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# Impact of duration of untreated psychosis and premorbid intelligence on cognitive functioning in patients with first-episode schizophrenia

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ABSTRACT

*Background:* The neurotoxic hypothesis suggests that psychosis is toxic to the brain leading to clinical consequences. In this study, we hypothesized that a longer duration of untreated psychosis (DUP) in first episode schizophrenia (FES) patients is associated with poorer cognitive functioning, and that higher premorbid intelligence buffers against DUP-related cognitive impairment.
*Method:* Eighty-one FES patients completed a neuropsychological battery, the Brief Assessment of Cognition in Schizophrenia (BACS). Composite scores of the BACS, which were normalized to a matched healthy control of seventy-three subjects, were used as an index of general cognition. A median split using the Wide Range Achievement Test–Reading Test scores was used to divide the patients into low versus high premorbid IQ groups. Hierarchical linear regression was performed to examine predictors of general cognition, including DUP.
*Results:* Longer DUP was found to be a significant predictor of poorer general cognition. In addition, DUP predicted general cognition in the low premorbid IQ group but not in the high premorbid IQ group.
*Conclusions:* Our findings demonstrate that longer DUP in FES patients is associated with worse cognitive scores, and that this association is more pronounced in a subgroup of patients who have lower premorbid intelligence. Our results suggest the importance of earlier identification and management of patients with low premorbid IQ, given that their cognition may be more vulnerable to the toxicity of psychosis.


## 1. Introduction

Psychosis has been suggested to be biologically toxic to the brain (Lieberman et al., 1993), leaving patients with a "damaging residual if it is allowed to proceed unmitigated" (Wyatt, 1991, p. 347). Due to the purported neurotoxicity of psychosis, there has been a great interest in understanding how the duration of untreated psychosis (DUP) relates to clinical outcomes (Shrivastava et al., 2010). The duration of untreated psychosis (DUP) is generally defined as the time period between the presentation of the first psychotic symptom to the initiation of adequate treatment (Marshall et al., 2005). Converging evidence indicates an association between longer DUP and poorer clinical sequelae in psychosis such as more frequent psychotic recurrences and hospitalizations (Dell'Osso et al., 2012), poorer response to antipsychotic medications (Perkins et al., 2005), poorer quality of life (Marshall et al., 2005), poorer functional outcomes and more severe positive and negative symptoms at follow up (Marshall et al., 2005; Perkins et al., 2005). Longer DUP has also been associated with gray matter reductions (Lappin et al., 2006; Malla et al., 2011) and decreased cortical activity (Chou et al., 2014) in the frontotemporal regions.

However, past studies looking at the associations between DUP and cognitive functioning have been inconsistent (Goldberg et al., 2009). Some studies have found a relationship between longer DUP and more severe cognitive impairment (Amminger et al., 2002; Joyce et al., 2002; Lappin et al., 2007; Gaynor et al., 2009; Cuesta et al., 2012; Zhou et al., 2012; Chang et al., 2013), whilst other studies have failed to find such a relationship (Hoff et al., 2000; Rund et al., 2004; Rund et al., 2007; Galderisi et al., 2009; Goldberg et al., 2009; Rapp et al., 2013). The differences in the findings could be attributed to the variability in the diagnoses of the study participants among these studies; study participants in most studies span a wide spectrum of psychotic disorders including brief psychotic disorder, schizophreniform, schizoaffective disorders and affective psychosis (Hoff et al., 2000; Amminger et al., 2002; Ho et al., 2003; Rund et al., 2004; Rund et al., 2007; Galderisi et al., 2009; Gaynor et al., 2009; Goldberg et al., 2009; Cuesta et al.,

*Abbreviations:* BACS, Brief Assessment of Cognition in Schizophrenia; DUP, duration of untreated psychosis; FES, first episode schizophrenia; PANSS, Positive and Negative Syndrome Scale; SCID-I/P, Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition; SCID-I/NP, Structured Clinical Interview for DSM-IV Axis I Disorders-Non-patient Edition; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WRAT-RT, Wide Range Achievement Test.

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2012; Chang et al., 2013; Rapp et al., 2013), while only a few studies focused on examining schizophrenia patients alone (Joyce et al., 2002; Lappin et al., 2007; Zhou et al., 2012). A study comparing the association between DUP and cognitive performance in two groups: schizophrenia and non-schizophrenia psychotic disorder, found that significant impairments in neurocognitive performance was only found in the schizophrenia group (Lappin et al., 2007) This suggests that the association between longer DUP and cognitive deficits may be specific to schizophrenia.

Of note, most of these studies did not distinguish between patients with different levels of premorbid intelligence. The cognitive reserve hypothesis suggests that individuals with higher premorbid intellectual function are able to tolerate greater brain damage before demonstrating functional impairment (Leeson et al., 2011). Childhood IQ, an index of premorbid intelligence, has been found to predict better social and functional outcomes among schizophrenia patients (Munro et al., 2002; Van Winkel et al., 2007). However, it is not clear whether premorbid intelligence can act as a buffer against the putative neurotoxic effects of untreated psychosis, and thus reduces the cognitive impairment experienced by most schizophrenia patients. In this regard, the toxic effects of prolonged untreated psychosis may be more severe for patients with low premorbid IQ because of inadequate functional capacity or brain structure reserve to adapt to or compensate for the neural insult (Leeson et al., 2011).

Cognitive deficits in schizophrenia are recognized as crucial determinants of various functional outcomes including employment, rehabilitation and social reintegration (Voruganti et al., 2007). Clinically, DUP is a potentially modifiable prognostic factor (Perkins et al., 2005). Hence in this study, we aim to extend previous studies by examining how DUP is related to cognitive functioning in patients with lower premorbid intelligence versus higher premorbid intelligence. As a marker of premorbid intelligence, we used the Wide Range Achievement Test-Reading Test (WRAT-RT) (Wilkinson, 1993), which has been commonly used to estimate premorbid intelligence in clinical populations as reading abilities are thought to be resistant to the effects of brain disease/injury (Crawford, 1992). Reading abilities have also been shown to adequately predict scores of more comprehensive intelligence tests such as the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981) as well as IQ scores (Johnstone et al., 1996). We focused our study on first episode schizophrenia (FES) patients, to mitigate the confounding effects of long-term illness and medications on cognitive performance. We hypothesize that longer DUP in FES patients is associated with lower neurocognitive scores, and that the neurotoxic effect of DUP on cognitive functioning is more pronounced in a subgroup of patients who have lower premorbid intelligence.

## 2. Methods

### 2.1. Participants

Eighty-one FES patients were recruited from the Institute of Mental Health, Singapore and through advertisements in the community respectively. Patients were diagnosed using information obtained from clinical history, existing medical records, interviews with closed ones, and the administration of the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P) (First et al., 1994). For all participants, the exclusionary criteria included a history of significant medical history such as head injury, neurological illness such as epilepsy, impaired thyroid function, and alcohol or other substance abuse in the preceding 3 months prior to the study. Patients did not have to stop medication for their participation. We also recruited seventy-three healthy controls, which were screened using the Structured Clinical Interview for DSM-IV Axis I Disorders-Non-patient Edition (SCID-I/NP) (First et al., 2002). Cognitive data from the healthy controls were used to calculate the standardized cognitive scores (see below for details). The study procedure was explained in detail before obtaining written informed consent from participants. Ethical approvals were obtained from the institutional review boards of the Institute of Mental Health, Singapore, as well as the National Neuroscience Institute, Singapore.

### 2.2. Clinical and neurocognitive assessments

In the patient cohort, the severity of psychotic psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). DUP was defined as the period from the onset of psychotic symptoms to the time when treatment was administered. Information relating to the date of onset of psychosis was assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P) (First et al., 1994). Date of treatment initiation was defined as the time of first consult at the psychiatric clinic and an appropriate course of treatment meted out. This information was retrieved from documented case notes. Information obtained from patients was verified against documented case notes as well as information provided by patients' caregivers or relatives when available.

The cognitive performance of all the participants, including healthy controls and the patients, was assessed using a neuropsychological battery, the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004). The constructs measured with BACS included verbal memory, working memory, motor speed, semantic fluency, letter fluency, attention and speed of information processing, and executive functions.

For patients, the raw scores of each test of the BACS (e.g. list learning) was standardized by creating z-scores whereby healthy control mean was set to zero and the standard deviation set to one. The composite score of BACS was calculated by averaging all of the 7 standardized measures from the BACS battery. We took this composite score to be an index of general cognition.

The Wide Range Achievement Test-Reading Test (WRAT-RT) was administered to assess premorbid intelligence (Wilkinson, 1993). The reading test consists of 15 letters and 42 individual words that the participant is required to name or pronounce, summing up to a possible maximum score of 57. A median split using the WRAT-RT scores was performed to separate patients into low premorbid IQ group (WRAT-RT $< 50$, $n = 36$) versus high premorbid IQ group (WRAT-RT $\geq 50$, $n = 45$).

### 2.3. Statistical analysis

All analyses were performed using SPSS version 20. Baseline demographic, clinical and cognitive characteristics were compared between patients and controls using *t*-test and chi-square test ($\chi^2$) for continuous and categorical variables, respectively. All the variables were assessed for multicollinearity, normality, linearity and homoscedasticity. Due to a strong positive skew in DUP, the DUP was log transformed ((LgDUP) + 3) and used in the subsequent primary analyses.

Hierarchical linear regression models were performed to study the predictive value of DUP on the composite index (general cognition). To account for the effects of time, we entered blocks of variables in chronological order: Demographic variables (gender, age) were first controlled for in the first block as they are fixed variables that are not influenced by other variables. Cognitive reserve factors (WRAT-RT scores, and years of education) were next added in the second block, before clinical variables, because cognitive capacity mediates clinical symptoms (Barnett et al., 2006). Clinical variables (positive symptom, negative symptom, general psychopathology subscale scores, duration of psychosis and daily medication dose) were added in the third block, and DUP was entered last to see if it explained additional significant variance of the composite index after controlling for other predictors. The outcome of interest was the incremental proportion of variance explained by DUP after other blocks of predictors were controlled. We consider the increment to be significant if the p value of $R^2$ change is $<0.05$. In order to investigate the neuroprotective role of cognitive reserve against the neurotoxicity of untreated psychosis, hierarchical

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