



The course of cognitive functioning after first-episode of psychosis: A six month follow-up study



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ABSTRACT

Our aim with the present study was to evaluate rank-order and mean-level cognitive functioning stability among first-episode psychosis (FEP) patients, measured using the Cambridge Neuropsychological Test Automated Battery (CANTAB), over a six month period. We also aimed to examine longitudinal measurement invariance and identify factors—such as age, gender, educational level, treatment and psychopathological change scores—potentially linked to cognitive change among patients. In addition, correlations between objectively measured and subjectively evaluated cognitive functioning were estimated. Neuropsychological assessments were administered to 85 patients after the initial stabilisation of their psychosis; 82 of the patients were retested. Subjectively perceived cognitive functioning was measured using a subscale derived from the Estonian version of the Subjective Well-Being Under Neuroleptic Scale (SWN-K-E). On average, executive functioning and processing speed improved significantly, while memory test scores decreased significantly, over time. Very high rank-order stability ($r = 0.80$ to 0.94 , $p < 0.001$) was observed with all measured ability scores. Confirmatory factor analysis revealed the loadings of a single (broad ability) factor model were equal across both measurement occasions, but the lack of intercept invariance suggested that mean-level comparisons are more appropriately carried out at a subtest level. On average psychopathology scores and antipsychotics doses declined over time, with the latter also significantly correlating with better executive functioning. Gender was a significant moderator of some domains of cognitive performance, and decline tended to be somewhat more pronounced for women. The results also indicated the lack of any relationship between objective and subjective measurements of cognitive functioning.

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1. Introduction

Among other symptoms, psychotic illnesses are accompanied by neuropsychological impairments (Green et al., 2004; Kurtz, 2005). Although individual patient's neuropsychological profiles may be heterogeneous (Joyce et al., 2005), they are typically characterised by attention, set shifting, processing speed, memory, learning, working

memory, and executive function deficits (Heinrichs and Zakzanis, 1998; Mesholam-Gately et al., 2009; Saykin et al., 1991), something that can be broadly summarised as generalised cognitive impairment (Dickinson et al., 2004; Mohamed et al., 1999). On average, schizophrenia patients tend to score 1.0 to 2.5 standard deviations lower in general cognitive ability compared to control subjects (CoS), however there is also some variability in the extent of impairment between domains (Bildler et al., 1992; Heinrichs and Zakzanis, 1998; Keefe, 2014; Mohamed et al., 1999). While some patients do fall within the normal range of ± 1 standard deviations of the mean of a generally healthy population (Kremen et al., 2000; Palmer et al., 1997). Hoff et al. (2005) concluded that although most FEP patients have undergone considerable cognitive decline by the time of their first hospitalisation, the exact

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course of cognitive impairment remains unknown. In addition, psychotic symptoms may even share some genetic aetiology with cognitive functioning (Kendler et al., 2015; McIntosh et al., 2013).

The available evidence is also contradictory as to whether cognitive functioning continues to decline during later stages of schizophrenia (Aas et al., 2014; Rund et al., 2007). It has been argued that the majority of such cognitive declines occurs just before or within a few years after the onset of psychosis (Bora and Murray, 2014). To date, longitudinal studies have investigated patients' cognitive functioning over the years following disease onset, but less is known about what specifically happens to their cognitive abilities during the months immediately following FEP diagnosis. Investigating the cognitive performance of patients during the early stages of chronic psychotic disorder may help to identify cognitive deficits related to schizophrenia, compared to cognitive dysfunction resulting from the long-term course of the schizophrenic illness or the treatment of either.

During the present study we investigated cognitive changes among FEP patients following their FEP. First, mean-level changes were calculated to ascertain the extent to which patients' cognitive abilities had changed during the six months following FEP. Second, the extent to which patients retained their cognitive test score ranking (rank-order stability) was examined. The lower the stability, the more likely there are potentially identifiable factors that result in deviation from the normative change pattern of a condition (Deary, 2014). Third, the structure of changes were examined, indicating the extent to which changes happened in lockstep, and therefore were likely to pertain to cognitive functioning in general, as opposed to specific cognitive domains. Fourth, individual differences in cognitive changes were compared to possible causal factors, including demographic characteristics, antipsychotic medication dosages, and the extent of psychopathology. In addition to cognitive functioning quantified using objective performance tests, subjective cognitive dysfunction may be an important early indicator of schizophrenia, as it can precede prodromal symptoms (Hambrecht et al., 2002; Nuechterlein and Dawson, 1984) is prevalent among patients with FEP (Moritz et al., 2000) and in the late stages of the disorder (Homayoun et al., 2011; Stip et al., 2003). During the present study, changes in subjective cognitive dysfunction were also recorded over the same timeframe. As it is currently unclear to what extent subjective and objective cognitive dysfunction measurements are in-line each other—some studies report positive correlations (Prouteau, 2004; Stip et al., 2003) and others no significant correlations (Homayoun et al., 2011; Zanello and Hoguelet, 2001)—we correlated levels of change between measurements of objective and subjective cognitive dysfunction.

2. Materials and methods

2.1. Study participants

The FEP patients were part of an on-going longitudinal research project of first-episode psychosis conducted by the Psychiatry Clinic of Tartu University Hospital, Estonia. A total of 85 patients (mean age 26.99 years old, *s.d.* = 6.96, range 18–43; 54.12% male; 92.94% right-handed) met the inclusion criteria: aged between 18 and 45; had experienced FEP; the duration of untreated psychosis was less than three years; they had received no antipsychotic treatment before their first contact with medical services for psychosis. At the time of recruitment, patients were in a stabilisation phase of the disease, with the initial florid psychotic symptoms had been controlled by medication. Diagnoses were based on clinical interviews that followed ICD-10 (WHO, 1992) criteria, a review of their medical history, information from family members, and were agreed upon by two clinical psychiatrists. Among the patients, the diagnoses were: acute polymorphic psychotic disorder without symptoms of schizophrenia (F23.0, *n* = 16); acute polymorphic psychotic disorder with symptoms of schizophrenia (F23.1, *n* = 16); acute schizophrenia-like psychotic disorder (F23.2, *n* = 21); other acute predominantly delusional psychotic disorder (F23.3, *n* = 4);

other acute and transient psychotic disorders (F23.8, *n* = 5); paranoid schizophrenia (F20.09, *n* = 19); catatonic schizophrenia (F20.29, *n* = 1); undifferentiated schizophrenia (F20.39, *n* = 2); other nonorganic psychotic disorders (F28, *n* = 2). F20.39 and F28 category patients had experienced psychotic symptoms for longer than one month. The patients had received an average of 21.42 (*s.d.* = 8.92) days of treatment prior to baseline neuropsychological testing. Follow-up data were collected approximately six months later (mean duration between baseline and follow-up testing was 6.35 (*s.d.* = 0.91) months). Follow-up data were available for a total of 82 patients (96.47%); two patients had dropped-out of the mental health care system, and one declined. Patients were being treated with various atypical antipsychotic medications as appropriate to their specific condition. At baseline, all patients were receiving only atypical antipsychotics; at follow-up, four patients (4.88%) were additionally being treated with neuroleptics. Neuropsychological assessments were performed when patients were clinically stable and willing to undergo the procedure. All FEP patients were fluent in Estonian, and had on average undergone 13.04 (*s.d.* = 2.51) years of fulltime education.

With regard to substance abuse, ten patients (11.8%; seven males) reported having tried cannabis; nine patients (10.6%; all male) reported having habitually used cannabis and amphetamine type stimulants at some point during their lifetime. None of the patients met substance dependence criteria.

The study was approved by the Ethics Review Committee on Human Research of the University of Tartu (Estonia) and carried out in accordance with The Code of Ethics of the World Medical Association. A complete description of the purpose and procedures of the study was read to the participants, and written informed consent provided by all. Participants were recruited between March 2009 and June 2015. The same sample has been partly involved in our previous research (Haring et al., 2015a; Haring et al., 2015b; Haring et al., 2016).

2.2. Measurements and procedures

2.2.1. Computerised neuropsychological assessment

A number of studies have used the comprehensive Cambridge Neuropsychological Test Automated Battery (CANTAB) (Robbins and Sahakian, 1994) to produce neuropsychological profiles that characterise FEP patients (Barnett et al., 2005; Haring et al., 2015b; Hutton et al., 1998; Leeson et al., 2009a). The CANTAB tests are administered using a computer with a touch-sensitive screen; application of the test and feedback are given in a standardised manner, which precludes examiner variation (Fray et al., 1996). The CANTAB has different forms for a certain subtest and adult population validity estimates, and for some subtests test–retest reliability indices are provided (Lowe and Rabbitt, 1998). However, the equivalence of these alternate forms, as well as their psychometric properties among an FEP group, have not been empirically established.

Eight CANTAB tests, shown to be sensitive to evaluating the cognitive dysfunction of patients with psychotic disorders, were administered in a fixed order to each patient in a one-to-one setting. The tests (see below) were run using CANTABclipse Version 3.0.0. All task stimuli were visual in nature, consisting of geometric designs or simple shapes, and required a non-verbal response. Instructions were given in Estonian from a literal translation of the CANTAB test manual that was produced by three clinical psychologists fluent in both English and Estonian. The battery of tests took approximately 1 h to administer. During test sessions, participants were offered to take a short break whenever they felt the need.

2.2.2. Visual memory tests

Pattern recognition memory (PRM) tests rely on cued memory functions, and the total number of correct responses was used as the outcome in the present analyses.

Spatial recognition memory (SRM) tasks measure a subject's spatial memory via a forced-choice paradigm. The total number of correct responses was used as the outcome in the analyses.

Paired-associates learning (PAL) tests assess visual memory and new learning. The first trial memory score was used as the outcome of this test.

2.2.3. Executive function, planning, and working memory tests

Intra/extradimensional shift (IED) tests assess visual discrimination, selective attentional set formation and maintenance, shifting, and flexibility of attention; the number of errors made in the extra-dimensional stage of the task was recorded as the outcome of the present study, and all participants reached this level of the task.

Stockings of Cambridge (SOC) is a spatial planning test, and the number of problems solved with minimal moves was recorded as the outcome.

Spatial span (SSP) assesses subjects' visuospatial short-term memory. The number of successes (in terms of being within a certain span length) was recorded.

Spatial working memory (SWM) tests evaluate subjects' ability to retain spatial information and manipulate these remembered items in their working memory. The number of errors was recorded, as well as a strategy score that consisted of the number of times an ineffective strategy was used.

2.2.4. Speed of processing

Rapid visual information processing (RVP) tests involve a sustained vigilance task. The probability of a correct hit (sensitivity for detecting sequences) was recorded as the outcome.

During the follow-up assessments, alternate test versions of PRM, SRM, PAL, and IED were used. For more detailed descriptions of these tests, see the CANTAB website (<http://www.cambridgecognition.com>).

2.2.5. Clinical assessments

Range and severity of psychopathology was assessed using the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). The BPRS consists of 18 symptoms and each item is measured on a seven-point Likert scale from "not present" to "extremely severe". A total score, as well as positive and negative BPRS symptom scores (derived from the subscales identified by Ventura et al. (2000)), were used as the outcome.

2.2.6. Medication data

Types and dosage of antipsychotic medications were recorded and subsequently converted into mean theoretical chlorpromazine (CPZ) equivalents (Gardner et al., 2010).

2.2.7. Subjective cognitive functioning

Patients' subjectively perceived cognitive functioning was evaluated using a 'mental functioning' subscale, obtained from the Subjective Well-being under Neuroleptics-Short Form (SWN) (Naber et al., 2001), Estonian version (Haring et al., 2013). The SWN consists of 20 items rated on a 6-point Likert type self-rating scale that refers to subjective experiences during the past seven days. The 'mental functioning' subscale comprises four items: "I find it easy to think"; "I am imaginative and full of ideas"; "My thinking is difficult and slow"; "My thoughts are flighty and undirected, it is difficult to think clearly". The values of the last two items were reversed during scoring and this global score was a more useful indicator of subjective mental functioning.

2.3. Statistical analysis

Ability test scores on both testing occasions were standardised in relation to the means and standard deviations of the first testing occasion, so that the mean scores at follow-up represented changes in standard deviation units. However, to control for age, gender, and educational

level, mean-level differences were estimated using random coefficients models (RCM), whereby the testing occasion was a categorical predictor of the respective test scores (with effect size representing the mean difference in standard deviation units of the first testing); age, gender, and educational level were covariates and the intercepts were allowed to vary across individuals. Effect sizes were interpreted as small, moderate, and large, with corresponding Cohen's *d* ranging from 0.20–0.49, 0.50–0.79, and ≥ 0.80 , respectively (Cohen, 1977). Mean-level changes in BPRS and CPZ dose equivalents were also estimated using a similar RCM; as CPZ dose equivalents already represent standardised values, raw data were used. Next, we examined rank-order stability across the two testing occasions using Pearson's correlation. Then, general linear models (GLM) were performed to quantify individual-level changes in cognitive ability test scores over time, whereby follow-up scores controlled for age, gender, and educational level were predicted from the baseline scores; deviations from individual's predicted scores (regression residuals) at follow-up were taken as their individual change score (CSs). Principal component analysis (PCA) was then used to investigate the structure of the CSs. We have previously demonstrated (Haring et al., 2015b) that different ability test scores were more strongly intercorrelated among patients than CoS; here we focused on the changes in scores over time. Following the PCA, the replicability of the cognitive traits structure between the two testing occasions (Widaman et al., 2010) was evaluated using multi-group (groups represented occasions) confirmatory factor analysis (CFA). Initial model fit (configural invariance with no parameter equality constraints imposed) was assessed using the comparative fit index (CFI) (Bentler, 1990), and the root mean square error of approximation (RMSEA) (Hu and Bentler, 1999). Goodness of fit is indicated by values ≥ 0.95 for CFI, and ≤ 0.06 for RMSEA (Hu and Bentler, 1999). After configural invariance was evaluated, weak measurement invariance (equality of factor loadings) between the six month time interval was tested using chi-square difference ($\Delta\chi^2$) and CFI difference (ΔCFI) (Horn and McArdle, 1992; Vandenberg and Lance, 2000), where $\Delta\chi^2$ of $p < 0.05$ and ΔCFI of > 0.01 indicated a statistically significant difference in fit. Models were fitted using the maximum-likelihood estimator using the 'lavaan' package of R (Rosseel, 2012). Next, to evaluate whether a significant changes in cognitive characteristics were correlated with age, gender, educational level, clinical symptom severity, or treatment-related variability, a psychopathology change scores (BPRS CSs) and antipsychotics equivalent dose change scores (AP DCs) were calculated, and cognitive CSs separately regressed with BPRS CSs, AP DCs, and demographic variables, using RCM.

Finally, separate Pearson's correlations between cognitive test scores and subjectively perceived mental functioning at baseline and six month follow-up were performed.

All analyses were conducted using R Statistical software (R Core Team, 2015).

3. Results

3.1. Patients characteristics

Females were older (27.49 years old, s.d. = 7.05) than males (26.57 years old, s.d. = 6.94) and had undergone more formal education (mean for females: 13.51 years, s.d. = 2.16; mean for males: 12.64 years, s.d. = 2.72), although these differences were not statistically significant ($t = -0.61, p = 0.55$; $t = -1.61, p = 0.11$, respectively). Mean general psychopathology score, measured using BPRS, was 24.18 (s.d. = 12.80) at baseline and 19.31 (s.d. = 11.37) at follow-up ($t = -4.24, p < 0.0001$). Total BPRS CSs was statistically significant ($t = 7.52, p < 0.00001$); gender was not a significant predictor ($t = -1.45, p = 0.15$) of CSs. BPRS negative and positive symptoms subscale mean scores at baseline were 3.98 (s.d. = 2.91) and 5.20 (s.d. = 3.65), and during follow-up 4.27 (s.d. = 3.10) and 3.56 (s.d. 3.50), respectively. BPRS negative and positive symptoms change scores

(CSs) between the two occasions were statistically significant ($t = 7.15$, $p < 0.00001$; $t = 6.51$, $p < 0.00001$, respectively). Gender differences were not significant for either negative ($t = 0.93$; $p = 0.36$) or positive ($t = -1.04$; $p = 0.30$) psychopathology CSs. The mean theoretical chlorpromazine (CPZ) dose equivalents of antipsychotic medications were 387.38 mg/day (s.d. = 165.44) at baseline and 319.97 mg/day (s.d. = 183.31) at follow-up. There was significant change in AP DCs between the two testing occasions ($t = 3.41$, $p = 0.001$); gender was not a significant predictor ($t = 0.45$, $p = 0.66$).

3.2. Mean-level change

When patients' mean-level changes over the six month period were examined (Table 1), small increases in set-shifting (IED), speed of processing (RVP), executive functioning (SOC), as well as in strategy usage and the ability to manipulate spatial information in working memory (SWM) appeared. In addition, there were large effect sizes for lower performance in episodic memory (PAL) and spatial recognition memory (SRM) tasks. Spatial working memory (SSP) and pattern recognition memory (PRM) tests showed mean-level stability over time.

3.3. Stability of cognitive functioning

We examined the rank-order stability of cognitive functioning over the test–retest interval of six months. The rank-order stability coefficients (Table 1) of the cognitive tests ranged from $r = 0.80$ to 0.94 , all significant at $p < 0.001$. Therefore, patients' relative standings regarding test performance were very stable, suggesting that mean-level changes tended to characterise most of patients in a similar way. These estimates also represent the lower-boundary estimates of the reliability of tests in psychotic patients.

3.4. Structure of cognitive function and measurement invariance

The one-factor (broad ability factor) solution accounted for 19% of total variance among the eight CANTAB subtest scores in the baseline

assessment of the FEP patient group, and primary loading values ranged between 0.13 and 0.82 (Fig. 1).

The dimension identified by the PCA was assumed to reflect an underlying broad cognitive ability trait. The plausibility of the model was estimated using CFA, which confirmed that the empirical model in which measures of CANTAB subtests were loaded on one broad ability domain demonstrated an excellent fit for the data ($\chi^2 = 25.451$; $df = 27$; CFI = 1.000; RMSEA = 0.000; 90% confidence interval for RMSEA = 0.000–0.079).

We then conducted a series of two time-point factor analyses across three levels of invariance testing, by first evaluating the absolute model fit at each level of invariance testing, and then calculating the relative fit of each nested model. Using the criteria of an RMSEA of ≤ 0.06 and CFI of ≥ 0.90 to evaluate absolute model fit, we found that the hypothesised one-factor model demonstrated an excellent fit (CFI = 0.950; RMSEA = 0.058; 90% confidence interval for RMSEA = 0.000–0.095; Table 2), suggesting it could be considered a feasible representation of the data at both time-points and justifying the evaluation of more restrictive invariance models. At the level of *weak invariance* testing, model fit remained acceptable (Table 2), indicating that estimated factor loadings were not significantly different between the two time-points. Indices of both relative and absolute model fit did not support the existence of *scalar invariance*, i.e. intercept values varied significantly between the two assessments. As scalar measurement invariance was not met, testing for stricter forms of invariance were not justified.

3.5. The relationship of cognitive stability with other variables

As described above, for SRM, PAL, IED, SOC, SWM errors, and strategy usage the models reached statistical significance. In order to test whether these changes were moderated by demographic variables (age, gender, educational level), BPRS CSs and AP DC CSs we used RCM analyses. Details of these results are provided in Table 3. Gender was a significant predictor of IED, SOC, SSP, and SWM test performances. Specifically, Fig. 2 shows that gender differences at baseline levels of performance (a) and longitudinal rates of change (b) were significant for the IED, SOC, SSP, and SWM tests, with males outperforming females. Therefore, cognitive decline tended to be somewhat more pronounced among the

Table 1
Longitudinal variability across multiple domains of cognitive functioning among first episode psychosis patients.

Measure	Mean-level difference ^a		t-Value	Rank-order stability (r)
	Estimate (SE)	CI		
PRM number correct	0.18 (0.14)	(-0.08, 0.45)	1.35	0.89***
SRM number correct	-0.94 (0.15)	(-1.24, -0.64)	-6.20***	0.94***
PAL memory score	-1.32 (0.12)	(-1.56, -1.08)	-10.84***	0.84***
IED total reverse errors	-0.33 (0.13)	(-0.58, -0.09)	-2.64*	0.80***
SOC problems solved in minimum moves	0.42 (0.11)	(0.20, 0.63)	3.80***	0.82***
SSP Span length	0.05 (0.11)	(-0.17, 0.27)	0.49	0.92***
SWM total errors	-0.42 (0.08)	(-0.58, -0.27)	-5.40***	0.84***
SWM strategy score	-0.45 (0.09)	(-0.61, -0.28)	-5.25***	0.90***
RVP sensitivity for detecting sequences	0.29 (0.10)	(0.10, 0.48)	2.96*	0.83***

PRM, pattern recognition memory; SRM, spatial recognition memory; PAL, Paired Associates Learning; IED, intra/extradimensional shift; SOC, Stockings of Cambridge; SSP, spatial span; SWM strategy, spatial working memory, strategy score; SWM errors, spatial working memory, errors score; RVP, rapid visual information processing.

Negative parameter estimates (effect sizes) for SRM and PAL demonstrate decline in the performance and negative estimates for SWM and IED indices characterise lower scores but better performance during follow-up testing. Positive parameter estimates for PRM, SOC, SSP, and RVP reflect to the contrary higher scores and stability or better performance during follow-up.

^a All within-group comparisons were made controlling for the effects of education, age and gender. Random effects estimates between six month in cognitive functioning are expressed in effect size units (Cohen's *d*), CI, confidence intervals of estimates (2.5%, 97.5%), SE, standard error, and rank-order stability (Pearson's *r*).

* $p < 0.05$.
*** $p < 0.001$.

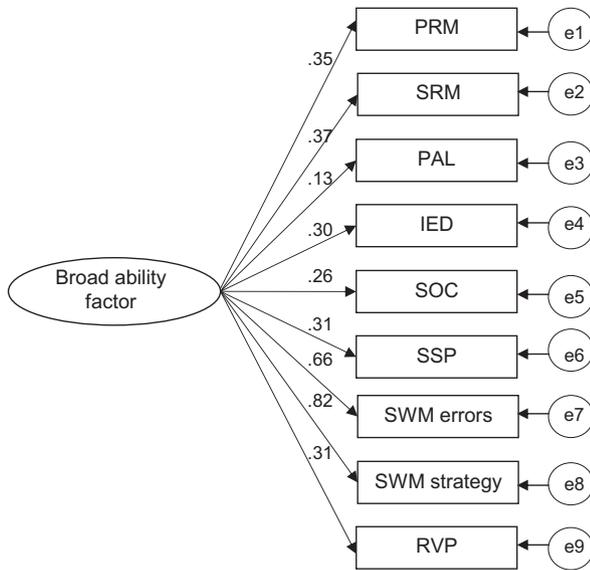


Fig. 1. Representation of the one-latent factor structural model derived from the exploratory factor analysis for first-episode psychosis patients. Variables in boxes represent observed measures and variable in oval represents latent variable. The paths from the latent constructs to the observed variables demonstrate the parameter estimates onto its representative construct. The “e” represents the unique variance and error associated with each observed variable. PRM, pattern recognition memory; SRM, spatial recognition memory; PAL, Paired Associates Learning; SOC, Stockings of Cambridge; SSP, spatial span; SWW strategy, spatial working memory, strategy score; SWM errors, spatial working memory, errors score; IED, intra/extradimensional shift; RVP, rapid visual information processing.

female patients. In addition, longer time in education was predictor for smaller change in IED, and bigger change in the RVP test performances. Younger age was associated with extensive changes in SRM, PAL, and SSP tests' performances and older age predicted bigger change in strategy score in SWM test.

BPRS CSs was not found to be a significant predictor of any cognitive test CSs. We conducted additional RCM analyses to separately evaluate the BPRS negative and positive symptoms CSs effects (in addition to gender, age, education and AP DCs) on the cognitive tests CSs. We did not detect statistically significant impact of negative symptoms CSs, measured by BPRS negative symptoms subscale, on the any of measured cognitive performance CSs (*t*-values ranged between -1.84 to 1.16). BPRS positive symptoms subscale CSs was a significant predictor for SWM errors CSs ($t = 2.17, p < 0.05$) and information processing (RVP) CSs ($t = -2.21, p < 0.05$).

Significant associations were found between mean daily AP DCs and patients' performance CSs of SOC, and SSP, indicating that significant improvement occurred as AP dose decreased. Individual antipsychotic dose and psychopathology raw scores were significantly correlated at both baseline and follow-up ($r = 0.35, p = 0.001$; $r = 0.34, p = 0.002$, respectively).

Table 2
Summary of tests of factorial invariance in first episode psychosis patients group at baseline compared to follow-up testing according to one latent factor solution.

Invariance	χ^2 (df)	$\Delta\chi^2$ (Δ df)	<i>p</i> -Value	CFI	Δ CFI	RMSEA
Configural	69.280 (54)			0.950		0.058
Weak	75.708 (62)	6.428 (8)	0.60	0.955	0.005	0.051
Scalar	197.028 (70)	121.320 (8)	0.00	0.586	0.369	0.147

χ^2 , chi-square; *df*, degree of freedom; *p*-value corresponds to change in χ^2 ($\Delta\chi^2$), CFI, comparative fit index and change in CFI (Δ CFI); RMSEA, root mean square error of approximation.

3.6. Correlation between objective and subjective cognitive functioning

No significant associations were found between objectively and subjectively measured cognitive functioning at baseline or follow-up (correlation coefficients ranged from $r = -0.22$ to $0.17, p \geq 0.05$). Pearson's correlation coefficient between baseline and follow-up measurements of subjectively perceived cognitive functioning had low temporal stability ($r = 0.20, p \geq 0.05$). Details about these correlation analyses are available on request from the corresponding author.

4. Discussion

The main aim with this study was to analyse whether and how cognitive functionality changes among 82 psychiatric patients directly after confirmation of an FEP diagnosis. In these data, mean-level changes (deviations from individuals' predicted scores based on performances at the first testing occasion) occurred in episodic memory, processing speed, mental flexibility, and executive functioning; patients tended to maintain their cognitive performance relative to other patients; there was structural stability in the factors that summarised cognitive performance among FEP patients; and changes in cognitive test scores were related to demographic and clinical characteristics. Furthermore, objectively measured ability scores did not correlate with subjectively perceived cognitive functionality.

Detecting change in individual patient's neuropsychological performances requires the use of appropriate methods. There are two specific types of change over time one can focus on: rank-order change and mean-level change. A rank-order change refers to a change in an individual's cognitive performance relative to other individuals', and mean-level change refers to changes in average performance over time. The two are independent of each other, i.e. perfect rank-order stability may characterise groups with substantial mean-level change, because individuals often change in the same way.

Limited information is available about the stability of the cognitive battery tests for different groups of patients. Previous research addressing rank-order or mean-level stability between two time points of the CANTAB subtests has been scarce and far less conclusive than research on the validity of the CANTAB among different samples, of which previous studies were mainly limited to the general public and patients with diagnoses of schizophrenia or dementia.

4.1. Mean-level change

In terms of mean-level trends, our results appeared to show that spatial recognition and episodic memory declined over a six month period. In contrast, mental flexibility, executive functioning, manipulation with items in one's working memory, and information processing speed seemed to improve. There was no evidence for changes in pattern recognition memory or working memory capacity. The present study tends to corroborate previous suggestions (Censits et al., 1997; Heaton et al., 2001; Rund, 1998) that there is no broad progression of cognitive deficits during the initial stages of chronic psychotic disorders. This supports the hypothesis of a primary neurodevelopmental deficit (Bora, 2015; Murray and Lewis, 1988; Weinberger, 1987), which may be accompanied by the formation of disturbed regenerative capacities during a person's life-time (Falkai et al., 2015), and be incorporated with epigenetic dysregulation, which is involved in neuronal plasticity mechanisms (Hasan et al., 2013).

Moreover, previous researchers have also demonstrated a cognitive improvement in CoS and FEP patients (Hoff et al., 2005; Nopoulos et al., 1994; Rodríguez-Sánchez et al., 2008; Olivier et al., 2015). However, one should consider the cognitive process being measured and how this may change with repeated assessments (Heilbronner et al., 2010). Measures of executive functioning generally show lower mean-level consistency. Notably, tests of executive function (IED, SOC, SWM) rely considerably on novelty. Thus, cognitive improvements in FEP patients

Table 3
Regression analysis for predictors (gender, age, education, psychopathology change score (BPRS CS), antipsychotics dose change (AP DC)) of CANTAB tests individual-level change score.

Change scores of cognitive measures	Parameter estimates (CI)				
	Gender	Age	Education (years)	BPRS CS ^a	AP DC ^b
PRM	−0.08	0.05	0.18	−0.02	−0.11
number correct	(−0.46, 0.30)	(−0.14, 0.25)	(−0.03, 0.38)	(−0.21, 0.17)	(−0.29, 0.06)
SRM	−0.08	−0.26*	0.18	−0.16	0.04
number correct	(−0.51, 0.35)	(−0.48, −0.04)	(−0.05, 0.41)	(−0.37, 0.05)	(−0.16, 0.23)
PAL	0.002	−0.26**	0.14	0.06	−0.08
memory score	(−0.34, 0.34)	(−0.44, −0.09)	(−0.04, 0.33)	(−0.11, 0.23)	(−0.24, 0.08)
IED	0.44*	0.08	−0.22*	0.13	0.04
total reverse errors	(0.11, 0.77)	(−0.09, 0.25)	(−0.40, −0.05)	(−0.04, 0.30)	(−0.12, 0.20)
SOC	−0.49**	0.06	0.15	−0.09	−0.16*
problems solved in minimum moves	(−0.81, −0.16)	(−0.10, 0.23)	(−0.02, 0.33)	(−0.26, 0.07)	(−0.31, −0.02)
SSP	−0.58**	−0.22*	0.11	−0.07	−0.16*
span length	(−0.95, −0.21)	(−0.41, −0.03)	(−0.09, 0.31)	(−0.24, 0.10)	(−0.31, −0.01)
SWM	0.50**	0.10	−0.11	0.12	0.08
total errors	(0.15, 0.85)	(−0.08, 0.28)	(−0.30, 0.07)	(−0.02, 0.25)	(−0.04, 0.20)
SWM	0.58**	0.20*	−0.02	0.12	0.002
strategy score	(0.22, 0.95)	(0.01, 0.39)	(−0.21, 0.18)	(−0.03, 0.26)	(−0.12, 0.13)
RVP	−0.11	−0.10	0.30**	−0.09	−0.04
sensitivity for detecting sequences	(−0.45, 0.23)	(−0.28, 0.07)	(0.12, 0.49)	(−0.24, 0.07)	(−0.18, 0.10)

CI, confidence intervals of estimates (2.5%, 97.5%).

PRM, pattern recognition memory; SRM, spatial recognition memory; PAL, Paired Associates Learning; IED, intra/extradimensional shift; SOC, Stockings of Cambridge; SSP, spatial span; SWM strategy, spatial working memory, strategy score; SWM errors, spatial working memory, errors score; RVP, rapid visual information processing.

^a Change score of the Brief Psychiatric Rating Score.

^b Dose change of the used antipsychotic medications in chlorpromazine equivalents.

* $p < 0.05$.

** $p < 0.01$.

during the early course of the disease may be related to a practice effect, a common process shared by CoS, and therefore an increase may not reflect real cognitive improvement, but rather stability or deficit (Goldberg et al., 2007).

In terms of the paired association learning test (PAL), our results are in line with previous studies that showed a decline in cognitive function during the early phases of FEP (Bilder et al., 1992; Hoff et al., 1999), particularly in learning and memory, or the encoding stage of memory formation (Cirillo and Seidman, 2003; Mesholam-Gately et al., 2009). With regard to memory function, Dikmen et al. (1999) argued that the lower consistency estimates for memory test performances suggest memory

itself may be substantially more variable than other cognitive abilities. In contrast, studies of FEP patients that have used memory and learning subtests from the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Cognitive Consensus Battery (Nuechterlein et al., 2004) have detected improvements in the performance of visual learning and working memory tests over a six month period (Olivier et al., 2015) or stable mean-levels over a year (Benoit et al., 2014). Inconsistent findings between these studies could be owing to them having patient groups with different symptom severities, using a different cognitive functioning measurement methodology, and employing different statistical methods.

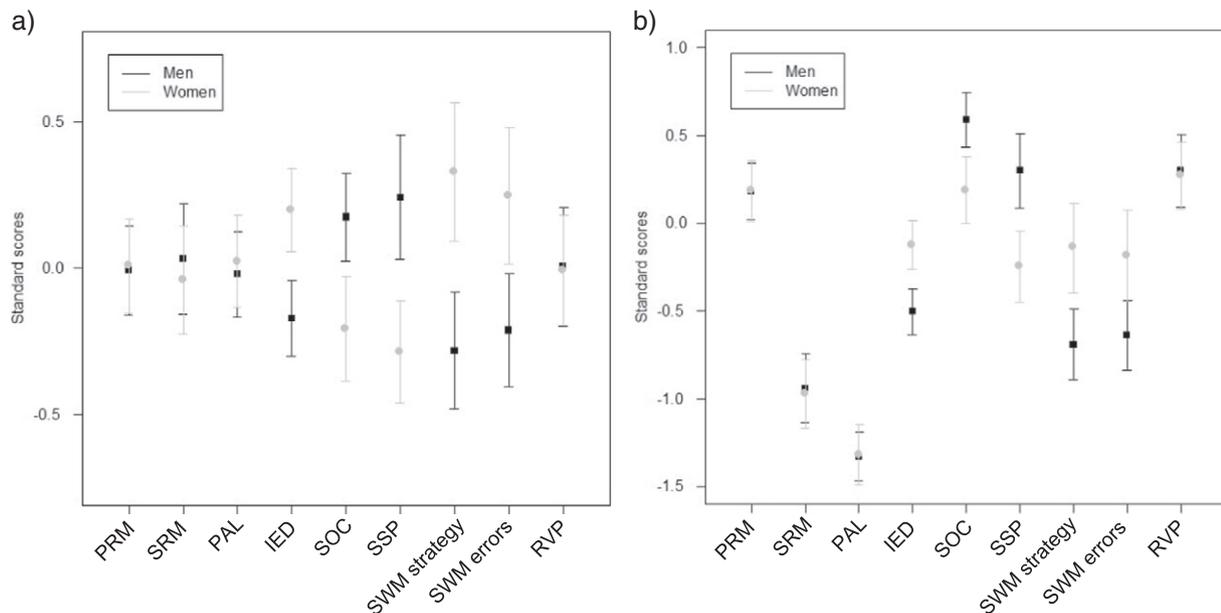


Fig. 2. Predicted means levels of cognitive performance separately for men and women at baseline (a) and follow-up (b). Results are based on random coefficient models. PRM, pattern recognition memory; SRM, spatial recognition memory; PAL, Paired Associates Learning; IED, intra/extradimensional shift; SOC, Stocking of Cambridge; SSP, spatial span; SWM strategy, spatial working memory, strategy score; SWM errors, spatial working memory, errors score; RVP, rapid visual information processing. Lower values (less errors and less ineffective strategy usage) for IED and SWM measures and higher values for PRM, SRM, PAL, SSP, and RVP indicate better performance.

4.2. Rank-order stability

The magnitude of the rank-order coefficients in our study revealed high stability ($r = 0.80$ to 0.94) in the rank ordering of patients over time. Using a sample of 164 elderly volunteers, an assessment of the CANTAB conducted at baseline and after four weeks by Lowe and Rabbitt (1998), revealed moderate stability indices for spatial memory score ($r = 0.57$) and executive function ($r = 0.60$), good stability indices for PAL first trial memory score ($r = 0.68$), spatial span length ($r = 0.64$), SWM total errors score ($r = 0.68$), and IED extradimensional shift errors score ($r = 0.70$), and very high stability indices for pattern recognition memory score ($r = 0.84$). Leeson et al. (2009b) evaluated temporal stability of the CANTAB executive tests reliability over 1 and 3 years within 25 CoS and 104 patients with schizophrenia, and found lower test–retest correlations ($r = 0.4$ – 0.6). Among a smaller sample (58 subjects) with chronic psychotic disorder, Barnett et al. (2010) reported test–retest correlations on executive functioning of approximately $r = 0.6$ – 0.8 after intervals of 12 to 14 weeks. However, it is important to remember that test–retest correlations can vary depending on the sample assessed, and the amount of time between test and retest (shorter retest intervals lead to higher reliability coefficients) (Duff, 2012). For a standard neuropsychological assessment, there is insufficient empirical data to produce appropriate guidelines on the minimal (or maximal) retest interval in clinical cases (Heilbronner et al., 2010). Furthermore, alternate forms of tests should be psychometrically equivalent; however, evidence suggests this is not the case for many measures (Lezak, 2012) and may result in lower stability values. This problem did not emerge in our study, because the correlations between scores on the parallel tests of PRM, SRM, PAL, and IED were very high ($r = 0.80$ – 0.94).

Among their other implications, the rank-order stability estimates can be seen as the lower-bound reliability estimates of the CANTAB subtests: their actual reliability can only be equal or higher, because the observed stability may have also reflected real change over time. The magnitude of the observed estimates supports the CANTAB as a reliable instrument to assess cognitive functioning in FEP patients.

4.3. Structure of cognitive function and measurement invariance

In addition, a high level of rank-order stability implies that stable factors may be supporting the maintenance of individual differences in cognitive functioning over time. Inspection of the goodness-of-fit statistics for the one-factor model of FEP patients indicated the model was a reliable representation of the data at the two time points. These results are consistent with our previous study (Haring et al., 2015b), which examined the potential relationships of an identical set of variables between CoS and FEP patient samples, and demonstrated that a broad latent ability factor model was the most appropriate representation of the relationships between the neuropsychological variables among FEP patients compared to CoS, as well as confirming the similar findings in previous studies that used a different kind of neuropsychological tests (Censits et al., 1997; Dickinson et al., 2006) or the same test battery (Leeson et al., 2009a). The results of the invariance analyses indicate that the structure of the one-factor solution and the magnitude of the correlation between the observed variables (obtained using CANTAB) and the latent construct was invariant between the baseline and follow-up assessments among the FEP patients, at the level of configural and weak invariance. The finding of invariance of the factor loadings, provides empirical evidence to support the assumption that test scores measured an invariant psychological trait, and that latent factors had the same meaning after six months among FEP patients. However, the observed scores' intercepts were not invariant between the two assessments, and misfit of scalar invariance suggest that comparisons of the factor means should be interpreted with caution, and when the FEP patients' neuropsychological performance is compared on a timeline, CANTAB subtest scores should be used. Of note is that the same

approach should be applied when FEP patients performance is compared with CoS (Haring et al., 2015b). These mean differences may reflect the significant heterogeneity of the patients' psychopathology, treatment regimes, and or motivational level at one or more time points. Moreover, one should take into consideration the possibility that among the FEP patients group, there may be patients with different kinds of diagnoses according to further disease course.

4.4. Correlations between cognitive stability and the other variables

Although heterogeneity in terms of mean-level change and high rank-order stability emerged over a six month period, it is of theoretical, practical, and clinical importance to examine how individuals differed from each other, and what variables, if any, could explain such individual differences.

Of the demographic characteristics taken into account, age and education seemed to have by far the most important impact on cognitive performance. In our study, being younger had the most prominent correlation with the paired associate learning subtest change scores (PAL), which is consistent with previous results among healthy control subjects (desRosiers and Iverson, 1988). A longer time in education was a strong predictor of performance change at the processing speed task (RVP).

Gender differences in cognitive functioning are well known among healthy individuals. In general, women tend to perform better than men at tasks measuring verbal abilities, whereas the opposite is the case regarding visuospatial skills (Halari et al., 2005). However, a recent review by Hyde (2016) suggests that males and females are quite similar in terms of most, but not all cognitive variables, and gender differences can vary substantially in magnitude with ages and the context in which the measurements occur. One of the most consistent finding is that men are younger than women at the onset of a chronic psychotic disorder (Eranti et al., 2013). In the present study, although men's mean age at onset was indeed lower compared to women, the difference was not significant.

Gender differences in cognitive functioning among patients with FEP are a controversial issue (Albus et al., 1997; Hoff et al., 1998; Ittig et al., 2015). In this study, men made less reverse errors at the set-shifting task, had better spatial executive functionality, higher spatial span length, and used strategies more effectively than women. Regarding visual and spatial recognition memory and paired associate learning, as well as information processing, men and women performed equally. A similar trend in gender differences was traceable among the change scores of the tests. It is worth mentioning that we used computerised tests that measure performance based on visuospatial abilities, and our findings on gender differences are in accordance with previous reports of the generally better performance of male patients in these domains (Albus et al., 1997). Among patients with schizophrenia, Perlick et al. (1992) found that women had lower performance at attention tasks, and Roesch-Ely et al. (2009) demonstrated that women scored lower than men on executive functioning, and working memory tasks. However, some previous literature has reported lower overall cognitive performance among males with schizophrenia (Goldstein et al., 1998; Seidman et al., 1997) or a lack of gender difference among schizophrenia, and FEP patients (Hoff et al., 1998; Ittig et al., 2015). There may be several factors that contribute to the heterogeneity of the results of these studies. For example, when discussing gender differences, it is important to consider the relative contributions of biological and psychosocial gender to the observed effects. Men and women may vary in their symptoms of expression over the course of illness and in response to treatment, and differences may be related to the selected study sample (e.g. patients with chronic illness or FEP, and early- or late-onset schizophrenia patients) (Mendrek and Mancini-Marie, 2016). In addition, we suspected that aspects of psychopathology might differentially account for any differences in cognitive functioning between the two test occasions. The associations between illness-dependent symptom

dimensions and cognitive functioning have been widely studied, and findings suggest that cognition is more closely associated with negative than positive symptoms (Heinrichs and Zakzanis, 1998). The vast majority of literature suggests that negative symptoms and executive functioning, verbal fluency, verbal memory, visual memory, attention, as well as processing speed have small to moderate associations (Dominguez et al., 2009; Nieuwenstein et al., 2001; Olivier et al., 2015). The results of our patients' cognitive functioning could not be attributed to changes in their negative symptoms. Consistent with our finding, Bell and Mishara (2006) demonstrated that changes in negative symptoms did not predict changes in cognition, and concluded that negative symptoms do not directly cause cognitive impairment or vice versa.

With regard to the relationships between positive symptoms and cognitive performance, the literature is less consistent. The meta-analytical review of Nieuwenstein et al. (2001) and Dominguez et al. (2009), suggested only a slight negative correlation occurs between processing speed and positive symptoms among patients with schizophrenia, whereas Nieuwenstein et al.'s (2001) meta-analysis found no associations between executive functioning and positive symptoms. Recent work by Olivier et al. (2015) found that a decline in the positive symptom dimension score of FEP patients was related to improvements in speed of processing, attention/vigilance, working memory, verbal memory, verbal and visual learning, as well as reasoning and problem solving tasks. The same trend was observed during other studies (Davidson et al., 2009; Trampush et al., 2015). Our results revealed that improved performances at spatial working memory and processing speed tests, were associated with lower positive symptom scores. However, we used both the broad psychopathology rating scale (BPRS), as well as its negative and positive symptom scores, to evaluate how symptom severity and any changes were potentially associated with cognitive performance over a six month period; these methodological aspects might also explain the inconsistent findings with previous studies. Specifically, the other studies employed different combinations of symptom constructs while attempting to measure ostensibly the same psychopathology.

In addition, we found significant changes in negative and positive symptom scores at the six month follow-up. Recent work by Ventura et al. (2015) demonstrated that although there was generally moderate stability in negative symptoms—assessed using BPRS and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984)—over a first year after recent-onset schizophrenia, a subgroup of patients (24%) had periods of exacerbated negative symptoms similar to positive symptom episodes. Furthermore, the prevalence of enduring negative symptoms in FEP patients has been estimated to be around 15% (Kirkpatrick et al., 2001). Accordingly, this may suggest that negative symptoms have more fluctuating nature among the subgroup of patients at the early stage of the disease than chronic patients and consistency between association studies of FEP patients cognitive functioning and negative symptom score might be lower.

We found clinically meaningful and statistically significant correlations between AP dose and BPRS ratings. The results indicate that patients with more severe treatment-refractory symptoms, received higher doses during the both assessment. During the six month period as patients continued to recover, psychopathology scores decreased, and as such AP doses were gradually reduced. Although all patients at baseline were treated with atypical APs—whereas at follow-up four patients were also receiving concomitantly neuroleptics—we analysed all patients homogeneously in terms of medication. This was because it has been previously established that groups of patients treated with a combination of typical and atypical APs showed very similar results to an only atypically medicated group (Ehlig et al., 2007). We found potential impact of changes to CPZ equivalent dosage on frontal lobe functionality: reduced doses appeared to mediate an improvement in working memory capacity (SSP span length), as well as change towards enhanced executive functioning (SOC problem solving). Previously, Sota

and Heinrichs (2003) found CPZ equivalent dose negatively related to learning and recall abilities. For these reasons, clinicians should carefully consider changing drug doses in terms of quantity and or frequency it is taken, when psychopathology severity has declined, and use a lowest-dose strategy whenever possible. However, it should be noted that a subgroup of FEP patients do not respond sufficiently to antipsychotic treatment, and thus do not attain sufficient remission of positive and negative symptoms (Benoit et al., 2014; Ventura et al., 2011). Therefore, an individual approach is recommended whenever any antipsychotic dosage change is considered.

4.5. Subjectively perceived compared to objectively measured cognitive performance

Evaluation of patients' subjective experiences of cognitive functioning has so far received too little scientific and everyday clinical attention. Existing studies have demonstrated that self-assessed cognitive dysfunction is prevalent among patients with FEP (Moritz et al., 2000), which constitutes a clinically important dimension of the disorder (Homayoun et al., 2011; Stip et al., 2003). Moreover, Chaytor and Schmitter-Edgecombe (2003) have highlighted problems with the ecological validity of traditional neuropsychological assessments, particularly in terms of their ability to reveal patients' actual level of everyday functioning, and have suggested not to assess the scope of cognitive functioning of psychotic patients with only neuropsychological test performances. In addition, previous research on subjective cognitive dysfunction mostly focused on patients with chronic illness; patients in the early illness stage have rarely been investigated in this regard (Chang et al., 2015; Ehmann et al., 2007; Moritz et al., 2000). Results of the present study are in line with others (Chang et al., 2015; van den Bosch and Rombouts, 1998; Zanello and Huguelet, 2001), in supporting the hypothesis of the independence of self-perceived cognitive disturbances, from objectively measured cognitive impairments, among FEP patients. The discrepancy between the evaluations of subjective and objective cognitive functioning suggests that patients' subjective perceptions of their cognitive function have a different theoretical basis than objective indicators, as patients do not conceptualise their cognitive functioning in terms of distinct cognitive domains, as clinicians and neuropsychologists do (Stip et al., 2003). Furthermore, such discrepancy may occur owing to variations in methodology (differences in the subjective cognitive scales employed) and study design. We used the SWN-K-E "cognitive functioning" subscale that comprises four simple statements about self-perceived cognitive functioning. This subscale did not seem to appropriately correspond to the specific cognitive test scores obtained using the CANTAB. In addition, one possible explanation for the low inter-correlation between measurements might be the different nature of the evaluations. The CANTAB tests were all visually presented to subjects and high performance relied on visual information processing, whereas the subjectively perceived cognitive functioning items referred to much broader indicators including among others verbal and arithmetical abilities, as well as semantic processing.

However, both methods (SWN-K and CANTAB subtests) have been validated among psychotic populations (Elliott et al., 1995; Haring et al., 2013; Haring et al., 2015b; Joyce et al., 2005; Leeson et al., 2009a; Naber et al., 2001). In addition, awareness of one's own cognitive deficits could be affected by awareness of one's condition as a mentally ill person, and schizophrenia is frequently accompanied by a lack of insight (Pini et al., 2001). However, the literature suggest that subjective and objective cognitive tests might have unique contributions, and thus both should be implemented to give a broader perspective about a patient's cognitive functioning to determine appropriate clinical practice regarding assessment and management of cognitive problems.

The results of the present study should be interpreted while bearing in mind certain aspects that may have influenced our findings. First, the recruited patients were virtually heterogeneous in terms of diagnosis,

medication, and duration of untreated illness—something which is difficult to avoid among any sample of FEP patients. Second, the sample was restricted to a group of patients that were clinically stable and willing to participate in the study. Our findings may thus not generalise to the overall cognitive performance characteristics of patients with FEP in Estonia or beyond. Third, because we had a relatively small sample size, we admit that our results about rank-order stability, mean-level change indices, and invariance analyses may not be representative of all FEP patients. In addition, patients were at the early stages of the illness when cognitive performance was evaluated, so results are not necessarily generalisable for different follow-up periods. Lastly, we did not control intra-individual factors that may influence test–retest consistency, such as poor motivation, fatigue, insufficient sleep, or cigarette smoking prior to the CANTAB test sessions. Despite these limitations, our research has some strengths, mainly related to the natural characteristics of the FEP patients sample, and the longitudinal design used to evaluate changes in cognitive functioning over time, and the low level of dropouts by the follow-up period.

In conclusion, our results provide new information on the different aspects of cognitive functioning during the early course of chronic psychotic disease. The findings suggest that there is variability in the type, direction, and size of the changes of different cognitive functions among FEP patients over time. We have also highlighted the need to examine the factor structure of the neuropsychological test battery and the level of measurement invariance when cognitive functioning is assessed over time, and our results contribute valuable data regarding usage of the CANTAB among FEP patients groups. Our study makes a case for clinicians and neuropsychologists to consider measurement invariance, as well as patients' demographic and clinical characteristics, when assessing neuropsychological change over time. Finally, the findings of the present study suggest that subjective and objective cognitive deficits are two distinct constructs, and should be measured separately in order to attain a more comprehensive assessment of each patient's day-to-day functioning. In clinical practice they are probably complementary, even if not directly comparable.

Conflict of interest statement

The authors declare no conflict of interest.

Contributors

Liina Haring designed the study, wrote the first draft of the manuscript. René Möttö conducted data analysis, edited the manuscript and provided guidance throughout writing. Liina Haring and Kärolin Kajalaid participated in collection of cognitive assessment data. Kärt Uppin and Kadri Koch contributed to subject recruitment and clinical assessment. Eduard Maron and Eero Vasar supervised this project. All authors have critically reviewed the manuscript for important intellectual content, and have approved the final manuscript.

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