Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

The relationship between level of cognitive impairments and functional outcome trajectories in first-episode schizophrenia

Susie Fu [a,b], Nikolai Czajkowski [a,c], Bjørn Rishovd Rund [a,b,*], Anne-Kari Torgalsbøen [a]

[a] Department of Psychology, University of Oslo, PO Box 1094, 0373 Oslo, Norway
[b] Vestre Viken Hospital Trust, PO Box 800, 3004 Drammen, Norway
[c] Division of Mental Health, Norwegian Institute of Public Health, PO Box 4404, 0403 Oslo, Norway

ARTICLE INFO

Article history:
Received 18 August 2016
Received in revised form 21 February 2017
Accepted 2 March 2017
Available online xxxx

Keywords:
Psychosis
Longitudinal
Cognition
Functional outcome
Recovery

ABSTRACT

Although cognitive impairments are consistently linked to functional outcome in chronic schizophrenia, the relationship remains unclear for patients with first-episode schizophrenia. The objective of this present study was to determine whether there are distinct developmental trajectories for functional outcome in patients with different levels of baseline cognition. The present study has a multi-follow-up design, and includes data from six follow-ups over four years. Assessments were conducted yearly, apart from the first year where assessments were conducted every six months. A total of 28 patients with first-episode schizophrenia participated in the study, with 79% of patients retained at the 4-year follow-up. Cognition was assessed with MATRICS Consensus Cognitive Battery. Functional outcomes were obtained through Global functioning: Social and Global functioning: Role. Data were analyzed with linear multilevel models. Results suggest steady improvements in social and role functioning among the patients across the four year period. Baseline attention, verbal learning, and verbal working memory were significantly associated with social outcome. Role functioning was significantly associated with attention, verbal working memory, and reasoning/problem solving. Furthermore, the rate of change in social outcome varies among patients depending on their baseline level of attention and verbal working memory, with the lowest scoring group showing the least improvement over the years. The subgroup of patients with the largest cognitive impairments at the onset of the disorder shows limited improvements in social functioning compared to higher functioning groups.

1. Introduction

Impaired cognition is considered a fundamental deficit in patients with schizophrenia (Kahn and Keefe, 2013). A number of studies have found cognition to be one of the most robust predictors of functional outcome (Green and Harvey, 2014). There is a growing interest in examining the relationship between cognition and functional outcome, as cognitive rehabilitation is recognized as a possible target in the treatment of the disorder. With the emerging knowledge of the existence of subgroups of schizophrenia patients, recent reports emphasize the importance of personalized schizophrenia treatment. An important goal is to understand the unique characteristics of a patient and how this affects individual risk of illness onset and treatment response (Insel, 2010; Ozomaro et al., 2013), thereby providing interventions that increase the chances of recovery.

In recent years, a large number of studies have examined the relationship between cognition and functional outcomes. For instance, better global cognition at stabilization is associated with full recovery, indicating symptom remission and adequate social and vocational functioning (Robinson et al., 2004). In a review of cross-sectional studies, Green et al. (2000) identified attention, along with executive functions and verbal memory, as promising neurocognitive domains that are consistently associated with functional outcome. When considering longitudinal studies, Green et al. (2004) concluded that there is convincing evidence for an association between cognition and functional outcome in chronic schizophrenia. However, when considering first-episode schizophrenia (FES), the longitudinal effects of cognition on functional outcome are not as well-established (Nuechterlein et al., 2011), even though the cognitive deficits in chronic patients and FES-patients are found to be comparable in magnitude and pattern (Mesholam-Gately et al., 2009). One reason is the scarcity of longitudinal studies which include cohorts of FES-patients (Milev et al., 2005). Furthermore, it is difficult to make direct comparisons across studies due to large differences in methodology (Allott et al., 2011).

Regarding the relationship between cognition and functional outcomes in FES, several longitudinal studies have attempted to identify

* Corresponding author at: Department of Psychology, University of Oslo, PO Box 1094, Blindern, 0317 Oslo, Norway.
E-mail addresses: susie.fu@psykologi.uio.no (S. Fu), n.o.czajkowski@psykologi.uio.no (N. Czajkowski), b.r.rund@psykologi.uio.no (B.R. Rund), a.k.torgalsboen@psykologi.uio.no (A.-K. Torgalsbøen).

http://dx.doi.org/10.1016/j.schres.2017.03.002
0920-9964/

specificity by exploring how various cognitive domains are differently linked to or predictive of outcome. For instance, Milev et al. (2005) found that attention and processing speed were related to the degree of work impairment in an average follow-up period of seven years. On the other hand, only verbal memory predicted the degree of relationship impairment. A study by Nuechterlein et al. (2011) found that three cognitive factors (attention and perceptual processing; working memory; verbal memory and processing speed), accounted for 52% of the variance in the rate of returning to work within a 9-month period. Another studies found that attention at baseline predicted work outcome at 2 year follow-up (Tandberg et al., 2011). When considering predictive factors of social outcome, studies have consistently found an association between attention and social outcome (Torgalsbøen et al., 2015), which is in accordance with findings on chronic schizophrenia (Addington and Addington, 2000; Velligan et al., 2000). However, a review by Allott et al. (2011) reported a predominance of negative findings in previous studies of FES, partially due to heterogeneous measurements of cognition and functional outcome. It has been suggested that these negative findings might not be attributable to FES, but instead to specific features of the individual studies (Nuechterlein et al., 2011).

Longitudinal studies on neurocognition in schizophrenia are rare, and many include only two measurement occasions. Multi-follow-up studies provide opportunities to discover long-term changes in neurocognition and fluctuations in illness trajectories. A recent multi-follow-up study of processing speed showed impairment in patients with schizophrenia compared to other diagnostic groups. Impairment in processing speed was most pronounced following the acute psychotic phase, and with the patients subsequently demonstrating improvements followed by stability (Bonner-Jackson et al., 2010). The current literature lacks studies that include both measures of neurocognitive variables and functional outcome, which is unfortunate given the value of long term multi-follow-up studies. Moreover, current multi-follow-up studies include assessment points many years apart, thereby being less sensitive to changes that occur in between the assessment points. Another issue pertaining to current studies is that they often examine the patient sample as a single group. However, since patients with schizophrenia experience varying degrees of neurocognitive deficits, it seems likely that the recovery processes will differ for different subgroups of patients. A recent multi-follow-up study by Rund et al. (2016) compared the cognitive trajectories of three subgroups of patients over 10 years. They found that patients with stable remissions in the first year improved in cognition compared to patients who experienced relapses and patients in continuous psychosis. Still, this study did not include measures of functional outcome.

In the Oslo schizophrenia recovery study, FES-patients are assessed annually over ten years with measures of cognition and functional outcomes. This procedure enables us to study the recovery process in greater detail than previous studies.

The present study addresses two research questions: Which cognitive domains at baseline predict later functional outcome? Are there distinct developmental trajectories for functional outcome in patients with different levels of baseline cognition?

2. Methods

2.1. Participants

A total of 28 patients with first-episode schizophrenia were recruited from mental health service institutions in the Oslo area. The patients were referred to the study by their treating clinicians, and were screened using the following inclusion criteria: age ≥ 18 years; the first episode of mental illness was within the spectrum of schizophrenia and psychosis according to DSM-IV (American Psychiatric Association, 1994); IQ > 70; presented no evidence of affective disorders, head trauma, and primary diagnosis of substance abuse; and referred to the study within five months of their first contact with mental health service institutions. Demographic and clinical characteristics of the participants are presented in Table 1.

In the follow-up period, patients were provided treatment by their local mental health service institutions, through medication, psychoeducation and case management. All patients could read and write Norwegian fluently, and written informed consent was obtained from all participants. The study was approved by the Regional Committee for Research Ethics (REK).

Here we present data from six follow-ups over four years: baseline, after six months and after a year. Thereafter, they were measured every year for three consecutive years. All patients were retained during the first three follow-ups, while three participants left the study during the 2-year follow-up and an additional three dropped out during the 3-year follow-up. On every measurement occasion, the patients completed all the assessments as described below.

2.2. Clinical instruments

The clinical interviews and tests of the participants were conducted within the first five months of their admission to a hospital or outpatient clinic, and were carried out by an experienced clinical psychologist. Diagnoses were established using the Structural Clinical Instrument of Diagnosis for DSM-IV Axis I disorders (SCID-I), modules A-D. Furthermore, a semi-structured interview was used, and based on this information a score of social and role functioning was given according to the Global Functioning: Social (GF:Social) and the Global Functioning: Role (GF: Role) (Cornblatt et al., 2007). A score ranging 1–10 was given. A higher score indicates better functioning.

2.3. Neurocognitive measures

Cognition was measured with the MATRICS Consensus Cognitive Battery (MCCB), which is a standardized test battery for use with adults with schizophrenia and related disorders (Nuechterlein and Green, 2006). The assessments were carried out by graduate students of clinical psychology trained in neuropsychological assessments, using the Norwegian version of MCCB. Norwegian reference data has been collected and reported (Mohn et al., 2012).

This battery consists of 10 tests measuring 7 different cognitive domains: Speed of processing: *Trail Making Test A (TMT-A)*, *Symbol Coding (Brief Assessment of Cognition in Schizophrenia, BACS)*, *Category Fluency*; Attention/Vigilance: *Continuous Performance Test – Identical Pairs (CPT-IP)*; Working memory: *Spatial Span (Wechsler Memory Scale, SS-WMS)*, *University of Maryland Letter Number Span test (LNS)*; Verbal learning: *The revised Hopkins Verbal Learning Test (HVLT-R)*; Visual learning: *The revised Brief Visuospatial Memory Test (BVMT-R)*; Reasoning/Problem solving: *Reasoning and Problem Solving* (*Neuropsychological*

Table 1
Demographic variables of the participants.

	Patients (n = 28)
Age in years	21.0 (SD 2.6)
Gender	17 (60.7%) men, 11 women
Level of education	
Elementary school	n = 11 (39.3%)
High school	n = 8 (28.6%)
Some college	n = 7 (25.0%)
BA degree or higher	n = 2 (7.2%)
Diagnoses	
Schizophrenia	21 (75.0%)
Schizoaffective disorder	6 (21.4%)
Psychotic disorder NOS	1 (3.6%)
Substance abuse earlier	18 (64.3%)
Substance abuse at baseline	1 (3.6%)
Treatment status	
Hospitalized	16 (57.0%)
Outpatient	12 (43%)

Please cite this article as: Fu, S., et al., The relationship between level of cognitive impairments and functional outcome trajectories in first-episode schizophrenia, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.03.002

Assessment Battery, NAB); and Social Cognition: *The Managing Emotions part of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT)*. The tests were scored using American norms (Mohn et al., 2012).

2.4. Data analyses

IBM SPSS Statistics version 22.0 was used for all statistical analyses. The data consist of two hierarchical levels: time (measurement waves) represents level 1, and are nested within individuals (level 2). Since multilevel models can handle missing data flexibly (Quené and van den Bergh, 2004), all available data are included in the analyses.

A series of multilevel growth curve models were fitted for social functioning and role functioning to estimate initial level and changes in functioning over time. We started with a growth model with a random intercept, then allowed for variations in both individuals' initial level of functioning (the intercept) and change in functioning over time (the slope). Lastly, a quadratic effect of time was added to the model.

Next, we conducted separate analyses for each cognitive domain, for which an interaction between baseline T-scores and time was introduced into the existing model. Lastly, in order to examine whether a stratification of the patients group would further improve our model, the participants were divided into three approximately equally large groups based on T-scores at baseline for each of the significant cognitive domains in the last model, e.g. low attention, medium attention, and high attention. Multilevel analyses were conducted for social functioning and role functioning to examine group-by-time interactions.

All models were fitted using maximum likelihood and an unstructured covariance structure. Sex and level of education at baseline were entered as covariates in the various multilevel models in forward stepping procedures. The covariates were removed from the final model if they were not significant. Education and cognition scores were grand-mean centered to facilitate the interpretation of the results. AIC was used to determine the best fitting models (Akaike, 1974), as well as the likelihood ratio test using maximum likelihood.

3. Results

3.1. Trajectories of social functioning and role functioning

The best fitting model included a fixed linear time effect, a random intercept, and a random slope. For social functioning the mean value at baseline was $\beta = 6.11$ (SE = 0.22), and the increase in the expected score per year was $\beta = 0.20$ (SE = 0.08) (Table 2 (Model 1)). For role functioning the mean value at baseline was $\beta = 4.11$ (SE = 0.31) (Table 3 (Model 1)), and the increase in the expected score was $\beta = 0.75$ (SE = 0.13). A quadratic effect of time was not significant for social functioning, $F(1, 96.09) = 1.22$, $p = 0.27$, but it was significant for role functioning, $F(1, 102.79.) = 8.13$, $p = 0.01$. These results indicate that there was a significant constant linear increase in the predicted mean level of social functioning, and a significant quadratic effect of time in the predicted mean level of role functioning over the six measurement waves.

3.2. Association between baseline cognition and social functioning and role functioning

When a time × baseline interaction was included into the existing model, social functioning was significantly predicted by attention ($\beta = 0.03$, $p \leq 0.001$), verbal learning ($\beta = 0.02$, $p = 0.03$), and verbal working memory ($\beta = 0.03$, $p = 0.003$). Role functioning was significantly predicted by attention ($\beta = 0.03$, $p = 0.001$), verbal working memory ($\beta = 0.03$, $p = 0.001$), and reasoning/problem solving ($\beta = 0.02$, $p = 0.01$). The other cognitive domains did not significantly predict functional outcome. Of the other demographic covariates added to the model, only education level at baseline was significantly associated

Table 2
The best fitting models (model 1–3) for social functioning.

	Model 1		Model 2						Model 3					
			Attention		Verbal working memory		Verbal learning		Attention		Verbal working memory		Verbal learning	
	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p
Fixed effects														
Intercept	6.111 (0.215)	<0.001	6.804 (0.293)	<0.001	6.568 (0.328)	<0.001	6.417 (0.342)	<0.001	6.479 (0.338)	<0.001	6.294 (0.367)	<0.001	6.217 (0.370)	<0.001
Time	0.202 (0.080)	0.021	0.212 (0.077)	0.012	0.216 (0.081)	0.015	0.202 (0.082)	0.023	0.388 (0.111)	0.003	0.367 (0.123)	0.008	0.359 (0.137)	0.018
Low			−1.694 (0.355)	<0.001	−1.322 (0.414)	0.004	−0.763 (0.461)	0.110	−0.998 (0.466)	0.041	−0.528 (0.512)	0.317	−0.462 (0.524)	0.385
Moderate			−0.287 (0.363)	0.436	−0.094 (0.404)	0.817	−0.168 (0.448)	0.711	−0.039 (0.478)	0.935	−0.025 (0.505)	0.960	−0.126 (0.509)	0.807
Low * time									−0.394 (0.156)	0.022	−0.440 (0.173)	0.020	−0.242 (0.202)	0.246
Moderate * time									−0.126 (0.159)	0.437	−0.037 (0.165)	0.826	−0.230 (0.189)	0.239
Random effects														
Residual	0.261 (0.039)	<0.001	0.263 (0.039)	<0.001	0.260 (0.038)	<0.001	0.260 (0.038)	<0.001	0.271 (0.041)	<0.001	0.264 (0.039)	0.001	0.260 (.038)	<0.001
Intercept	1.169 (0.348)	0.001	1.021 (0.318)	0.001	1.239 (0.388)	0.001	1.129 (0.344)	0.001	0.907 (0.278)	0.001	1.087 (0.327)	0.001	1.114 (0.334)	0.001
Slope	0.135 (0.054)	0.012	0.125 (0.048)	0.010	0.144 (0.056)	0.011	0.141 (0.057)	0.013	0.079 (0.038)	0.035	0.092 (0.042)	0.028	0.133 (0.054)	0.014
Model fit[a]														
-2 log likelihood	355.313		338.456		346.834		352.596		333.199		339.924		350.696	
AIC	367.313		354.456		362.834		368.596		353.199		359.924		370.696	

Abbreviations: Low = low baseline group, Moderate = moderate baseline group.
[a] The model fit index presented here is the -2 log likelihood and AIC.

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Table 3
The best fitting models (model 1-3) for role functioning.

	Model 1		Model 2						Model 3					
			Attention		Verbal working memory		Reasoning/ problemsoving		Attention		Verbal working memory		Reasoning/ problemsoving	
	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p	Estimate (SE)	p
Fixed effects														
Intercept	3.866 (0.317)	<0.001	4.205 (0.410)	<0.001	4.407 (0.403)	<0.001	4.670 (0.378)	<.001	3.721 (0.560)	<0.001	3.969 (0.558)	<0.001	4.692 (0.485)	<0.001
Time	1.302 (0.232)	<0.001	1.297 (0.229)	<0.001	1.326 (0.230)	<0.001	1.296 (0.230)	<.001	1.507 (0.282)	<0.001	1.529 (0.290)	<0.001	1.295 (0.274)	0.001
Time*time	-0.145 (0.051)	0.005	-0.144 (0.050)	0.005	-0.151 (0.050)	0.003	-0.146 (0.050)	0.005	-0.146 (0.050)	0.005	-0.154 (0.050)	0.003	-0.147 (0.051)	0.004
Low			-1.203 (0.408)	0.007	-1.470 (0.399)	0.001	-1.378 (0.392)	0.002	-0.239 (0.766)	0.758	-0.519 (0.780)	0.511	-0.830 (0.694)	0.242
Moderate			0.287 (0.418)	0.498	-0.198 (0.379)	0.606	-1.118 (0.384)	0.007	0.721 (0.782)	0.364	0.171 (0.760)	0.824	-1.734 (0.694)	0.019
Low*time									-0.421 (0.280)	0.145	-0.431 (0.304)	0.167	-0.286 (0.282)	0.319
Moderate*time									-0.175 (0.285)	0.544	-0.165 (0.291)	0.577	0.299 (0.278)	0.292
Education			0.251 (0.089)	0.009	0.242 (0.081)	0.006	0.227 (0.082)	0.010	0.261 (0.089)	0.007	0.239 (0.081)	0.006	0.213 (0.082)	0.015
Random effects														
Residual	0.849 (0.122)	<0.001	0.851 (0.121)	<0.001	0.844 (0.120)	<0.001	0.846 (0.120)	<0.001	0.852 (0.122)	<0.001	0.845 (0.120)	<0.001	0.852 (0.122)	<0.001
Intercept	2.215 (0.698)	0.001	2.401 (0.781)	0.002	2.500 (0.802)	0.002	2.142 (0.720)	0.003	2.258 (0.730)	0.002	2.348 (0.750)	0.002	1.893 (0.634)	0.003
Slope	0.344 (0.122)	0.005	0.309 (0.107)	0.004	0.339 (0.117)	0.004	0.330 (0.114)	0.004	0.275 (0.099)	0.006	0.309 (0.109)	0.004	0.272 (0.099)	0.006
Model fit[a]														
-2 log likelihood	499.874		482.235		482.688		483.051		480.077		480.713		479.390	
AIC	513.874		502.235		502.688		503.051		504.077		504.713		503.390	

Abbreviations: Low = low baseline group, Moderate = moderate baseline group.
[a] The model fit index presented here is the -2 log likelihood and AIC.

with role functioning.

AIC showed that compared to Model 1, this model provided a better fit for social functioning and role functioning when a baseline × time interaction was included.

3.3. Social functioning and role functioning for groups with varying baseline cognition

In the subsequent set of analyses the sample was divided into three different groups for each of the cognitive domains that were significant in the previous models.

For social functioning, a time × baseline attention interaction was found to be significant (Table 2 (Model 3)). All groups showed an increase in social functioning over time. However, the gain in social functioning was significantly lower for the low attention group compared to the high attention group ($\beta = -0.39$, SE = 0.16, $p < 0.05$). There were no differences in social functioning score between the medium attention and high attention groups ($\beta = -0.13$, SE = 0.16, $p > 0.05$). A time × baseline verbal working memory was also found significant. The gain in social functioning over time was again significantly lower for the low working memory group compared to the high working memory group ($\beta = -0.44$, SE = 0.17, $p < 0.05$). A time × baseline verbal learning interaction was not significant. The other covariates, sex and education level, did not significantly predict social functioning. Fig. 1 shows the mean levels of social functioning across the six measurement waves for the three groups.

For role functioning, analyses based on a stratification of the patient group did not provide any significant results (Table 3 (Model 3)).

Compared to the two previous models (Table 2 (Model 1–2)), model 3 provided a better fit for social functioning with AIC comparison.

4. Discussion

The purpose of the present study was to identify cognitive predictors of functional outcome. Differences in social functioning were seen among the patients. A subgroup of patients who scored the lowest on baseline cognitive measures of attention and verbal working memory, displayed a significantly smaller rate of change in social functioning compared to patients with a higher cognitive level. Although the patient group as a whole displayed a steady improvement in social and role functioning, a subgroup of patients only had a limited improvement in functional outcomes over three years. When examining their social functioning score, this patient group is more socially secluded, and has fewer steady friendships and intimate relationships compared to other patients. Their social relationships are characterized by more conflicts with peers and less involvement with family members. Our statistical models were indeed enhanced when we divided the patient group into subgroups, supporting the idea of schizophrenia being a heterogeneous disorder with many possible trajectories to recovery. Although functional outcome is a major focus in schizophrenia research, specific predictors of different outcome domains have not yet been established (Green et al., 2015). In this study, attention and verbal working memory predicted social functioning.

We found an association between cognition and role functioning which is consistent with previous studies. The differences in role functioning within the patient group were not significant. One possible explanation for the lack of differences may be explained by the extensive support Norwegian health institutions provide to patients, in order for them to get back to work after mental illness. Probably this subgroup of patients experiences more difficulties with simultaneously maintaining a satisfying work and social life; being able to master work, but struggling in the personal arena.

Cognitive impairments may influence everyday functioning directly, but also indirectly influence how well a person responds to rehabilitation. It has been suggested that the relationship between cognition and function is not just a matter of cause and effect. Consistent with

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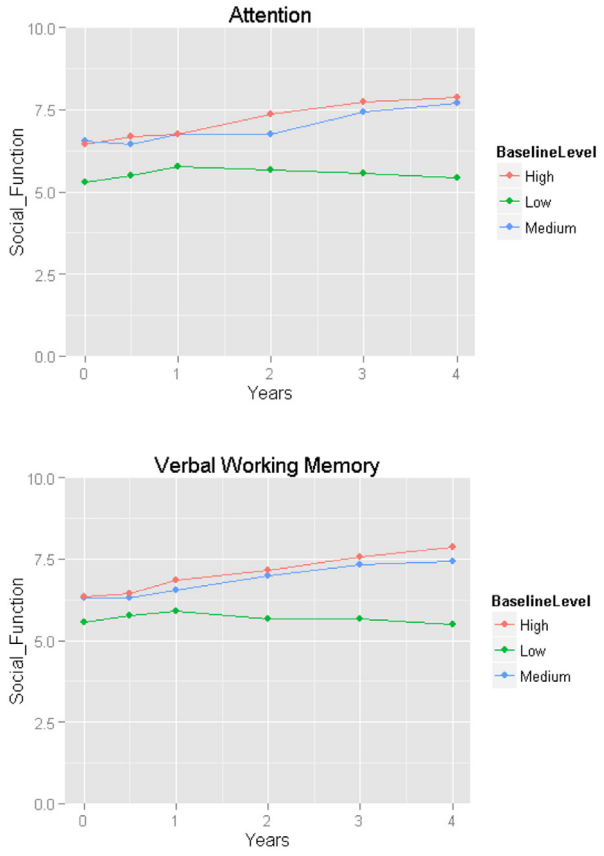

Fig. 1. Mean levels of social functioning across six measurement waves. Values are raw scores. The participants are divided into three groups based on attention and verbal memory baseline T-scores.

this view, earlier studies of cognitive rehabilitation in schizophrenia have shown limited effects of cognitive training on clinical measures (Benedict et al., 1994; Pilling et al., 2002). By examining studies that provided cognitive remediation in conjunction with other psychiatric rehabilitation, some studies have found a stronger positive association between cognitive remediation and functional outcome (McGurk et al., 2007; Wykes et al., 2011). We argue that the group with the lowest score on baseline cognition in the current study represents a more severely ill group with the least resources in daily life, thus responding less effectively to rehabilitation. Since these differences between subgroups of patients increase with time, it is important to identify patients with poorer outcomes as early as possible and provide suitable interventions. Our findings indicate that with FES, it is possible to identify this subgroup of patients within the first five months of hospitalization. This may have important implications for clinical practice.

Previous findings are conflicting concerning which cognitive domains predict functional outcome in FES (Allott et al., 2011). Nevertheless, the majority of recent studies have found significant relationships between cognition and functional outcome, thereby strengthening the importance of cognition in the recovery from schizophrenia. Consistent with previous findings (González-Blanch et al., 2010; Mesholam-Gately et al., 2009; Nuechterlein et al., 2011), baseline levels of attention and verbal working memory predicted functional outcome.

By including multiple assessments and stratifying the patient group in our analyses, we identified a poor outcome group early in the course of illness, as well as fluctuations and stability in functioning over time. Our findings support the notion that schizophrenia is a heterogeneous disease with different recovery processes, and that the subgroup of patients with the largest cognitive impairments at the onset of the disorder may have special rehabilitation needs in order to recover and improve their quality of life.

So far many research groups have studied cognition as a continuous predictor of functional outcome, and some consistent findings have emerged. By creating subgroups we have been able to explore this relationship even further. We are aware that there are a small number of patients in each group, but even so we were able to discover a significant effect of cognition on social functioning trajectory. Future studies with larger sample sizes may apply more sophisticated methods to create subgroups.

The study's strengths are the high retention rate, yearly measurement occasions, and the inclusion of the same assessment instruments in each follow-up, making it possible to examine the trajectory of social and role functioning over time. The main limitation is the small sample size. Yet, a large sample may be hard to attain for longitudinal studies with many repeated measurements. It has been suggested that more reliable estimates of growth models can be obtained by increasing the number of measurement waves (Quené and van den Bergh, 2004). Moreover, the aim of this study is exploratory in nature and replication is therefore needed with larger sample sizes. Another potential limitation is the possibility of medication effects on cognition. However, we did not find any significant correlations between daily doses of medication and cognitive scores (Torgalsbøen et al., 2015; Torgalsbøen et al., 2014). Therefore, we argue that there is no direct relationship between medication dose and test performance.

Role of the funding source

This study is internally funded by the Department of Psychology, University of Oslo. This funding source had no role in the design of this study, nor during its execution, analyses, interpretation of the data, and decision to submit results.

Author disclosure

Fu and Torgalsbøen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Torgalsbøen designed the study and wrote the protocol. Fu and Czajkowski undertook the statistical analysis. Fu wrote the first draft of the manuscript, and all authors provided valuable feedback. All authors contributed to and have approved the final manuscript. This work was supported by the Department of Psychology, University of Oslo.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgements

This work was supported by the Department of Psychology, University of Oslo.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2017.03.002.

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Please cite this article as: Fu, S., et al., The relationship between level of cognitive impairments and functional outcome trajectories in first-episode schizophrenia, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.03.002