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Relationship between duration of untreated psychosis and neurocognition and social cognition in first-episode psychosis

Zhi Xiang On [a], Susan Cotton [b,c], John Farhall [a], Eóin Killackey [b,c], Kelly Allott [b,c,*]

[a] Department of Psychology and Counselling, La Trobe University, Australia
[b] Orygen, The National Centre of Excellence in Youth Mental Health, Australia
[c] Centre for Youth Mental Health, The University of Melbourne, Australia

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ABSTRACT

Cognitive impairment is common in first-episode psychosis (FEP); however, the relationship between duration of untreated psychosis (DUP) and neurocognition remains controversial, and no studies have examined the relationship between DUP and social cognition. This study involved secondary data analysis of baseline data from a randomised controlled trial of supported employment; 122 out 146 young people with FEP met inclusion criteria for this study. Results showed that DUP was not associated with neurocognitive or social cognitive performance. Results do not provide support for the neurotoxicity hypothesis of psychosis.

1. Introduction

Cognitive impairment, in both neurocognitive and social cognitive domains, is a well-established clinical feature of first-episode psychosis (FEP; Mesholam-Gately et al., 2009). A recent meta-analysis of 25 studies of FEP and ultra-high risk (UHR) samples confirmed that cognitive impairments are evident early before the onset of psychosis with no clear evidence of progression (i.e., worsening) after the first episode (Bora and Murray, 2014). These findings lend support to the neurodevelopmental rather than the neurodegenerative model of cognitive impairment in psychosis (Bora and Murray, 2014).

Nevertheless, it has been hypothesised that ongoing and untreated psychosis may be psychologically or neurologically toxic, potentially leading to worsening cognitive function (Sheitman and Lieberman, 1998). The neurotoxicity hypothesis suggests that delayed treatment may cause psychosis to become more biologically entrenched and thus, respond poorly to treatment (Rund, 2014). Neuroimaging studies have shown structural abnormalities in brain morphology in the early stages of FEP (Carletti et al., 2012; Fusar-Poli et al., 2012). The neurotoxicity hypothesis suggests that there may be a relationship between duration of untreated psychosis (DUP) and structural brain changes in FEP (Anderson et al., 2015). Thus, delayed treatment for individuals with psychosis could impair prognosis, while shortening the delay could improve it (Wyatt, 1991). DUP is defined as the time elapsing between psychosis onset and treatment intervention (Polari et al., 2011). While longer DUP has consistently been associated with poorer symptomatic and functional outcomes in psychosis (Harrigan et al., 2003; Harris et al., 2005; Marshall et al., 2005; Penttila et al., 2014), research into the relationship between DUP and cognition has been less clear, with many studies showing no significant relationship (Rund, 2014).

In contrast to the body of research on neurocognition, to our knowledge, no studies have specifically examined the relationship between DUP and social cognition in FEP. This is an important area of inquiry because in psychosis, social cognition is more strongly associated with functional outcome than neurocognition (Fett et al., 2011). Although there is evidence supporting a relationship between DUP and social functioning, the relationship between DUP and social cognition has yet to be investigated. Thus, the aim of the current study was to investigate whether longer DUP is negatively associated with poorer social cognitive and neurocognitive functioning in FEP.

2. Materials and methods

This study involved secondary data analysis of baseline data from 146 young people with FEP who had participated in a single-blind randomised controlled trial (RCT) of a vocational intervention (Australia New Zealand Clinical Trials # ACTRN12608000094370). A detailed description of the methodology and outcome measures of the RCT has been published elsewhere (Killackey et al., 2013). The study was approved by the Melbourne Health Research and Ethics Committee (HREC

* Corresponding author at: Orygen, The National Centre of Excellence in Youth Mental Health, 35 Poplar Road, Parkville, VIC, 3029, Australia.
E-mail address: kelly.allott@orygen.org.au (K. Allott).

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Table 1
Demographic and clinical characteristics of participants.

Characteristic	Statistic	Total
		(*N* = 122)
Demographics		
Gender % female	% (n)	30.3 (37)
Age	M (SD; range)	20.4 (2.4; 15–25)
Premorbid IQ	M (SD; range)	92.2 (13.6; 57–118)
Marital status		
Never married	% (n)	97.5 (119)
Country of birth		
Australian born	% (n)	75.4 (92)
Clinical characteristics		
Diagnosis	% (n)	
Schizophrenia		45 (36.8)
Schizophreniform		8 (6.6)
Schizoaffective		16 (13.1)
Delusional disorder		6 (4.9)
Brief psychotic disorder		1 (0.8)
Psychotic disorder NOS		14 (11.5)
Bipolar disorder with psychosis		16 (13.1)
Major depression with psychosis		16 (13.1)
Duration of untreated psychosis[a] (days)	M (SD; range)	256.4 (460.9; 0–2251)
Duration of treatment (days)	M (SD; range)	259.4 (196.9; 9–1081)
SANS composite	M (SD; range)	25.2 (11.8; 3–60)
BPRS – psychotic subscale	M (SD; range)	8.6 (4.4; 4–20)

Note: IQ, intelligence quotient; NOS, not otherwise specified; SANS, Scale for the Assessment of Negative Symptoms; BPRS, Brief Psychiatric Rating Scale.
[a] Duration of untreated psychosis was log-transformed in the regression analysis.

2007.648). All participants provided written informed consent, including parental/guardian consent for those <18 years of age.

Participants had to meet the criteria for a DSM-defined psychotic disorder using the Structured Clinical Interview for DSM-IV-TR (First et al., 2001) and express a desire to pursue a vocational goal. Those with intellectual disability or with florid psychosis that prevented the ability to provide informed consent, and those with insufficient English competency to complete the assessments, were excluded. For the current analysis, 13 participants were also excluded due to a history of traumatic brain injury ($n = 7$), epilepsy ($n = 5$), or other neurological impairment ($n = 1$), or if there was not data on DUP ($n = 9$) or all cognitive measures ($n = 2$). The final sample was $N = 122$.

Demographic information was collected to describe the sample and to capture potential confounding variables, such as education level and premorbid intelligence quotient (IQ). Premorbid IQ was measured by the Wide Range Achievement Test – Fourth Edition (WRAT-4) Word Reading subtest (Wilkinson and Robertson, 2006). DUP was operationally defined in days and calculated as the date of registration with the Early Psychosis Prevention and Intervention Centre (EPPIC) minus the date of self-reported first onset of positive psychotic symptoms (e.g., hallucinations, delusions). The date of onset of frank psychotic symptoms was obtained through a clinical interview and assessed by a trained research assistant. Duration of treatment was also measured as a possible confounding variable and operationally defined in days and calculated as the date of cognitive assessment minus the date of first registration with EPPIC. Diagnostic group and symptomatology of participants was also measured (Table 1). A broad test battery that covered the neurocognitive domains known to be impaired in FEP (Mesholam-Gately et al., 2009) was administered (see Table 2). Theory of mind (ToM) and facial and prosody emotion recognition were the social cognitive domains examined. ToM was assessed both verbally and non-verbally because some ToM tasks place demands on neurocognitive abilities (working memory or verbal skills), which may confound performance (Allott et al., 2013). Further descriptions of the tasks are provided elsewhere (Allott et al., 2013; Arnold et al., 2015).

All statistical analyses were performed using IBM® SPSS® Version 22 (Statistical Version). Exploratory factor analysis of the 18 cognitive variables was used as a data reduction technique and six factors were identified and interpreted as: (i) social cognition; (ii) verbal and learning memory; (iii) processing speed; (iv) attention and working memory; (v) visual organisation and memory; and (vi) verbal comprehension (Table 2). The contribution of DUP to the prediction of neurocognition and social cognition was examined via six separate hierarchical regressions, while controlling for premorbid IQ, gender, age, duration of treatment, negative symptoms (SANS – Scale for the Assessment of Negative Symptoms composite) and positive symptoms (BPRS – Brief Psychiatric Rating Scale positive subscale). Bonferroni correction was applied and statistical significance (α) was set at 0.008 according to the six dependent cognitive variables (i.e., 0.05/6).

3. Results

The findings of the hierarchical multiple regression analyses are shown in Tables 3 (neurocognition) and 4 (social cognition). Only premorbid IQ contributed significantly to the five neurocognition factors and the social cognition factor. Negative symptoms also contributed significantly to the prediction of performance on processing speed and

Table 2
Factor loadings, eigenvalues, percentage of variance and communalities for principal axis factor analysis with promax rotation for the final cognitive battery.

	Social cognition	Attention & working memory	Verbal learning & memory	Processing speed	Verbal comprehension	Visual organisation & memory	h^2
DANVA paralanguage total	0.88						0.59
DANVA faces total	0.51						0.35
Picture sequencing	0.48						0.34
Hinting	0.41						0.48
FBDST	0.41						0.50
Digit span backward		0.93					0.80
Letter number sequencing		0.67					0.77
Digit span forward		0.64					0.51
RAVLT A5			0.98				0.92
RAVLT A7			0.82				0.73
SDMT				0.82			0.72
TMT_A reverse score				0.77			0.54
TMT_B reverse score				0.55			0.54
Similarities					0.88		0.82
Information					0.83		0.67
RCFT figure delay						0.71	0.67
RCFT figure copy						0.55	0.47
RCFT figure organisation						0.49	0.23
Eigenvalues	6.85	1.59	1.29	1.20	1.07	0.89	
% of variance	35.98	6.98	4.96	4.41	3.80	2.94	

Note. DANVA-2 = Diagnostic Analysis of Nonverbal Accuracy; FBDST = False Belief And Deception Stories Task; RAVLT = Rey Auditory; Verbal Learning Test; SDMT = Symbol Digit Modalities Test; TMT = Trial Making Test; RCFT = Rey-Osterrieth Complex Figure Test.

Table 3
Summary of hierarchical regression analyses for duration of untreated psychosis as a predictor of neurocognition.

Outcome	Predictor variables	β	R^2	ΔR^2
Verbal learning and memory	Step 1		0.25	
	Premorbid IQ	0.41*		
	Gender	0.14		
	Age	0.02		
	Duration of treatment	0.07		
	SANS	−0.20		
	BPRS	0.06		
	Step 2		0.26	0.01
	Premorbid IQ	0.41*		
	Gender	0.16		
	Age	0.03		
	Duration of treatment	0.06		
	SANS	−0.19		
	BPRS	0.03		
	DUP	0.11		
Processing speed	Step 1		0.36	
	Premorbid IQ	0.55*		
	Gender	0.01		
	Age	−0.07		
	Duration of treatment	0.03		
	SANS	−0.28*		
	BPRS	0.21		
	Step 2		0.36	0
	Premorbid IQ	0.55*		
	Gender	0.01		
	Age	−0.07		
	Duration of treatment	0.02		
	SANS	−0.28*		
	BPRS	0.20		
	DUP	0.02		
Attention and working memory	Step 1		0.45	
	Premorbid IQ	0.68*		
	Gender	−0.06		
	Age	0.07		
	Duration of treatment	0.05		
	SANS	−0.06		
	BPRS	0.05		
	Step 2		0.45	0.004
	Premorbid IQ	0.68*		
	Gender	−0.04		
	Age	0.08		
	Duration of treatment	0.05		
	SANS	−0.06		
	BPRS	0.03		
	DUP	0.07		
Visual organisation and memory	Step 1		0.21	
	Premorbid IQ	0.28*		
	Gender	0.02		
	Age	0.15		
	Duration of treatment	0.03		
	SANS	−0.32*		
	BPRS	0.06		
	Step 2		0.21	0
	Premorbid IQ	0.28*		
	Gender	0.02		
	Age	0.15		
	Duration of treatment	0.03		
	SANS	−0.32*		
	BPRS	0.06		
	DUP	0.06		
Verbal comprehension	Step 1		0.42	
	Premorbid IQ	0.60*		
	Gender	−0.04		
	Age	0.14		
	Duration of treatment	0.02		
	SANS	−0.07		
	BPRS	−0.05		
	Step 2		0.42	0.006
	Premorbid IQ	0.60*		
	Gender	−0.03		
	Age	0.14		
	Duration of treatment	0.01		
	SANS	−0.07		
	BPRS	−0.07		
	DUP	0.08		

Table 4
Summary of hierarchical regression analysis for duration of untreated psychosis as a predictor of social cognition.

Outcome	Predictor variables	β	R^2	ΔR^2
Social cognition	Step 1		0.38	
	Premorbid IQ	0.55*		
	Gender	0.09		
	Age	0.03		
	Duration of treatment	0.05		
	SANS	0.18		
	BPRS	0.02		
	Step 2		0.39	0.006
	Premorbid IQ	0.41*		
	Gender	0.16		
	Age	0.03		
	Duration of treatment	0.06		
	SANS	−0.19		
	BPRS	0.03		
	DUP	0.09		

Note. N = 122.
* p ≤ 0.008.

visual organisation and memory. DUP did not significantly add to the variance in neurocognitive or social cognitive factor scores.

4. Discussion

DUP was not found to be significantly associated with the neurocognition and social cognition factors. The lack of evidence supporting a relationship between DUP and neurocognition is consistent with the findings of a recent critical review (Rund, 2014) and suggests that DUP does not have a 'toxic' effect on neurocognitive function. This finding is consistent with the neurodevelopmental hypothesis, which posits that neurocognitive impairment is neurodevelopmental in origin, precedes full-threshold psychotic disorder, and is a relatively stable trait marker of illness. A possible clinical implication of this finding is that reducing DUP may not in turn improve cognitive performance, as impairment seems to be unrelated to the course of psychotic symptoms.

This is the first study to our knowledge that has explicitly examined the relationship between DUP and social cognitive performance. The findings parallel those of neurocognition and suggest that longer DUP is unrelated to poorer social cognition. While past studies have found a relationship between DUP and social functioning (Barnes et al., 2008), the absence of statistically significant associations between DUP and social cognition suggests that social cognition may not play a role in the association between DUP and social functioning. Further studies to replicate and understand the relationships between DUP, social cognition and social functioning are warranted.

It is important to note that the recruited sample in this study may be higher functioning than the general psychosis population given they were individuals pursuing a vocational goal. Thus, the findings might not be generalisable to the general FEP population. In conclusion, the finding of an absence of relationships between DUP and neurocognition and social cognition is inconsistent with the neurotoxicity hypothesis.

Conflict of interest
All authors declare that they have no conflict of interest.

Contributors
K.A., S.C., and E.K. designed the study. ZX.O undertook the literature search, statistical analysis and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Notes to Table 3
Note. N = 122.
* p ≤ 0.008.

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