Title: Cognitive course in first-episode psychosis and clinical correlates: A 4 year longitudinal study using the MATRICS Consensus Cognitive Battery

Authors
Joanne Kenney[1], Heike Anderson-Schmidt[2], Cathy Scanlon[1], Sophia Arndt[1], Elisabeth Scherz[1], Shane McInerney[1,3,4], John McFarland[1], Fintan Byrne[1], Mohamed Ahmed[1], Gary Donohoe[5], Brian Hallahan[1], Colm McDonald[1], Dara M Cannon[1]

Author Affiliations
[1]Centre for Neuroimaging and Cognitive Genomics (NICOG), Clinical Neuroimaging Laboratory, NCBES Galway Neuroscience Centre, College of Medicine, Nursing and Health Sciences, National University of Ireland Galway, Galway, Ireland.
[2]Department of Psychiatry and Psychotherapy, University Medical Centre Goettingen, Georg-August University, Goettingen, Germany.
[3]Department of Psychiatry, St Michaels Hospital, Toronto, Canada.
[4]Department of Psychiatry, University of Toronto, Canada.
[3]Centre for Neuroimaging and Cognitive Genomics (NICOG), School of Psychology, National University of Ireland Galway, Galway, Ireland.

Corresponding Author:
Joanne Kenney,
Clinical Neuroimaging Laboratory,
Room 202, Comerford Suite,
NUI Galway, Galway, Ireland.
Tel: +353-91-495681
Fax: +353-91-494563
Email: j.kenney1@nuigalway.ie

Abstract

While cognitive impairments are prevalent in first-episode psychosis, the course of these deficits is not fully understood. Most deficits appear to remain stable, however there is uncertainty regarding the trajectory of specific cognitive domains after illness onset. This study investigates the longitudinal course of cognitive deficits four years after a first-episode of psychosis and the relationship of performance with clinical course and response to treatment.

Twenty three individuals with psychotic illness, matched with 21 healthy volunteers, were assessed using the MATRICS Consensus Cognitive Battery at illness onset and 4 years later. We also investigated the relationship between cognitive deficits and quality of life and clinical indices.

Verbal learning and two measures of processing speed had marked poorer trajectory over four years compared to the remaining cognitive domains. Processing speed performance was found to contribute to the cognitive deficits in psychosis. Poorer clinical outcome was associated with greater deficits at illness onset in reasoning and problem solving and social cognition. Cognitive deficits did not predict quality of life at follow-up, nor did diagnosis subtype differentiate cognitive performance.

In conclusion, an initial psychotic episode may be associated with an additional cost on verbal learning and two measures of processing speed over a time spanning at least four years. Moreover, processing speed, which has been manipulated through intervention in previous studies, may represent a viable therapeutic target. Finally, cognition at illness onset may have a predictive capability of illness course.

Keywords: First-episode psychosis; cognition; clinical; longitudinal; MATRICS Consensus Cognitive Battery

1. Introduction

Deficits in many areas of cognition are prevalent in individuals who experience a first-episode of psychosis (FEP), many of which are also present in the prodromal phase of psychosis. Visual memory, verbal learning, attention, working memory, executive function and social cognition are common cognitive domains impaired in FEP compared to the performance of healthy controls (Bora et al., 2014, Aas et al., 2014, Üçok et al., 2013). It is important to elucidate the trajectory of cognitive dysfunction following an initial psychotic episode, and any clinical or biological determinants of such progression, which can only be established by longitudinal studies of cognitive function.

In general, it has been shown that the majority of cognitive deficits remain stable following an initial psychotic episode (Bozikas and Andreou, 2011; Bora and Murray, 2013), although there is variability throughout the literature. For example, verbal learning has variously been reported to either remain stable over 3 years (Ayesa-Arriola et al., 2013), to deteriorate over 10 years and 13 years (Bozikas and Andreou, 2011, Øie et al., 2010); or to improve over 6 months and 2 years (Jahshan et al., 2010; Barder et al., 2013). A table of recent longitudinal studies, consisting of studies additional to the meta-analysis by Bora and Murray (2013) is provided in Table 1.

The heterogeneity of results in the literature may partly relate to the lack of a congruent set of cognitive tests administered to assess cognitive performance, which also restricts comparison of findings across studies. Measuring performance of a cognitive construct using alternative tests can result in incongruent findings (Liu et al., 2011). The current study aimed to address this issue by implementing the MATRICS Consensus Cognitive Battery (MCCB), which was developed by the National Institute of Mental Health's (NIMH) Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS). The MCCB identified seven separable dysfunctional cognitive factors in the disorder, two of which (attention and working memory) are concurrent with the cognitive constructs of the NIMH Research Domain Criteria (RDoC) (Cuthbert and Insel, 2010).
The MCCB demonstrates excellent test-retest reliability and minimal practice effects (Roseberry and Kristian Hill, 2014, Nuechterlein et al., 2008). Of the few FEP longitudinal studies that implemented the MCCB, Juuhl-Langseth et al. (2014) found that most neurocognitive deficits were relatively stable over two years apart from the course of processing speed.

The current study additionally sought to investigate the relationship between cognitive deficits in psychosis and other clinical and quality of life measures as the nature of these relationships remain inconclusive. In terms of clinical symptomatology, cognitive deficits are proposed to be more closely associated with negative and disorganised aspects of psychosis compared with positive symptoms (Bora and Murray, 2013; Dominguez et al., 2009). Attention, psychomotor speed and verbal learning in particular have been found to correlate with negative symptoms in schizophrenia(August et al., 2012; Bora and Murray, 2013; O'Gráda et al., 2009), while disorganised symptoms were related to lower verbal and visual learning, processing speed and social cognition (August et al., 2012; Flaum et al., 2000). Whether or not cognitive performance differs significantly between subtypes of psychosis, such as affective and non-affective subtypes, has not been determined conclusively. Some evidence has suggested verbal learning performance to differ between individuals with schizophrenia from those with affective disorders (Fitzgerald et al., 2004) but this is not a consistent finding (Bora et al.,

2009). Finally, longitudinal associations between cognitive deficits and quality of life outcome in schizophrenia have been supported by a review of 18 studies (Green et al., 2004), albeit with considerable variability (Tolman et al., 2010).

This study aims to characterise the longitudinal course of cognitive deficits four years after a first episode of psychosis using the standardised MCCB, to determine the nature and degree of variation in cognitive performance and critically, to examine the relationship of performance with clinical course and response to treatment.

Tables

Table 1. Recent longitudinal studies examining cognitive change across the course of psychosis from the first episode (shaded rows indicate studies with repeated testing of healthy control group included)

Study	Group (n)	Follow-up	Age at baseline	Cognitive Domain (Cognitive Tests)*	Significant findings for each domain/test	Medication Effect
Chang (2014)	FES (n=93); no HC	3 years	31±10	Logical memory - WMS-R Visual reproduction test -WMS-R Forward digit span -WAIS-R Category verbal fluency Modified WCST	ΔFES ↑ ΔFES ↑ ΔFES↑ ΔFES ↔ ΔFES↑	No information given
Rodriquez-Sanchez (2013)	FEP non-affective (n=78), HC (n=43)	1, 3 years	FE (29 ± 9); HC (28± 8)	Verbal memory (RAVLT) Visual memory (RCFT) Motor dexterity (grooved pegboard) EF-SOP (TMT A and B, WAIS III-BD + DS) Attention (CPT-DS – total score + BTA) Impulsivity (CPT-DS – EOC)	ΔFEP<ΔHC ΔFEP<ΔHC ΔFEP↔ΔHC ΔFEP↔ΔHC ΔFEP↔ΔHC ΔFEP↔ΔHC	No information given
Ayesa-Arriola (2013)	FES (n = 79); randomised to 3 groups: haloperidol; olanzapine; risperidone; HC (n=41)	6 mths, 1 year, 3 years	haloperidol (27±7 yrs); olanzapine (27±8 yrs); risperidone (28±9 yrs); controls (28±8 yrs)	Verbal memory (RAVLT) Visual memory (RCFT) Motor coordination (grooved pegboard) EF (TMT-B and FAS) Working memory (WAIS-III-BD) Speed of processing (WAIS-III-DS) Attention (CPT-DS) Decision-making capacity (IOWA gambling task)	ΔFES (haloperidol + olanzapine)<ΔHC ΔFES (haloperidol)<ΔHC ΔFES↔ΔHC ΔFES↔ΔHC ΔFES↔ΔHC ΔFES (haloperidol + risperidone)<ΔHC ΔFES↔ΔHC ΔFES↔ΔHC	Randomised into 3 treatment groups: Verbal learning + decision making: - Δolanzapine>Δhaloperidol; SOP: - Δolanzapine>Δrisperidone
Barder (2013)	FEP(n =62), No HC	1, 2 and 5 years	28 ± 9 yrs	Verbal learning (CVLT) Motor-speed index (FFT) EF (WCST) Working memory (COWA, digit span, CPT-IP hits) Impulsivity (CPT-IP RT+FA)	ΔFEP ↑2 yrs, ↓5 yrs ΔFEP↔2yrs, ↓5yrs ΔFEP ↔2yrs, ↔5yrs ΔFEP ↑2 yrs, ↔5yrs ΔFEP ↑2 yrs, ↔5yrs	After controlling for medication, all key findings remained significant.

Liu (2011)	FES (n = 31); no HC	1 year, 3 year	28±10	EF: Modified SET + Modified WCST	ΔFEP ↔ ΔFEP ↑	No information given
Popolo (2010)	FEP (n = 15); no HC	1 year	22.9±2.9	Verbal learning (RAVLT) Attention (SSA + SAM) Semantic-lexical memory (FAS) Logical deductive capabilities (CPM) Flexibility + Problem solving (WCST)	ΔFEP ↔ ΔFEP ↔ ΔFEP ↔ ΔFEP ↔ ΔFEP ↔	No information given
Leeson (2009)	FEP(n= 60); HC (n = 27)	3 years	FEP (Low IQ = (24±7), deteriorated IQ (25±8), preserved IQ (27±9); HC (27±7)	Verbal learning (RAVLT) CANTAB: Working memory (SS + SWM) Planning (TOL)	ΔFEP↔ΔHC ΔFEP↔ΔHC ΔFEP↔ΔHC	No information given

Note: FEP, first-episode psychosis; FES, first-episode schizophrenia; HC, healthy controls; EOS, early-onset schizophrenia; ΔFEP, rate of change in scores over time in the FEP group; ΔHC, rate of change in scores over time in the HC group; FEP<HC, less improvement in rate of change of scores over time in FEP group compared to HC group ; FEP>HC, greater improvement in rate of change of scores over time in FEP group compared to HC group; FEP↔HC, no difference in rate of change between groups (stability); ↑ increase in score over time; ↓ decrease in scores over time; ↔no significant change in score over time; WMS, Weschler Memory Scale; WAIS, Weschler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test; CF, Category Fluency; SC, Symbol Coding; CPT-DS, Continuous Performance Test- Identical Pairs; MSCEIT, Mayer–Salovey–Caruso Emotional Intelligence Test; RAVLT, Rey Auditory Verbal Learning Test; RCFT, Rey Complex Figure Test; EF, Executive Functions; SOP, Speed of Processing; FAS, Fluency test; TMT, Trail Making Test; BD, Backward Digits; DS, Digit Symbol; SS, Spatial Span; SWM; Spatial Working Memory; CPT-DS, Continuous Performance Test- Degraded Stimulus; EOC, total number of corrections of errors of commission; BTA, Brief Test of Attention; Modified SET, Six Elements Test; KRFT, Kimura Recurring Figure Test; SSA, Span Selection Attention; SAM, Spinnler Attention Matrices; CPM, Coloured Progressive Matrices; TOL, tower of London task; RT, reaction time; FA, false alarms; * where cognitive domains not explicitly stated, cognitive tests presented only

2.Methods

2.1. Participants

Initially, 36 individuals who experienced a first episode of psychosis (FEP) and 59 healthy controls (HC) participated in cognitive and clinical assessments. Individuals with a diagnosis of psychosis were from the mental health services at University Hospital Galway and the surrounding mental health services in the west of Ireland. All subjects were aged between 18-49 years at baseline (Table 2). The recruitment and clinical assessment of these individuals is described previously (McFarland et al., 2013; Scanlon et al., 2014). Exclusion criteria for both groups were as follows: a history of neurological disorders (including epilepsy), comorbid substance or alcohol abuse in the last year, a history of head injury resulting in loss of consciousness for over 5 minutes, a history of oral steroid use in the previous three months, loss of weight in excess of 12% of the original body weight in the previous year and a history of viral infection in previous 1 month. Individuals in the control group were also excluded if there was a personal or family history of psychotic or affective disorder. Written informed consent was obtained from all participants. The study was approved by the research Ethics Committees of the National University of Ireland Galway and Galway University Hospitals.

Table 2. Demographic Characteristics of the study sample

	FEP group	HC group	Comparison (T/χ2,p)
Baseline N	37	59	
Follow-up N	23	21	
Attrition Rate %	38%	65%	
Age at onset (mean yrs±SD)	24.8±8.6		
Age Baseline (mean yrs±SD)	28.3±7.7	29.0±7.7	0.3,0.8
Gender N (% fem) (ratio)	15, 8 (35%) (1.88:1)	13, 8 (38%) (1.63:1)	0.05, 0.8
NART (mean score±SD)	112.7±7.6	115.2±6.6	1.2, 0.3
Education (mean years±SD)	15.8±3.2	18.1±2.7	2.6, 0.012*
Time between testing (mean years±SD)	4.65±0.81	3.86±0.79	-3.3, 0.002*

Note: FEP = first episode psychosis; HC = healthy control; NART = national adult reading test; N = sample number; FU = follow-up; * = significant difference

At follow-up, on average four years later (4.3±0.9 years), 23 FEP and 21 HC subjects were successfully re-recruited. Two individuals from the original cohort were un-contactable, 1 individual was unwell, 8 individuals declined the invitation to participate and 2 had relocated to another country. Many individuals in the control group had also relocated making it difficult to re-recruit in that cohort. There was no significant difference in the mean age, gender or baseline diagnosis of

individuals from the original cohort who were successfully recruited at follow-up compared to those not recruited.

2.2.Materials

2.2.1.Cognitive Measures

The MCCB was administered to individuals at the time of their first psychotic episode and to a psychiatrically healthy control group. Follow-up testing was completed four years later. A summary of the seven cognitive domains which constitute the MCCB can be found in Table 3.

Table 3. The seven cognitive domains which constitute the MCCB and a description of their respective tests.

Cognitive Domain	Cognitive Tests	Description of tests
Speed of Processing	Trail Making Test (TMT): Part A	a test of visual scanning and visuomotor tracking
	Brief assessment of Cognition in Schizophrenia (BACS)	primarily a measure of visuomotor speed
	Category Fluency: Animal Fluency	a verbal index of speed of processing
Attention/Vigilance	Continuous Performance Test – Identical Pairs (CPT-IP)	a measure of attention or vigilance (Cornblatt et al., 1989)
Working Memory	Wechsler Memory Scale (WMS®-III): Spatial Span forward and backward (WMS-SS)	a measure of nonverbal working memory
	Letter number span (LNS)-	a test of verbal working memory including maintenance and manipulation of components of working memory
Verbal Learning	Hopkins Verbal Learning Test – Revised (HVLTR)	a list of 12 words presented 3 times, which must be recalled from memory
Visual Learning	Brief Visuospatial Memory Test-Revised (BVMT-R)	the participant is required to draw 6 geometrical figures as accurately as possible from memory
Reasoning & Problem Solving	Neuropsychological Assessment Battery (NAB): Mazes	this test involves planning and foresight which are elements of reasoning and problem solving
Social Cognition	Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT): Managing Emotions	this test measures how well people solve emotional problems (Mayer et al., 2003)

2.2.2.Clinical Assessment

The severity of symptoms in the FEP group were clinically assessed by a trained psychiatrist at both time points using the Positive and Negative Syndrome Scale (PANSS) (Kay and Qpjer, 1982) and the

Structured Clinical Interview for DSM-IV Research Version (American Psychiatric Association, 2000). The Quality of Life Scale (QLS) was administered (Heinrichs et al., 1984) at follow-up. Total antipsychotic medication taken was recorded and converted to chlorpromazine (CPZ) equivalents (Lehman and Steinwachs, 1998; Woods, 2003).

To assess whether affective and non-affective subtypes present differentially, diagnoses at follow-up were categorised into two groups. Schizophrenia (n=6), schizophreniform disorder (n=1), schizoaffective disorder (n=3), psychotic disorder not otherwise specified (4) and delusional disorder (n=1) were defined as non-affective types of psychoses whereas bipolar I disorder (n=6) and major depressive disorder, recurrent (n=2) defined as affective types of psychoses (Table 4).

Table 4. Clinical features at illness onset and follow-up of study sample who were successfully recruited after 4 years (n =23)

	Baseline	Follow-up	Comparison (t/Z,p)
Duration of Untreated Psychosis (months)	13.2 (14.7)		
Diagnosis (N)			
Schizophrenia	2	6	
Schizophreniform disorder	9	1	
Psychotic disorder NOS	5	4	
Bipolar I disorder	2	6	
Schizoaffective disorder	1	3	
Delusional disorder	2	1	
Major depressive disorder, recurrent	2	2	
Symptoms levels			
PANSS positive score	17±5	10±4	-3.5, <0.001*†
PANSS negative score	14±6	12±7	-1.2, 0.30†
PANSS general score	31±5	23±6	4.7, <0.001*
PANSS total score	62±11	45±15	-3.5, 0.001*†
Functionality			
Global Assessment of Functioning	53±10	69±22	-3.2, 0.001*†
Medication at FU (N)			
Antipsychotics		11	
Mood stabilisers		2	
Anti-depressants		7	
No medication		8	
Missing information		1	
Chlorpromazine equivalent	159±268	204±224	-1.1, 0.266†
Usual Symptom Severity at FU (N)			
No further episodes		2	
Mild		1	
Moderate		10	
Severe		9	
Missing information		1	
Diagnosis Type (SCID)			
Non-affective	16	15	
Affective	7	8	

Note: N = sample number; PANSS = Positive and Negative Syndrome Scale; FU = follow-up; SCID = Structured Clinical Interview for DSM, * = significant difference between baseline and follow-up values; † = non-normal distribution (Wilcoxon Rank Test used)

2.3.Statistics

Raw scores of the cognitive tests were age and gender corrected using the MCCB computerised program, and converted to T-scores, which were then used in all subsequent statistical analyses. Normative data were obtained from administering the battery to 300 individuals across five sites in the U.S. (Kern et al., 2008) stratified into three age ranges and accounting for gender and education. All statistics were conducted using IBM SPSS (v.21).

Shapiro-Wilk tests were used to test for normal distribution of each cognitive variable. Most cognitive variables at onset of psychosis were normally distributed (W=0.94-0.99,p=0.19-0.93) except for attention (W=0.96,p=0.006), visual learning (W=0.94,p<0.001), speed of processing (w=0.97,p=0.04) and the composite cognition score (W=97,p=0.03). All cognitive measures were normally distributed at follow-up (W=0.92-0.98,p=0.08-0.90) apart from the composite cognitive score (W=0.93,p=0.01). ANOVA models were used to compare group differences in cognitive performance at both time points and the Kruskal-Wallis test was used for the non-normally distributed measures.
Cognitive change variables (scores at follow-up minus those at baseline of each cognitive test) were tested for normality of distribution. Positive cognitive change values indicated improvement in performance over time; negative values indicated a decrease over time. Most measures did not deviate from a normal distribution (W=0.94-0.98;p=0.11-0.92), with the exception of a measure of working memory, the spatial span test (W=0.94,p=0.02). This test was transformed for normal distribution using square root transformation (W=0.95,p=0.08) to allow covariates to be accounted for in an ANCOVA model. ANCOVA models with each cognitive change variable were analysed with baseline cognitive scores and years of education included as covariates.

When investigating the longitudinal relationship between any cognitive change variables with significant group differences and clinical and quality of life variables, Pearson's correlation analyses (r) and regression models were used. Non-parametric tests such as Spearman's correlation (ρ) were used with non-normally distributed clinical variables.

3.Results

Healthy controls (HC) performed significantly better than individuals experiencing their first episode of psychosis (FEP) on all measures of cognition at baseline and follow-up, the only exception being social cognition scores at follow-up where no group difference was found (Table 5).

Table 5. Baseline and follow-up (FU) cognitive scores of FEP group and healthy controls on the seven cognitive domains of the MCCB

	Baseline			Follow-up		
Cognitive Domains	FEP (n=37) Mean ± SD	HC (n=59) Mean ± SD	%Difference	FEP (n=23) Mean ± SD	HC (n=21) Mean ± SD	%Difference
Speed of Processing	36±13 †	59±9 †	-29%*	38±14	59±11	-36%***
Attention/Vigilance	39±13 †	48±8 †	-21%*	44±13	52±5	-15%*
Working Memory	38±10	48±8	-21%*	43±13	54±9	-20%**
Verbal Learning	40±9	46±10	-28%*	44±10	53±8	-17%**
Visual Learning	40±14 †	51±11 †	-31%*	41±14	49±11	-16%*
Reasoning/Problem Solving	38±8	50±10	-22%*	42±9	53±11	-21%**
Social Cognition	43±16	55±9	-22%*	48±13	53±9	-9%
Total Cognition	32±13 †	50±10 †	-30%*	39±15 †	56±9 †	-30%**

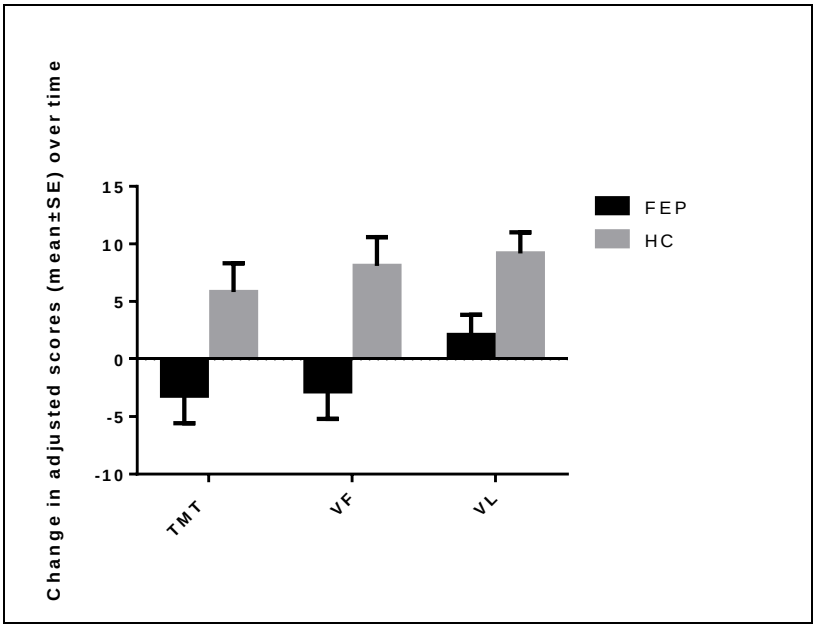
Note: FEP = first episode psychosis; HC = healthy controls; † median used where non-normal distribution; *** p< 0.001 **p< 0.01 * p < 0.05; % difference = percentage difference of FEP scores relative to HC scores

A significant group difference was found between the FEP group and controls on the change in performance over time on a visuomotor test of processing speed, the Trail Making Test and a verbal index of processing speed, the Verbal Fluency test. A significant group difference was also found on the change in verbal learning performance over time (Table 6; Figure 1). There was no significant group difference in the change in performance on the remaining cognitive metrics (Table 6). The results remained similar without covarying for years of education or when the NART (National Adult Reading Test; Nelson et al., 1991) was covaried in place of years of education (Table 6). Similarly, the magnitude and direction of the findings remained the same when time between testing was additionally covaried for (Table 2). Results also remained similar when patients on no medication were removed from analysis (n=8), however, there was an additional significant group difference in the composite speed of processing score between this subgroup of FEP individuals taking medication and healthy controls (p=0.02;FEP(m±se)=-4.42±2.4,HC=4.3±1.9). Total chlorpromazine equivalents were not related to those cognitive measures found to have significant group differences (ρ=-0.3- -0.1,p=0.1-0.6).

Table 6. Change in scores over time on the cognitive domains and separable cognitive tests of the MCCB

Tests	FEP change	HC change	Partial η^2	CI 95%	F (†)	P(†)
Speed of Processing	-0.66±2.14	4.82±2.27	0.06	[-1.8,12.8]	2.31(2.94)	0.14(0.09)
Trail Making Test	-2.94±2.5	5.56±2.62	0.10	[0.4,16.61]	4.49(5.5)	0.04*(0.02)
BACS:SC	1.84±1.9	0.23±2.06	0.006	[-8.3,5.03]	0.24(0.09)	0.63(0.93)
Verbal Fluency	-2.94±2.4	8.23±2.5	0.18	[3.56,18.8]	8.81(7.21)	0.005*(0.01)
Attention/Vigilance	1.45±1.7	2.58±1.85	0.004	[-4.34,6.6]	0.17(0.04)	0.68(0.85)
Working Memory	4.26±1.83	6.71±1.94	0.02	[-3.4,8.4]	0.70(0.41)	0.41(0.53)
WMS: Spatial Span	4.82±0.19	5.24±0.21	0.04	[-0.2,1.05]	1.74(0.71)	0.19(0.40)
Letter Number Span	3.85±2.01	6.16±2.11	0.01	[-4.0, 8.63]	0.55(0.42)	0.46(0.52)
Verbal Learning	2.0±1.8	9.28±1.88	0.15	[1.67,12.9]	6.86(5.58)	0.01*(0.02)
Visual Learning	-0.09±2.04	1.81±2.15	0.009	[-4.5, 8.3]	0.36(0.49)	0.55(0.48)
Reasoning	1.52±2.07	5.28±2.19	0.03	[-3.1, 10.6]	1.25(1.25)	0.27(0.27)
Social Cognition	2.87±1.99	-1.0±2.04	0.04	[-10.1, 2.4]	1.55(0.48)	0.22(0.49)
Total Cognition	4.24±1.64	4.83±1.75	0.001	[-4.9,6.16]	0.05(0.04)	0.83(0.85)

Note: adjusted means ± standard error reported; FEP = first episode psychosis; HC = healthy controls; partial η^2 = effect size, partial eta squared; CI = 95% confidence intervals; BASC:SC = Brief assessment of Cognition in Schizophrenia: Symbol Coding; WMS = Working memory scale; *significant group difference; (†) F and p values when years of education omitted as covariate

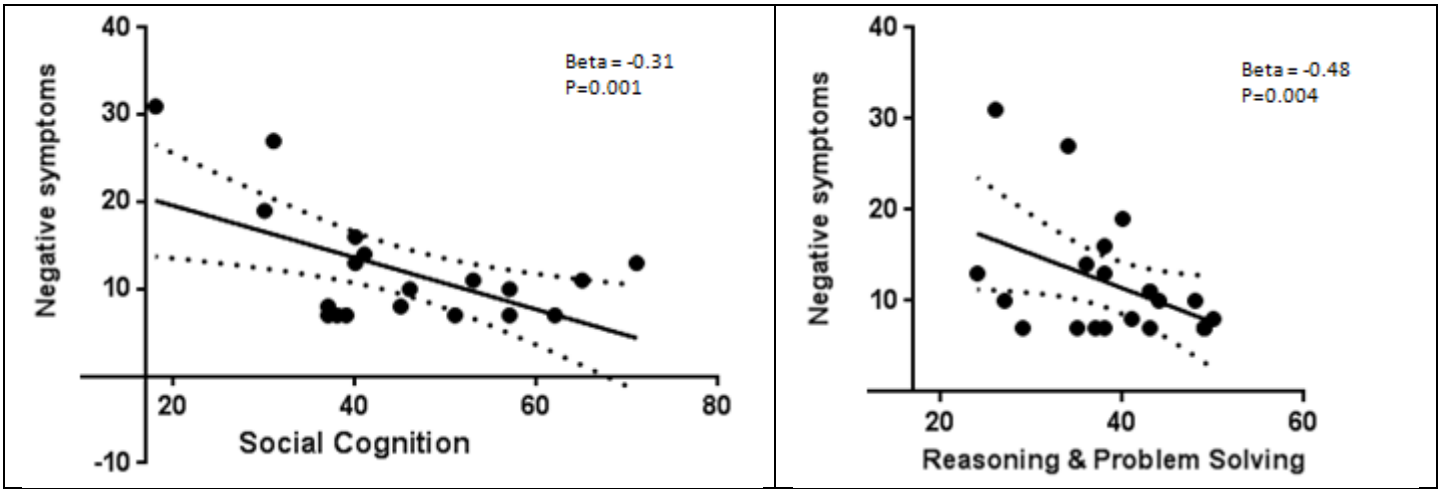


Title-Figure 1: Four years after illness onset, the first episode psychosis (FEP) group demonstrate significantly lower change in two measures of speed of processing (Trail Making Test; TMT and Verbal fluency; VF) and verbal learning (VL) scores compared to a healthy control (HC) group

In the FEP group, the change in cognitive performance on the visuospatial and verbal index of processing speed or verbal learning was not related to the change in clinical symptom profile, positive (ρ=-0.2-0.2,p=0.4-0.8) or negative (r=-0.1-0.4,p=0.1-0.6) symptoms on the PANSS. Diagnosis subtype (affective vs. non affective) did not significantly differentiate cognitive performance on these measures (F=0.05-4.1,p=0.1-0.8). Reasoning and problem solving (Beta=-0.48,p=0.004) and

social cognition (Beta=-0.31,p=0.001) at onset of psychosis significantly predicted negative symptoms severity at follow-up (F=12.54,p<0.001, Figure 2). No cognitive tests at illness onset related to severity of positive symptoms four years later (r=-0.15-0.26,p=0.25-0.98) or quality of life at follow-up (r=0.03-0.38,p=0.09-0.89).

Post-hoc analyses were conducted to determine the extent of the influence processing speed and verbal learning had on other cognitive domains. After controlling for processing speed on cognitive scores at illness onset and follow-up (Table 6), group differences on cognitive measures decreased substantially and many became non-significant (average % decrease in F value of both time points was 82%). When covarying for verbal learning, group differences on more cognitive tests remained significant although F values moderately decreased (average % decrease in F value was 56%, Table 7).



Title-Figure 2: Capacity for social cognition and reasoning and problem solving at onset of illness to predict the severity of negative symptoms four years later

Table 7. *Post-hoc* analysis of group differences with and without covarying for speed of processing and verbal learning

	Baseline (n = 37)					Follow-up (n = 23)				
Tests	Before covarying F, p	After covary for SOP F, p	% diff	After covary for VL F, p	% diff	Before covarying F, p	After covary for SOP F, p	% diff	After covary for VL F, p	% diff
Speed of Processing	43.07, <0.001*			25.29, <0.001*	-41%	32.62,<0.001* 5.91, 0.02*			18.11, <0.001*	-45%
Attention/Vigilance	21.18, <0.001*	1.54, 0.22	-93%	10.82. 0.001*	-49%	9.34, 0.004* 10.44, 0.002*	1.25, 0.27	-79%	1.66, 0.21	-72%
Working Memory	24.97, <0.001*	2.67, 0.11	-89%	9.65, 0.003*	-61%	4.65, 0.04*	0.26, 0.61	-97%	4.68, 0.04*	-50%
Verbal Learning	23.32, <0.001*	8.54, 0.004*	-63%			13.67, 0.001*	1.11, 0.30	-89%		
Visual Learning	18.58, <0.001*	3.72, 0.06	-76%	5.97, 0.02*	-68%	2.18, 0.15	3.2, 0.08	-31%	0.59, 0.45	-87%
Reasoning	30.02, <0.001*	2.64, 0.11	-91%	17.92, <0.001*	-40%	10.18, 0.003*	1.27, 0.27	-91%	8.12, 0.007*	-41%
Social Cognition	12.54, 0.001*	1.08, 0.30	-91%	6.33, 0.01*	-50%		0.15, 0.70	-93%	1.01, 0.32	-54%
Total Cognition	56.03, <0.001*	10.04, 0.002*	-82%	26.72, <0.001*	-52%		2.17, 0.15	-79%	3.03, 0.08	-70%

Legend. % diff = percentage decrease (-) in F scores following covarying; SOP = speed of processing; VL = verbal learning; * = significant group difference

4. Discussion

Longitudinal cognitive performance remained significantly poorer over the four years following a first-episode of psychosis relative to psychiatrically healthy controls (Table 5). Two measures of speed of processing, the Trail Making Test and Verbal Fluency test, showed a significant reduction in performance over time, whereas verbal learning displayed a reduced rate of improvement over time, compared to other domains which improved at the same rate as controls (Table 6; Figure 1). These data suggest that the initial psychotic episode may be associated with an additional cost on a persons' cognitive course in these domains over a time spanning at least four years. Secondly, processing speed performance accounted for a considerable amount of variance in the impairments of the other cognitive domains. Finally, poorer clinical outcome, specifically negative symptoms, was associated with greater deficits at illness onset in reasoning and problem solving and social cognition.

The comprehensive deficits in cognitive capacity in individuals with psychosis are consistent with the literature, specifically a reduced improvement in processing speed and verbal learning over time relative to other cognitive domains has previously been reported (Juuhl-Langseth et al., 2014; Rodríguez-Sánchez et al., 2013; Bozikas and Andreou, 2011), although not uniformly (Leeson et al., 2009). Stability in the remaining cognitive deficits has also been identified in measures of attention (Rodríguez-Sánchez et al., 2013; Ayesa-Arriola et al., 2013) social cognition (Horan et al., 2012) working memory (Ayesa-Arriola et al., 2013; de Mello Ayres et al., 2010) reasoning and problem solving (Juuhl-Langseth et al., 2014) and visual learning (Ayesa-Arriola et al., 2013).

While a broad array of symptoms and deficits in ability contribute to real world disability in schizophrenia, cognition in particular has been identified as a determinant of quality of life. While the current study found no relationship between cognitive deficits in psychosis and quality of life outcome, this may be the result of poor statistical sensitivity or due to the use of the Heinrich's quality of life scale which includes both objective and subjective measures, the latter being associated less with cognition (Tolman et al., 2010).

As two measures of speed of processing demonstrated reduced performance over time in psychosis, *post-hoc* analysis additionally examined the processing speed hypothesis, which proposes that slower performance on this measure reduces the ability to process information automatically and effectively and contributes to the deficits in a wide array of cognitive skills (Kelleher et al., 2013; Rodríguez-Sánchez et al., 2007). In our study, processing speed appeared to play a significant role in the impairment in other cognitive measures such as working memory and attention. Future studies may specifically investigate the impact of cognitive remediation on processing speed for individuals experiencing a first psychotic episode and whether performance on other cognitive domains benefits as a result.

The relationship between cognition and negative symptoms in first episode psychosis and schizophrenia has been well replicated by many groups (Bora and Murray, 2013, Lam et al., 2014) if not all (Hoff et al., 1999). When investigating the clinical relevance of our cognitive findings we found poorer cognitive ability, specifically reasoning and problem solving and social cognition at

illness onset, to predict greater negative symptom severity four years later. Longitudinally, performance on a variety of cognition domains at illness onset, such as processing speed, IQ, working memory and verbal learning, have been found to relate to the course of negative symptom severity (Leeson et al., 2010; Carlsson et al., 2006; Bora and Murray, 2013; González-Ortega et al., 2013). Taken together, these data support cognition at illness onset as a potential predictive indicator of illness course; however, there is yet heterogeneity as to which exact cognitive domain which relates to negative symptom severity.

At follow-up, no deficit in social cognition was evident in the individuals who experienced a psychotic episode, potentially due to the possibility of a baseline ceiling effect in the control group. Despite the absence of a deficit in social cognition at follow-up relative to onset, these data do not definitively support a normalisation in this domain. During and following establishment of the MATRICS battery the sensitivity and specificity of the social cognition domain has repeatedly been questioned, and its relationship to other cognitive domains and other social cognition measures remains uncertain (Pinkham, 2014). In light of compelling evidence of social cognition deficits among patients with chronic schizophrenia, the failure to observe the expected differences between individuals with psychosis and controls at follow-up leads us to recommend this be explicitly examined in future longitudinal studies.

On nearly all measures, there was a tendency for all participants to score more highly at the second time point, consistent with the existing literature (Bora and Murray, 2013; Rodríguez-Sánchez et al., 2013). The MCCB has been shown to have minimal practice effects, reducing the likelihood that these improvements reflect practice effects. The young mean age of the sample in this study may have contributed to the improvement in longitudinal cognitive scores, perhaps a reflection of further brain development or education.

A strength of the current study is the well characterised longitudinal sample which is likely to be representative of the first-episode psychosis population. The sample was relatively heterogenous compared to a sample of first episode schizophrenia, although *post-hoc* analysis did not identify differences between affective and non-affective subtypes which may contribute positively to the generalisability of the findings to the population. Use of the standardised neurocognitive battery also enables compatible comparison of findings in future studies that administer the MCCB. However, as is common in longitudinal studies, a proportion of the sample was lost to follow-up rendering a relatively low sample size which may have reduced statistical power to detect more subtle effects. Additionally, it is possible that the reduced performance in verbal learning and the two measures of processing speed over time may not be directly attributed to the presence of an initial psychotic episode. Other factors that typically co-occur with the onset of psychotic disorders such as social isolation, lack of employment or education may also impact adversely on neurodevelopment and these cognitive skills.

5. Conclusion

Widespread cognitive deficits persist over four years after an initial psychotic episode. There was a tendency for stable deficit in the majority of cognitive deficits, with the exception of verbal learning and two measures of processing speed, which have a marked poorer trajectory. However, these

cognitive impairments in psychosis are malleable as cognitive remediation has improved performance in first episode psychosis and schizophrenia (Østergaard Christensen et al., 2014; Sartory et al., 2005). Speed of processing performance may moderate deficits in additional cognitive domains in psychosis and negative symptoms four years after a psychotic episode appeared to be partially predicted by performance on reasoning and problem solving and social cognition at illness onset. Targeted early cognitive remediation intervention therefore appears valuable and could potentially impact the course of negative symptoms following a first psychotic episode.

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