early-onset schizophrenia. As studies of early onset schizophrenia usually confirm rather neurodevelopmental then neurodegenerative component (Rapoport & Gogtay 2011) we expected that after acute psychotic symptoms resolution the cognitive deficit would be relatively stable.

METHODS

Participants

Group 1: patients during first episode of early onset schizophrenia. Assessment T1 and T2.

Sixteen inpatients, aged 13–18 hospitalized due to the first episode of early onset schizophrenia in adolescent psychiatry ward from January 2005 to May 2009 were recruited. The psychiatric diagnosis was made in the few-steps procedure. Preliminary diagnosis was proposed by attending clinician after semi-structured psychiatric interview with a patient and his/her parents at the admission stage. The semi-structured interview was focused on the patient's history and clinical assessment and followed the practical guidelines of adolescent mental state examination. The preliminary diagnosis was established following the ICD-10 guidelines (ICD-10 diagnostic criteria, WHO 1993). Final diagnosis was established after further observation of symptoms during admission and verification within a multidisciplinary treatment team including experienced senior psychiatrists. Patients were assessed during their first psychotic episode, either antipsychotic-naïve (n=4) or within the first week of first antipsychotic therapy in the lifetime (n=12). The only antipsychotic used

was risperidone. None of them had been treated with antipsychotics previously, previous antidepressant therapy was allowed, as well as additional sedatives ($n=3$). The second assessment of this group took place within a week before discharge from the hospital or as soon as logistically possible after discharge. Psychiatric and general medical history was obtained and the physical examination was performed at the admission.

Group 2: stable outpatients

Twenty four stable outpatients, aged 16–19 with diagnosis of early-onset schizophrenia, with at least one previous hospitalization (mean period after the last discharge 5.6 ± 5.7 months) and illness duration of minimum one year had been recruited.

All participants had been diagnosed with schizophrenia according to the diagnostic criteria specified in International Classification of Disease–10 (WHO, 1993). All patients being treated with second generation antipsychotics (olanzapine, risperidone, quetiapine, clozapine) administered in stable standard daily dosage. For both groups exclusion criteria comprised current or past diagnosis of psychoactive substance abuse, diagnosis of mental retardation according to ICD-10 criteria, pervasive developmental disorders and serious neurological or somatic disorder.

Control group

The control group consisted of healthy 16 girls and 16 boys, aged 13–19, whose age, sex and education were matched to the EOS patients. .

Study design

The group in their first episode of schizophrenia (FES) is a subsample of participants of risperidone cognitive efficacy study in early onset psychosis (Remberk *et al.* 2012). The group 2 (stable outpatients – SO) is a subsample of study focusing on profile of cognitive impairment in EOS. In the current study inclusion criteria in relation to previous studies were narrowed to define two distinct group in definitely different stages of illness.

The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Bioethics Committee of the Institute of Psychiatry and Neurology in Warsaw and the Ethics Committee of the Academy of Special Education in Warsaw accepted the design of the studies. All subjects and their legal guardians signed an informed consent.

Procedure

The assessments took place during single session. FES patients were assessed with Wisconsin Card Sorting Test and Positive and Negative Syndrome Scale at the admission. First assessment point (T1) was settled before introduction of pharmacotherapy or during the first week of risperidone therapy. Second assessment point (T2) for FES group was performed in the week preceding hospital discharge or as soon as possible after that.

The assessment of psychopathological symptoms in the SO group were done by psychiatrists before neuropsychological testing. The patients were assessed in an outpatient clinic or rehabilitation center.

Control subjects were evaluated with the WCST once, at schools that they regularly attended or in the Academy of Special Education office.

Measures

Severity of symptoms was assessed with Positive and Negative Syndrome Scale (PANSS) (Kay *et al.* 1987). Polish validated version was used (Rzewuska *et al.* 2002). Total score and positive, negative and general psychopathology subscales scores were analyzed.

For the evaluation of executive functions and working memory the Wisconsin Card Sorting Test (WCST) the CV 4 test computer version was used (Heaton *et al.* 1993). This single test can measure few aspects of executive functioning, is very well-studied in schizophrenia samples and easy for administration. In the evaluation of the results, the following parameters were taken into account: number of trials administered, percentage of perseverative and nonperseverative errors and number of completed categories.

Data analysis

Statistical calculations were performed with the use of the STATISTICA 7 software. To evaluate normality distribution of the variables, the Shapiro-Wilk test was applied. The Student's *t* test was used for continuous variables to evaluate the differences in means between two groups. For intergroup comparisons Mann-Whitney *U* test and intragroup comparisons and Wilcoxon Matched Pairs Test were used, because the data did not meet the parametric analysis criteria. For correlation analysis the Spearman Rank Order correlations were used.

All statistical tests were 2-tailed, with $p<0.05$ considered positive with statistically significant, and $p<0.08$ considered a statistical trend.

RESULTS

General data

Demographic and clinical data are summarized in Table 1. Group FES (first episode) and group SO (stable state) did not differ in gender distribution and age of onset. Significant differences which were the consequences of the study design were length of illness and number of hospitalizations. The group SO was slightly older, but the difference did not reach the level of statistical significance.

Patients cognitive and psychopathology assessment

There were significant differences in the severity of psychopathological symptoms between first (T1) and second (T2) assessment point of group FES, but remarkably the negative symptoms did not improve. The mean interval between first and second assess-

Tab. 1. Demographic characteristics of EOS groups and control group.

Demographic and clinical characteristics	Group I - FES N=16			Group II - SO N=24			Control group N=32			t-value (df) / Z-value
	Mean	SD	min-max	Mean	SD	min-max	Mean	SD	min-max	
Age	16.55	1.85	13.33–18.83	17.40	0.89	15.80–19.20	16.85	1.57	12.90–18.80	t=-1.96 (38)A
Age at onset (years)	15.80	1.73	12.33–18.16	15.33	1.30	12.00–17.00				t=-0.60 (46)B
Hospitalizations	1.00	0.00	1.00–1.00	2.67	1.76	1.00–7.00***				t=1.52 (54)C
Length of illness (years)	0.56	0.76	0.01–3.00	2.21	1.03	1.00–5.00***				t=0.98 (38)A
										Z=-4.19 A
										Z=4.56 A
Gender	N	%		N	%		N	%		
Female	8	50		11	45.84		16	50		
Male	8	50		13	54.16		16	50		

*** $p < 0.001$; Group I FES - inpatients with first episode of early-onset schizophrenia; Group II SO - stable outpatients with early-onset schizophrenia; comparison concern Group I FES and Group II SO -A; comparison concern Group I FES and control group-B; comparison concern Group II SO and control group-C

Tab. 2. PANSS scale results in clinical groups with early-onset schizophrenia, inpatient (I EOS T1 and T2) and outpatients (II EOS), in comparison between groups and in the II Group.

PANSS scores, mean SD min-max	Group I FES (N=16) Mean (SD) min-max		Group II SO (N=24) Mean (SD) min-max	Z-value	Z-value	Z-value
	EOS T1	EOS T2				
Positive symptoms	18.38 (5.20) 11.00–27.00	11.38 (3.74) 7.00–20.00	12.95 (4.44) 7.00–21.00	Z= 3.27**	Z = 2.91**	Z = -1.02
Negative symptoms	24.75 (4.78) 17.00–34.00	21.94 (5.06) 11.00–30.00	23.67 (7.25) 11.00–41.00	Z = 1.84	Z = 0.65	Z = -0.63
General symptoms	39.00 (10.12) 21.00–55.00	30.94 (6.46) 19.00–46.00	38.04 (10.94) 18.00–55.00	Z= 2.74**	Z = 0.33	Z = -2.16*
Total score	82.13 (17.41) 51.00–113.00	64.88 (12.49) 37.00–94.00	74.67 (19.45) 40.00–106.00	Z = 3.12**	Z = 1.09	Z = -1.68

* $p < 0.05$; ** $p < 0.01$; Group I FES - inpatients with first episode of early-onset schizophrenia, T1 - assessment during acute psychosis symptoms, T2 - assessment after treatment; Group II SO - stable outpatients with early-onset schizophrenia; comparison concern in Group I FES between T1 and T2 - Wilcoxon Matched Pairs Test; comparison concern Group I FES T1 and Group II SO - Mann-Whitney U test; comparison concern Group I FES T2 and Group II SO - Mann-Whitney U test

ment point was 47 days (6.7 ± 3.7 weeks). There were significant difference of severity of positive symptoms between results of first assessment in group FES (T1) and the stable outpatients group. The severity of positive and negative symptoms in the second assessment point (T2) did not differ from the stable patients group. The severity of general symptoms however was higher in the stable outpatient group.

In executive function assessment the WCST performance for patients in acute psychotic state (FES T1) was significantly worse than in this group after treatment (FES T2) and worse than in the stable outpatients group (SO). There were no statistically significant differences between the second assessment in the first episode group (FES T2) and the outpatients group (SO).

Correlations between WCST results and symptoms severity

In all three assessments percent of perseverative errors correlated (for FES group at the statistical trend level)

with severity of negative symptoms. No other correlations were statistically significant. Results are summarized in Table 5.

Patients and controls comparison

The above results suggest the possibility of executive function improvement after resolution of acute psychotic symptoms. Thus we decide to assess if improved cognitive functions are comparable with normal level of functioning. We compared both assessment in the FES group and stable outpatients (SO) group with matched controls.

No significant differences between patients and control group in demographic variables were observed. First episode patients compared to controls at the beginning of pharmacotherapy presented pronounced executive impairment which partly resolved after mean 6.7 weeks of treatment. Only completed categories remained lower than in controls at the tendency level. The stable outpatients group had more perseverative errors than controls.

Tab. 3. WCST test results in clinical groups with early-onset schizophrenia, inpatient (I FES T1 and T2) and outpatients (II SO) in comparison between groups.

WCST score	Group I FES (N=16) Mean SD		Group II SO (N=24) Mean SD	Z-value FES T1 and FES T2	Z-value FES T1 and SO	Z-value FES T2 and SO
	FES T1	FES T2				
trials administered	117.25 (16.70)	101.06 (24.91)	98.25 (22.74)	Z= 2.55*	Z= 2.65 **	Z=0.44
% perseverative errors	19.75 (12.78)	18.75 (19.88)	12.38 (6.88)	Z= 1.30	Z=2.54*	Z=0.23
% nonperseverative errors	25.75 (18.26)	16.81 (19.48)	11.88 (6.90)	Z= 2.43*	Z=2.82 **	Z=-0.65
% total errors	45.50 (19.97)	35.62 (26.76)	24.25 (11.79)	Z= 2.93 **	Z=3.49 ***	Z=0.43
% conceptual level responses	41.88 (25.48)	56.13 (34.63)	69.75 (16.96)	Z= 3.11 **	Z=-3.55***	Z=-0.39
categories completed	3.31 (2.41)	3.87 (2.66)	5.50 (0.98)	Z= 1.48	Z=-2.68**	Z=-1.49
trials to complete 1st category	39.00 (46.39)	38.75 (48.96)	16.25 (8.97)	Z= 0.53	Z=-0.29	Z=-0.62

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; Group I FES - inpatients with first episode of early-onset schizophrenia, T1 - assessment during acute psychosis symptoms, T2 - assessment after treatment; Group II SO - stable outpatients with early-onset schizophrenia; comparison concern in Group I FES between T1 and T2 - Wilcoxon Matched Pairs Test; comparison concern Group I FES T1 and Group II SO - Mann-Whitney U test; comparison concern Group I FES T2 and Group II SO - Mann-Whitney U test

Tab. 4. WCST test results in clinical groups with early-onset schizophrenia, inpatient (FES T1 and T2) and outpatients (SO) in comparison with control group.

WCST score	Group I FES (N=16) Mean SD		Group II SO (N=24) Mean SD	Control group (N=32) Mean SD	Z-value FES T1 and control	Z-value FES T2 and control	Z-value SO II and control
	FES T1	FES T2					
trials administered	117.25(16.70)	101.06 (24.91)	98.25 (22.74)	88.09 (19.41)	Z=3.90***	Z=1.68	Z=1.67
% perseverative errors	19.75 (12.78)	18.75 (19.88)	12.38 (6.88)	9.03 (5.14)	Z=4.57***	Z=1.80	Z=2.49*
% nonperseverative errors	25.75 (18.26)	16.81 (19.48)	11.88 (6.90)	9.69 (7.60)	Z=3.77**	Z=0.36	Z=1.59
% total errors	45.50 (19.97)	35.62 (26.76)	24.25 (11.79)	18.72 (10.23)	Z=4.60***	Z=1.45	Z=2.17*
% conceptual level responses	41.88 (25.48)	56.13 (34.63)	69.75 (16.96)	77.50 (13.30)	Z=-4.66***	Z=-1.41	Z=-2.09*
categories completed	3.31 (2.41)	3.87 (2.66)	5.50 (0.98)	5.63 (0.94)	Z=-3.02**	Z=-1.88t	Z=-0.52
trials to complete 1st category	39.00 (46.39)	38.75 (48.96)	16.25 (8.97)	14.00 (9.62)	Z=1.30	Z=0.42	Z=1.65

t=0.06; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; Group I FES - inpatients with early-onset schizophrenia, T1 - assessment during acute psychosis symptoms, T2 - assessment after treatment; Group II SO - outpatients with early-onset schizophrenia; comparison concern Group I FES T1 and Group II SO - Mann-Whitney U test; comparison concern Group I FES T2 and Group II SO - Mann-Whitney U test

Tab. 5. Spearman Rank Order Correlations between WCST parameters and PANSS results.

		Positive subscale	Negative subscale	General subscale	Total
FES T1	Trials administered	ns	ns	ns	ns
	% perseverative errors	ns	0.52 ($p < 0.08$)	ns	ns
	% nonperseverative errors	ns	ns	ns	ns
	Categories completed	ns	ns	ns	ns
FES T2	Trials administered	ns	ns	ns	ns
	% perseverative errors	ns	0.46 ($p < 0.08$)	ns	ns
	% nonperseverative errors	ns	ns	ns	ns
	Categories completed	ns	ns	ns	ns
SO	Trials administered	ns	ns	ns	ns
	% perseverative errors	ns	0.58 ($p < 0.01$)	ns	ns
	% nonperseverative errors	ns	ns	ns	ns
	Categories completed	ns	ns	ns	ns

Only statistically significant correlations are shown. Group FES - inpatients with first episode of early-onset schizophrenia, T1 - assessment during acute psychosis symptoms, T2 - assessment after treatment; Group SO - outpatients with early-onset schizophrenia

DISCUSSION

Impaired performance in WCST is almost universally reported in early-onset and adult-onset psychosis (Bombin *et al.* 2013; Green *et al.* 2002; Schuepbach *et al.* 2002). Our study was not unique in this regard. In the previous studies on EOS with the follow-up design (Bombin *et al.* 2013; Frangou *et al.* 2008; Cervelione *et al.* 2007), no significant executive function change other than associated with symptoms fluctuation is observed. In our study introduction of treatment was associated with non-perseverative errors improvement, while the parameters considered usually more specific for executive deficit namely percent of perseverative errors and number of completed categories were not improved. As number of completed categories may be interpreted as a final performance outcome assessing the total effectiveness of thinking this result seem to be important. A comparison between healthy controls and T2 assessment of FES subjects confirms this observation – number of completed categories remains lower in patients than in controls. Stable outpatients group also achieved worse WCST results than healthy controls, namely higher percentage of perseverative errors. Moreover in all three assessments percent of perseverative errors correlated with severity of negative symptoms, what is in agreement with most previous findings (Nieuwenstein *et al.* 2001).

The second assessment of FES group took place just before the discharge from the hospital, after mean seven weeks of first antipsychotic treatment. In the stable outpatient group first treatment took place at least one year ago. As the groups did not differ in cognitive functioning and level of psychopathological symptoms (with even higher results in general psychopathology subscale in the outpatients group) we must conclude that the long-term treatment efficacy is not satisfactory. Efficacy of cognitive remediation had been studied in adults (Wykes *et al.* 2011) and two studies also confirmed the beneficial effect of cognitive remediation in EOS (Wykes *et al.* 2007; Puig *et al.* 2014). Thus we believe that cognitive remediation should be considered as an treatment augmentation strategy in EOS.

The neurodevelopmental component of schizophrenia, especially the severe form of illness with early onset is widely accepted (Remschmidt & Theisen 2012). However stable vs. progressive nature of the illness' effects is still discussed. In adult neuroimaging study Andreasen *et al.* (2011) find, that in at least in subgroup of schizophrenia patients the brain volume changes are progressive and are related to cognitive impairment. There is a dearth of longitudinal data of early onset psychoses, however most medium-term studies suggest rather stable deficit than cognitive deterioration. Our results confirm this interpretation. However in the study with longer observation period (13 years) progression of cognitive deficit is observed (Øie *et al.* 2010). Similarly, review focusing on functional outcome in EOS finds

that with observation period longer the 10 years percentage of unfavourable outcomes increases (Øie *et al.* 2010). Our results does not confirm neurodegenerative, progressive deficit hypothesis. However long-term follow-up studies assessing cognitive functioning in EOS are warranted.

The major advantage of the current study was enrollment of patients with the same age of onset but in the different phases of illness. Also, the control group of healthy adolescents was individually matched by demographic variables and type of education, which allowed a reliable assessment of the severity of cognitive and communication impairment.

The main limitation of the study is a small sample size. Due to the same age of onset and longer illness course the stable outpatients (SO) group was slightly older than the first episode (FEP) group. The difference however did not reach the statistical significance.

CONCLUSIONS

Patients with the first psychotic episode at the very beginning of treatment presented pronounced executive impairment. Some improvement was observed after resolution of acute symptoms and executive functioning in the later phase of illness seemed to be relatively stable. The patients at each phase of illness differed from healthy controls. These results suggest the arrest of cognitive development in EOS and are concordant with neurodevelopmental model of schizophrenia; the progressive nature of the illness may be discussed.

ACKNOWLEDGEMENTS

First episode of schizophrenia (FES) group assessment was sponsored with Polish Ministry of Science and Higher Education research/educational grant N 407 005 32/0085.

Stable outpatients (SO) group assessment was sponsored by Academy for Special Education statutory grant to the author BW 01/09-III

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