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Cognitive improvement in first-episode schizophrenia and healthy controls: A 6-year multi-assessment follow-up study

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

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

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ABSTRACT

The development of individual cognitive domains over time is not yet fully examined in first-episode schizophrenia (FES). This study's objective was to explore the cognitive trajectories of FES-patients (n = 28) and compare them to a pairwise matched healthy control group (n = 28, total n = 56). This study has a multi-assessment design, and includes patient data from seven assessments over six years. Healthy controls were assessed at baseline, after two years and after six years. Cognition was assessed with the MATRICS Consensus Cognitive Battery. Data were analyzed with linear multilevel models. FES-patients scored significantly lower than the control group across all cognitive domains at baseline. Over six years, improvements were seen in attention, verbal learning, processing speed, reasoning/ problem solving, working memory and social cognition. The overall trend points toward a similar cognitive change in both groups. The patient group's improvement in reasoning/ problem solving was significantly larger that the control group, but improvement in working memory was smaller. Cognitive improvements were seen under and after the initial psychosis episode and throughout the recovery process with 45.5% of the patients fully recovered by 6-year follow-up. Cognitive improvements were seen in almost every cognitive domain that is consistently impaired in FES.

1. Introduction

Cognitive impairment is a core deficit in schizophrenia. Compared to healthy individuals, patients with schizophrenia show impaired cognitive functioning across a broad array of cognitive domains including attention, executive functioning, processing speed and verbal learning (Schaefer et al., 2013). These findings are consistent both in first-episode schizophrenia (FES) (Mesholam-Gately et al., 2009) and in individuals with prolonged illness (Heinrichs and Zakzanis, 1998).

Less is known about the longitudinal development of cognition over the course of illness. Studies of psychosis prodrome showed that cognitive impairments are already present in at-risk individuals (Niendam et al., 2006), although to a lesser degree than in FES (Keefe et al., 2006). The cognitive performance of at-risk individuals who later progress to psychosis show no further cognitive decline from pre- to post-psychosis onset (Carrión et al., 2018; Keefe et al., 2006), suggesting that cognitive deficits are established before the prodromal phase (Becker et al., 2010; Bora and Murray, 2014). After psychosis onset the cognitive composite performance in FES-patients remains stable over time (Rund et al., 2016), which is in line with the idea that schizophrenia is a static encephalopathy disorder (Rund, 1998).

There is a knowledge gap regarding the changes in individual cognitive domains over the course of illness. In their meta-analysis Bora and Murray (2014) found significant improvements in all cognitive domains except from working memory. Bozikas and Andreou (2011) also found stability in most cognitive domains with the possible exceptions of verbal learning and executive functioning, where the evidence of change remains inconclusive. Most of the reported studies have follow-up intervals of two to five years. Three studies of FES-patients reported a follow-up length of ten years (Hoff et al., 2005; Rund et al., 2016; Sterling et al., 2003), but these either did not include a healthy control group or the control group was not matched to the patient group. Barder et al. (2013) reported stability in most cognitive domains apart from motor speed which declined in a follow-up period of five years, but again this study did not include healthy controls. The lack of a healthy control group renders it difficult to conclude that the cognitive changes were genuine improvements (Szöke et al., 2008). A recent meta-analytic review report that the degree of overall cognitive change can be expected to be similar in FES and controls (Bora and Murray, 2014), but yet again the follow-up intervals were mostly two

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

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years or less. As described by Bozikas and Andreou (2011), the current literature has a few limitations that affect the interpretability of results: lack of control group or different attrition rates in healthy and control groups; differences in how patients are recruited; differences in the timing of baseline cognition assessments; differences in cognitive measurements and various durations between follow-ups.

Studies of cognitive development in FES are important because cognition seems to be related to functional outcomes. For instance, stability or improvement in cognition are respectively associated with stability/decline or improvement in social functioning (Niendam et al., 2007). While the relationship between symptoms and global cognitive dysfunction has been debated, recent findings by Rund et al. (2016) showed an association between improved cognitive trajectories and symptom remission during the first year of illness.

In the Oslo schizophrenia recovery study, we seek to further clarify the cognitive trajectories in FES while remedying some of the limitations mentioned above. FES-patients were assessed annually over six years with the MATRICS Consensus Cognitive Battery (MCCB), which is considered to be the gold standard for the assessment of cognition in schizophrenia clinical trials (Buchanan et al., 2011). This cognitive battery covers the seven cognitive domains that are found to be persistently impaired in schizophrenia (Neuchterlein et al., 2004). Earlier longitudinal studies varied in the number of cognitive domains that were assessed, and there was no clear consensus in how to measure these cognitive domains (Mesholam-Gately et al., 2009). Cognitive domains were hence assessed with a vast array of different cognitive measures, hampering the comparableness of studies. So far few studies have investigated the longitudinal development of different cognitive domains using the MCCB with multiple yearly assessments. Juuhl-Langseth et al. (2014) found cognitive improvements in most cognitive domains assessed with the MCCB, but the follow-up period was only two years and the patient group consisted of individuals with early onset schizophrenia (EOS).

Earlier longitudinal studies have mostly included two or three assessment points, but by including yearly cognitive assessments we are able to examine the cognitive trajectories more closely. Bonner-Jackson et al. (2010) assessed individuals with schizophrenia seven times over a time span of 20 years. They found that processing speed and verbal knowledge were most impaired during the acute phase, followed by improvements at 2-year follow-up and stability throughout the 20-year time period. However, their study did not include any other cognitive domains, nor did they include a healthy control group. In one of our previous papers that reported data from the 2-year follow-up, we saw a statistically significant decline in verbal learning and improvements in reasoning/problem solving and social cognition in FES compared to healthy controls (Torgalsbøen et al., 2015), indicating differentiated trajectories for different cognitive domains. Yet, two years is a short amount of time in the clinical course of schizophrenia, and these cognitive trajectories need to be reexamined in order to determine the cognitive development beyond the first episode of schizophrenia.

To our knowledge this is the first study where the patient group is matched pairwise with a healthy control group to examine the differences in cognitive development over time using the MCCB. The two groups remain matched over the current research period of six years.

The present study addresses the following research question:

Do the cognitive domains develop similarly in FES and healthy controls over a six year interval?

2. Methods

2.1. Participants

A total of 31 patients with first-episode schizophrenia were referred to the study from mental health service institutions in the Oslo area by their treating clinicians. The patients 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. 28 patients fulfilled the criteria and were included in the study. In the follow-up period, the patient group were provided treatment by their local mental health service institutions, through medication, psychoeducation and case management.

A healthy control group with 28 participants was matched pairwise with the patient group on gender, age and education level (± one year). The youngest participants in the control group were recruited through inquiries at junior and senior high schools in and around the Oslo metropolitan area. The older participants were recruited through electronic advertisements on the Vestre Viken Hospital Trust (VVHF) homepage. The VVHF provides state funded healthcare to the south-eastern part of Norway and consists of rural areas as well as city centers. Exclusion criteria were a history of schizophrenia or other severe mental disorders; mental retardation; a history of neurological disease; head injury and/or loss of consciousness for more than 10 minutes; current psychotropic medication; chronic somatic illness inducing significant fatigue or pain; current narcotics for pain; a history of alcohol or substance abuse; dyslexia or other significant learning difficulties; inability to understand spoken and written Norwegian sufficiently to comprehend testing instructions. Demographic and clinical characteristics of the participants are presented in Table 1.

All participants 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 seven assessment points over six years. The patient group was assessed on baseline, after six months and after a year. Thereafter, they were assessed every year for four consecutive years. Beginning from the 5-year follow-up the patient group was assessed every other year. All patients were retained during the first three assessments, while three participants left the study during the 2-year follow-up and an additional three dropped out during the 3-year follow-up. The healthy control group was assessed on baseline, after two years and after six years. Three participants were unable to participate on the 2-year follow-up only. On every measurement occasion, the

Table 1
Demographic and clinical characteristics of the participants at baseline.

	Patients (n = 28)	Controls (n = 28)
Age in years	21.0 (SD 2.6)	21.1 (SD 2.7)
Gender	17 (60.7%) men, 11 women	17 (60.7%) men, 11 women
Level of education		
Elementary school	n = 11 (39.3%)	n = 9 (32.1%)
High school	n = 8 (28.6%)	n = 16 (57.1%)
Some college	n = 7 (25.0%)	n = 2 (7.1%)
BA degree or higher	n = 2 (7.1%)	n = 1 (3.6%)
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%)	
Duration of untreated psychosis (months)	15.9 (SD 15.4)	
Drug-naïve at baseline	2 (7.1%)	
Fully recovered on year 6	10 (45.5%)	

participants completed the neurocognitive test battery as described below.

2.2. Clinical instruments

The clinical interviews and tests of the patients were conducted within the first five months of their admission to a hospital or out-patient 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.

2.3. Neurocognitive measures

Cognition was measured with the 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, and it concludes that US norms may be employed for the Norwegian population (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 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.

2.4. Data analyses

IBM SPSS Statistics version 22.0 was used for all statistical analyses. The data consist of two hierarchical levels: 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 each neurocognitive domain to estimate initial level and changes in cognitive functions over time. We started with a random intercept model, then allowed for variations in both individuals' baseline cognition (the intercept) and change in cognition over time (the slope).

Next, in order to further improve our base models, we introduced group effect as a parameter. Lastly, an interaction between baseline *T*-scores and time was introduced into the existing model 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 one at a time to test for inclusion in the models. The covariates were removed from the final model if they were not significant. Akaike information criterion (AIC) was used to determine the best fitting models (Akaike, 1974).

3. Results

The best fitting models (model 1–3) all included a fixed linear time effect, a random intercept, and a random slope. The final models are shown in Table 2.

3.1. Cognitive trajectories for all participants (model 1) and baseline differences between FES- patients and healthy controls (model 2)

Analyses with all participants showed a significant linear increase in cognition across all cognitive domains over six years (model 1) with the exception of visual learning. Compared to healthy controls, the FES patients scored significantly lower on all cognitive domains at baseline except for social cognition (model 2). Also, AIC comparisons showed that model 2 had a better fit than model 1 for all cognitive domains except social cognition. We therefore included all cognitive domains in the final multilevel model to examine whether an added interaction parameter would further improve the fit of these models. The effects of sex and level of education were insignificant and were subsequently removed from the final models.

3.2. Cognitive trajectories of FES-patients compared to healthy controls (model 3)

Model 3 included a group*time interaction parameter. Regarding model 2, where insignificant group effects were shown for social cognition, the added interaction parameter did not improve the model fit for social cognition according to AIC comparisons. Nor did the model fit improve for processing speed, verbal learning and visual learning. AIC comparisons showed that model 3 had a better model fit than model 2 for attention, working memory and reasoning/ problem solving.

There was a significant difference in slope between patients and healthy controls in working memory and reasoning/ problem solving. Both groups showed an increase in cognitive scores over time, but the increase in working memory was significantly lower for the patient group compared to the control group ($\beta = -0.84$, $SE = 0.42$, $p < 0.05$). Meanwhile, the increase in reasoning/ problem solving was significantly higher for the patient group than the control group ($\beta = 1.03$, $SE = 0.41$, $p < 0.05$). For the rest of the cognitive domains, no significant interaction effects were found. Moreover, the analyses did not achieve convergence for processing speed, attention and visual learning. Another set of analyses were therefore performed for these cognitive domains where time was removed as a random effect in order to simplify the model and facilitate convergence. The group*time interaction remained insignificant, although the *p*-value for attention was close to being significant ($\beta = 0.56$, $SE = 0.29$, $p < 0.051$). Fig. 1 shows the mean levels of different cognitive domains across the 7 measurement waves.

4. Discussion

The purpose of the present study was to examine the cognitive development in FES-patients over six years, and compare their cognitive domain trajectories to those of healthy controls.

Compared to the healthy control group, the patient group performed worse on baseline on all cognitive domains. This was to be expected given the large amount of evidence indicating generalized cognitive impairments in schizophrenia compared to healthy controls (Fioravanti et al., 2012). When compared over time however, some interesting findings emerged in the present study.

Firstly, the analyses comparing cognitive trajectories between patients and healthy controls yielded mostly insignificant results. A comparable improvement in both groups was seen in processing speed. As for attention, verbal learning and social cognition, the cognitive trajectories suggested a larger improvement for the patient group than for the control group over time. However, the difference between the groups were not statistically significant and remained non-significant with a simpler model, although attention was significant on a trend level. There is a possibility that we were unable to discern the differences due to a small sample size, but another explanation is that the cognitive change is of comparable magnitude in the two groups. In their longitudinal study on first-episode schizophrenia, Hoff et al. (1999)

Table 2
The best fitting models for the cognitive domains.

	Attention		Processing speed		Working memory		Verbal learning		Visual learning		Reasoning/ problem solving		Social cognition	
	Estimate (SE)	*p*	Estimate (SE)	*p*	Estimate (SE)	*p*	Estimate (SE)	*p*	Estimate (SE)	*p*	Estimate (SE)	*p*	Estimate (SE)	*p*
Model 1														
Fixed effects														
Intercept	40.349 (1.218)	<0.001	42.893 (1.508)	<0.001	44.658 (1.344)	<0.001	44.087 (1.212)	<0.001	44.368 (1.256)	<0.001	45.900 (1.268)	<0.001	45.590 (1.369)	<0.001
Time	1.068 (0.148)	<0.001	1.399 (0.180)	<0.001	0.710 (0.217)	0.002	0.528 (0.243)	0.034	0.265 (0.200)	0.186	1.350 (0.214)	<0.001	0.757 (0.242)	0.003
Random effects														
Residual	24.967 (2.858)	<0.001	35.013 (3.616)	<0.001	44.754 (5.158)	<0.001	46.771 (5.372)	<0.001	48.915 (4.920)	<0.001	45.802 (5.246)	<0.001	49.506 (5.636)	<0.001
Intercept	69.230 (15.623)	<0.001	108.301 (24.036)	<0.001	76.515 (19.166)	<0.001	56.531 (15.972)	0.001	61.528 (15.636)	<0.001	64.279 (17.219)	<0.001	77.560 (19.819)	<0.001
Slope	0.008 (0.229)	0.720	0.198 (0.000)		0.532 (0.503)	0.291	1.074 (0.582)	0.065	0.065 (0.000)		0.438 (0.468)	0.350	0.951 (0.604)	0.115
Model fit														
AIC	1684.932		1785.798		1821.982		1822.677		1811.442		1801.324		1841.603	
Model 2														
Fixed effects														
Intercept	45.638 (1.470)	<0.001	50.945 (1.658)	<0.001	49.336 (1.756)	<0.001	47.422 (1.570)	<0.001	48.679 (1.481)	<0.001	48.302 (1.651)	<0.001	47.026 (1.839)	<0.001
Time	1.028 (0.149)	<0.001	1.326 (0.201)	<0.001	0.716 (0.216)	0.002	0.498 (0.243)	0.045	0.267 (0.197)	0.178	1.334 (0.214)	<0.001	0.745 (0.242)	0.003
Group	−10.192 (2.014)	<0.001	−15.327 (2.240)	<0.001	−8.955 (2.257)	<0.001	−6.189 (2.007)	0.003	−8.123 (1.828)	<0.001	−4.535 (2.125)	0.037	−2.706 (2.364)	0.257
Random effects														
Residual	24.709 (2.801)	<0.001	35.908 (3.940)	<0.001	44.530 (5.098)	<0.001	46.741 (5.364)	<0.001	48.408 (4.796)	<0.001	45.815 (5.250)	<0.001	49.501 (5.632)	<0.001
Intercept	43.056 (10.451)	<0.001	50.354 (13.048)	<0.001	68.195 (17.611)	<0.001	44.446 (13.607)	0.001	40.729 (11.609)	<0.001	53.282 (15.345)	0.001	73.426 (19.086)	<0.001
Slope	0.104 (0.231)	0.451	0.573 (0.000)		0.552 (0.502)	0.271	1.074 (0.581)	0.064	0.038 (0.000)		0.430 (0.467)	0.357	0.930 (0.598)	0.119
Model fit														
AIC	1666.592		1757.289		1810.689		1815.970		1797.425		1799.393		1842.357	
Model 3														
Fixed effects														
Intercept	45.940 (1.481)	<0.001	50.943 (1.658)	<0.001	47.962 (1.877)	<0.001	47.894 (1.681)	<0.001	49.531 (1.653)	<0.001	49.871 (1.769)	<0.001	48.031 (1.983)	<0.001
Time	0.734 (0.223)	0.001	1.264 (0.299)	<0.001	1.173 (0.313)	<0.001	0.292 (0.357)	0.416	−0.006 (0.307)	0.986	0.755 (0.312)	0.018	0.387 (0.355)	0.279
Group	−10.516 (2.023)	<0.001	−15.273 (2.248)	<0.001	−6.561 (2.549)	0.013	−6.993 (2.254)	0.003	−9.555 (2.207)	<0.001	−7.136 (2.378)	0.004	−4.458 (2.693)	0.103
Group*time	0.523 (0.296)	0.083	0.114 (0.404)	0.777	−0.843 (0.416)	0.048	0.385 (0.486)	0.432	0.465 (0.400)	0.246	1.026 (0.413)	0.016	0.659 (0.480)	0.175
Random effects														
Residual	24.328 (2.722)	<0.001	35.906 (3.940)	<0.001	44.425 (5.077)	<0.001	46.732 (5.360)	<0.001	48.095 (4.767)	<0.001	45.497 (5.181)	<0.001	49.391 (5.609)	<0.001
Intercept	43.367 (10.432)	<0.001	50.371 (13.048)	<0.001	65.664 (16.956)	<0.001	44.518 (13.588)	0.001	40.868 (11.485)	<0.001	52.681 (14.897)	<0.001	73.445 (18.930)	<0.001
Slope	0.089 (0.228)	0.696	0.571 (0.000)		0.347 (0.460)	0.451	1.048 (0.575)	0.068	0.047 (0.000)		0.240 (0.418)	0.567	0.879 (0.583)	0.132
Model fit														
AIC	1665.534		1759.187		1808.871		1817.348		1798.262		1795.475		1842.499	

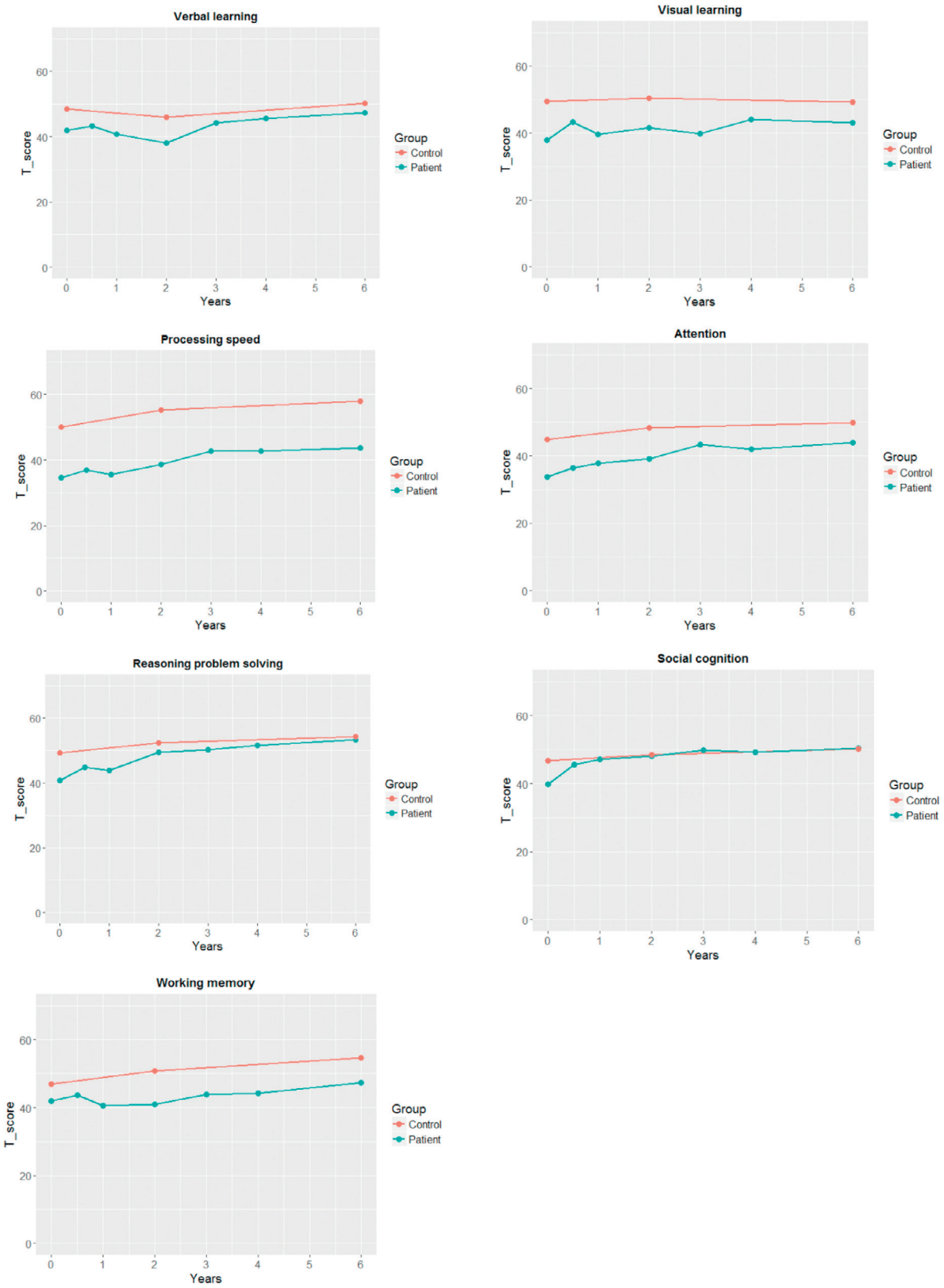

Fig. 1. Mean levels of cognitive domains across 7 measurement waves. *X*-axis represents time measured in years. *Y*-axis is cognitive scores reported as *t*-scores.

have demonstrated that patients scored below controls on all cognitive domains on baseline, and although many cognitive domains improved over time, the cognitive deficits remained 1 to 2 standard deviations below controls throughout a five-year period. Other studies have reported domain specific differences between patients and controls, but the overall trend points toward a similar cognitive change in both groups with the possible exception of executive functions and verbal learning (Bozikas and Andreou, 2011).

Studies of patients with EOS have reported a lack of improvement and even decline in cognition over time (Øie et al., 2011). Many EOS

and FES-patients are often of similar age when they first receive treatment. However, the prospect of cognitive improvement seems to be different for the two groups, as our results show stability or improvement in all cognitive domains, supporting the view of EOS being more severe than first-episode schizophrenia (Raji et al., 2009; Øie et al., 2011).

When comparing the current results with our paper on the 2-year follow-up (Torgalsbøen et al., 2015), we made an interesting finding. In that paper, the patient group showed decline on verbal learning and improvement on reasoning/ problem solving and social cognition compared to healthy controls. However, analyses of the six-year follow-up suggest that these cognitive changes are only temporary. Verbal learning improves after two years, while social cognition stabilizes. Only reasoning/ problem solving continues to improve over time. This points to the importance of assessing cognitive development over many years with multiple assessments when exploring cognitive impairments in schizophrenia. It has been reported that the evidences of change in verbal learning remain inconclusive (Bozikas and Andreou, 2011). However, this may be due to short follow-up periods, as most of the earlier studies had only a follow-up period of two years, and the studies with a longer follow-up period had only two or three assessments in total (Rund et al., 2016). According to the figures, social cognition seems to stabilize over time, and the cognitive trajectories of patients and healthy controls seem to be on the same level after one year. This is interesting as social cognition is increasingly recognized as a potential mediator in the relationship between cognition and functioning (Green et al., 2015). The initial improvement in social cognition may be due to psychoeducation and/or psychotherapy provided to the patients. As symptoms decreases and their illnesses stabilizes, the patients may not attend psychotherapy as frequently anymore, and maybe this is reflected in a stable social cognition score. Holmén et al. (2010) found no difference in social cognition between patients with EOS and healthy controls as measured with the MCCB. They suggested that patients with schizophrenia may have no problems with knowing how to act in social situations, but still have problems performing these actions in real life. They also noted that both patients and controls were younger and performed poorer than the lowest age group in the American norms, suggesting that the test may not be suitable for adolescents. Our populations consisted of older individuals, and neither patients or controls underperformed on the tests. However, it still remains to be determined whether the MSCEIT subtest would yield the same results as role-play tests.

The second interesting finding in our study was that two cognitive domain trajectories were significantly different between control group and FES-patients. Compared to the control group, the patient group showed a larger improvement in reasoning/ problem solving over time, whereas the improvement in working memory was smaller than the control group. There is some evidence of domain specific differences between FES-patients and healthy controls, although the findings remain inconclusive due to heterogeneous measurements and study designs. Most studies have a follow-up period of one to two years, and the comparative groups are seldom matched. These studies have reported differences in cognitive change between patients and controls, for instance in verbal and non-verbal recall and inhibitory processes (Hoff et al., 2005); visual memory and executive function (Crespo-Facorro et al., 2009); verbal fluency and verbal memory (Albus et al., 2006). Studies regarding verbal memory show varied results indicating smaller differences, no differences or larger changes in FES-patients than healthy controls. In the current study where the two groups are matched, we found no differences in verbal memory development as discussed earlier. A larger improvement in reasoning/ problem solving in the patient group was found, suggesting that patients are able to use more flexible problem solving techniques when symptoms subside. On the other hand, patients showed smaller improvements in working memory compared to controls. Working memory is one of the core cognitive deficits in first-episode schizophrenia, and baseline working memory is associated with later social functioning (Fu et al., 2017) and role functioning (Torgalsbøen et al., 2014). This result indicates that the gap in performance seen between the two groups on baseline will only grow larger over time. The current results support our earlier findings (Torgalsbøen et al., 2015) that there are different trajectories for different cognitive domains. From a clinical perspective, this may speak in favor of a targeted rehabilitation of different cognitive domains, such as working memory. Further research into how long-term cognitive development affects functioning is needed.

By including annual assessments over six years we aim to elucidate the cognitive trajectories of patients both under and after the initial psychosis episode and throughout the recovery process. Since we have more frequent assessment points in the early stages of illness, we can see in the figures that improvements are already discernable after 6 months following illness outbreak. Moreover, these improvements continue up to six years and are seen in almost every cognitive domain that are consistently impaired in FES. Studies have consistently shown an association between cognitive functions and functional outcome (Green et al., 2015; Green and Harvey, 2014). However, full recovery from schizophrenia is a lengthy process where clinical symptoms may fluctuate over time. For instance, cognitive improvements have been found to disappear when symptoms are controlled for, suggesting a common origin or a moderating effect (Mayoral et al., 2008). In the present study, most cognitive functions in FES-patients improved in the same rate as healthy individuals, also when symptoms stabilized and patients regained their roles in society. One characteristic with the current study is that 45.5% of the patients are fully recovered by 6-year follow-up (Table 1), with some patients showing signs of partial recovery as early as the first two years. Full recovery is defined as working or studying, having symptoms that are stably mild or absent for two years or more, having contact with friends and/or dating, participating in leisure activities and living independently (Liberman and Kopelowicz, 2005). This may explain why most of the cognitive trajectories start to improve within the first year of illness as seen in the figures. The high recovery rate may also indicate that the cognitive impairments are less manifested in our patient sample, thus we see continued improvements over many years. As the rate of fully recovered patients reported in our study is somewhat higher than what has been reported in other studies, it might be another reason for why our results did not match earlier reports that showed stability in cognitive functioning. In a study by Kopelowicz et al. (2005), it was reported that recovered subjects scored significantly better than non-recovered subjects on executive function, verbal learning, verbal working memory and verbal fluency.

The study's strengths are a healthy control group that is matched pairwise to the patient group, high retention rate in both groups, complete assessments with the MCCB at each assessment point, and multiple measurement occasions across 6 years, which is substantial.

The study's main limitations are a small sample size and uneven assessment points for the two research groups. A small sample size limits the generalizability of our results. However, the drop-out rates from both groups were low, and we were able to analyze all available data with multi-level analyses, thus strengthening our findings. Out of the 56 participants, 84% completed every assessment over the six-year period. Regarding practice effects, we are aware that there is uncertainty regarding whether the changes are due to genuine improvements in cognition or to practice effects, especially when the groups were assessed a different number of times. It has been argued that in samples of patients with schizophrenia, improvements in cognition are mostly accounted for by practice effects (Szöke et al., 2008). However, these studies did not use a consensus based cognitive battery. MCCB has shown small practice effects in validation studies with a test-retest periods as brief as 15 days (Buchanan et al., 2011; Keefe et al., 2011; Nuechterlein et al., 2008). Goldberg et al. (2010) found that practice effects are largest between the initial and second assessments, with smaller increases with subsequent follow-ups. The practice effects are

also comparable between patients and healthy controls. Although it is likely that improvements in both groups are partly due to practice effects, the magnitude of the improvements are comparable in both groups and we argue that no deterioration in FES-patients has been masked by practice effects. Since our patient sample consists of many individuals that are either partially or fully recovered, we also find it likely that the improvements in cognition reflect the improvements in clinical status. Another potential limitation is the possibility of medication effects on cognition. Husa et al. (2014) reported that the cumulative use of antipsychotics affected cognitive functioning negatively, while Takeuchi et al. (2013) found improved cognitive performances following antipsychotics dose reduction. However, the populations in these studies were not FES-patients. We did not find any significant correlations between daily doses of medication and cognitive scores (Torgalsbøen et al., 2014, 2015). Therefore, we argue that there is no direct relationship between medication dose and test performance in our sample. Finally, we did not examine the effects of IQ, which may be associated with cognitive performance at baseline and cognitive change over time.

Conflict of interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi: 10.1016/j.psychres.2018.06.016.

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