Impacts of duration of untreated psychosis on cognition and negative symptoms in first-episode schizophrenia: a 3-year prospective follow-up study

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Background. Cognitive impairment is a core feature of schizophrenia. Its relationship with duration of untreated psychosis (DUP), a potentially malleable prognostic factor, has been less studied, with inconsistent findings being observed in the literature. Previous research investigating such a relationship was mostly cross-sectional and none of those prospective studies had a follow-up duration beyond 2 years.

Method. A total of 93 Hong Kong Chinese aged 18 to 55 years presenting with first-episode schizophrenia-spectrum disorder were studied. DUP and pre-morbid adjustment were measured using a structured interview incorporating multiple sources of information. Psychopathological evaluation was administered at intake, after clinical stabilization of the first psychotic episode, and at 12, 24 and 36 months. Cognitive functions were measured at clinical stabilization, and at 12, 24 and 36 months.

Results. DUP exerted differential effects on various cognitive domains, with memory deficits being the most related to DUP even when potential confounders including pre-morbid adjustment and sex were adjusted. Prolonged DUP was associated with more severe impairment in visual memory at clinical stabilization and verbal memory at 24 and 36 months. Further, patients with a long DUP were found to have worse outcomes on negative symptoms at 36 months. The effects of DUP on verbal memory remained significant even when negative symptoms were taken into consideration.

Conclusions. Our findings provided further supportive evidence that delayed treatment to first-episode psychosis is associated with poorer cognitive and clinical outcomes. In addition, DUP may specifically affect memory function and its adverse impact on verbal memory may only become evident at a later stage of the recovery process.

Introduction

Duration of untreated psychosis (DUP) has been considered as a potentially modifiable prognostic factor of schizophrenia. The majority of studies examining DUP have focused on its relationships with clinical and functional outcomes, and they revealed that prolonged DUP predicts a higher level of symptoms, worse psychosocial functioning and poorer quality of life (Marshall *et al.* 2005; Perkins *et al.* 2005).

Cognitive impairment is a core feature of schizophrenia (Elvevag & Goldberg, 2000). A substantial body of evidence has demonstrated that patients presenting with first-episode schizophrenia exhibit pronounced deficits across various cognitive domains,

particularly in memory, attention and executive function (Mesholam-Gately *et al.* 2009). As cognitive dysfunction has consistently been shown to predict functional disability (Green *et al.* 2000) and remains an unmet therapeutic need due to its limited response to antipsychotic treatment (Goldberg *et al.* 2007), clarifications of correlates associated with cognitive impairment, in particular those being potentially malleable to interventions such as DUP, are of significant clinical relevance. Nonetheless, relatively few studies have been conducted to investigate the relationship between DUP and cognitive functions in schizophrenia. Among those few studies, some have indicated that prolonged DUP is related to more severe cognitive impairment (Scully *et al.* 1997; Amminger *et al.* 2002; Joyce *et al.* 2002; Lappin *et al.* 2007), while others have failed to find such a relationship (Hoff *et al.* 2000; Norman *et al.* 2001; Townsend *et al.* 2002; Ho *et al.* 2003; Addington *et al.* 2004; Rund *et al.* 2007; Barnes *et al.* 2008; Goldberg *et al.* 2009).

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Inconsistency in findings regarding the association between DUP and cognitive functions in schizophrenia may partly be attributed to methodological variations in sampling, measurements of DUP and outcome variables, choice of cognitive assessments administered, and lengths of follow-up. Of note, cognitive performance may change substantially from treatment initiation to the time when psychosis has been stabilized (Townsend *et al.* 2002). In addition, certain cognitive functions may improve over a longer period of time after the initial psychotic episode (Gold *et al.* 1999; Albus *et al.* 2002). On the other hand, most previous studies that addressed the relationship between DUP and cognitive functions were cross-sectional with focus on initial presentation of the first psychotic episode (Hoff *et al.* 2000; Norman *et al.* 2001; Amminger *et al.* 2002; Joyce *et al.* 2002; Ho *et al.* 2003; Lappin *et al.* 2007). For those very few prospective longitudinal studies, their lengths of follow-up ranged from 4 months to 2 years only (Townsend *et al.* 2002; Addington *et al.* 2004; Rund *et al.* 2007; Barnes *et al.* 2008; Goldberg *et al.* 2009). In this regard, studies with such a short follow-up interval may fail to capture an evolving course of cognitive recovery, and hence its association with DUP in the early phase of the illness.

Discrepant findings have also been observed with respect to the relationship between DUP and negative symptoms. Whereas several past studies (Scully *et al.* 1997; Harrigan *et al.* 2003; Melle *et al.* 2008) and two meta-analyses (Marshall *et al.* 2005; Perkins *et al.* 2005) found that longer DUP predicted worse outcome on negative symptoms, other investigators revealed a lack of independent contribution of DUP on severity of negative symptoms when pre-morbid adjustment was taken into consideration (Harris *et al.* 2005; Jeppesen *et al.* 2008).

In this article, we present a prospective 3-year follow-up study in a representative cohort of Chinese patients having first-episode schizophrenia-spectrum disorder in Hong Kong with an aim to examine the influence of DUP on longitudinal trajectories of cognitive and clinical measures. DUP was measured using a standardized instrument incorporating multiple sources of information when patients first presented to treatment. The potential confounding effects of pre-morbid functioning on cognitive and clinical outcomes were adjusted to enable a better estimation of a unique contribution of DUP to these outcome measures.

Method

Participants

Participants were recruited from both out-patient and in-patient psychiatric units that provide service for a catchment area in Hong Kong with a population of approximately 1.3 million. A total of 138 patients aged 18–55 years who were consecutively diagnosed as having first-episode schizophrenia, schizophreniform disorder or schizo-affective disorder were included. Patients with known neurological disorder or learning disability were excluded from the study. Of the initial cohort, 93 subjects completed the 3-year follow-up, 40 defaulted, four committed suicide and one died of medical disease. There were no significant differences between completers and non-completers in socio-demographics, DUP, baseline symptom ratings and cognitive functions. Patients in this study were initially treated with low-dose first-generation antipsychotic medications. Among 93 subjects, 48 were first assessed in a medication-naive state, and the rest were evaluated within 7 days of starting antipsychotic treatment.

The current study was part of a prospective 3-year follow-up study in first-episode schizophrenia-spectrum disorder patients and findings regarding persistent negative symptoms and cognitive predictors of relapse have been reported elsewhere (Chen *et al.* 2005; Chang *et al.* 2011). The study was approved by the local institutional review board and all of the subjects gave written informed consent before participation.

Diagnostic, clinical and cognitive assessments

Diagnostic assignment was based on a longitudinal approach taking into consideration that diagnostic change may take place over time (Chang *et al.* 2009). The 3-year diagnosis of each subject was determined according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria (APA, 1994) using all available information encompassing the whole follow-up period including the Chinese-bilingual Structured Clinical Interview for DSM-IV (Axis I, Patient version) (CB-SCID-I/P, So *et al.* 2003) administered at baseline and at 3 years, informant histories and medical records. A previous validation study showed that the CB-SCID-I/P yields reliable DSM-IV diagnoses in Chinese patients with psychotic disorders (So *et al.* 2003). Independent diagnostic assessments on a subset of the sample ($n = 38$) demonstrated a satisfactory concordance rate of 86%.

Pre-morbid functioning was measured with the Premorbid Adjustment Scale (PAS; Cannon-Spoor *et al.* 1982) based on information obtained via interviews with patients and relatives. We only included childhood ($\leqslant 11$ years) and early adolescence (12–15 years) periods for assessment to avoid any possible confounding with early symptoms because the onset of prodrome and psychosis usually occurs in

late adolescence and early adulthood (Cassidy *et al.* 2010). The PAS total score was calculated by summing the scores on all items encompassing both childhood and early adolescence periods and dividing by the total possible score (score range 0 to 1; a higher score indicates lower functioning).

DUP, which was defined as the time interval between the onset of positive psychotic symptoms and treatment initiation, was assessed with the Interview for the Retrospective Assessment of the Onset of Schizophrenia (Häfner *et al.* 1992) incorporating information from patients, relatives and medical records. Positive symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS; Kay *et al.* 1987) with intra-class correlation coefficient (ICC) being 0.83 for the positive symptoms subscale. The High Royds Evaluation of Negativity Scale (HEN; Mortimer *et al.* 1989) was employed to measure negative symptoms. It comprises six subscales and 18 items that are rated along an anchored five-point severity scale (range 0–4; a higher score indicates more severe negative symptoms). Validation of the HEN for use in Chinese schizophrenia patients has previously been reported (Chen *et al.* 1996). ICCs for the subscales ranged from 0.74 (Thought) to 0.85 (Speech). In this study, we only included four of the six subscales, i.e. Affect, Behaviour, Speech and Functioning subscales for analysis (Chang *et al.* 2011) as the remaining two, namely Thought and Appearance subscales, were more related to the disorganization dimension.

A comprehensive battery of cognitive assessments was administered to all subjects, comprising a logical memory test (Wechsler Memory Scale Revised; WMS-R-HK, Hong Kong Psychological Society, 1989*b*), a visual reproduction test (WMS-R-HK), forward digit span (Wechsler Adult Intelligence Scale; WAIS-R-HK; Hong Kong Psychological Society, 1989*a*), semantic category fluency and the Modified Wisconsin Card Sorting Test (Nelson, 1976). General verbal intelligence was estimated at baseline using the information subscale from the WAIS-R-HK (Chen *et al.* 2005).

Psychopathological evaluation was conducted for each subject at intake, after clinical stabilization of the first psychotic episode (a mean of 42.6 days after initial assessment), and at 12, 24 and 36 months. To maximize cooperation and to reduce state effects of acute psychosis, the cognitive assessment undertaken when patients were clinically stabilized was regarded as the baseline cognitive measure. The cognitive assessment was re-administered to each subject at 12, 24 and 36 months. A group of healthy controls, matched for age, sex and educational level, were recruited via advertisements and were evaluated with the same battery of cognitive assessments as patients at baseline only. Research staff who administered symptom and cognitive assessments was blind to the DUP measure.

Statistical analysis

Differences between patients and matched controls on baseline cognitive functions were evaluated using the independent *t* test. The patient sample was divided into short and long DUP groups based on median split at 180 days. Pre-morbid functioning, and sociodemographic and treatment characteristics between the two groups were compared using the independent *t* test and χ^2 test as appropriate. To compare symptom and cognitive outcomes between the two groups at each assessment time point, an analysis of covariance (ANCOVA) was performed with sex and PAS total score as covariates. Longitudinal changes in symptom ratings and cognitive deficits over 3 years were compared between the two DUP groups using a repeated-measures ANCOVA with time points as the within-subject level, and sex and PAS total score as covariates. The Greenhouse–Geisser correction was used when the sphericity assumption was not met. All analyses were two-tailed and the level of significance was set at $p < 0.05$.

Results

Characteristics of the sample

Of the 93 subjects who were followed up for 3 years, 84 completed DUP assessments and thus constituted the final sample of the study. The 84 subjects were predominantly single (72.6%), and 42.9% were male. The mean age of the sample at intake was 31.5 years (S.D. = 9.5, range 18–55 years) and the average educational level was 10.49 years (S.D. = 3.0). The median DUP of the sample was 180 days and the mean was 473.7 days (S.D. = 786.4, range 2–3650 days). Diagnoses for the cohort were schizophrenia ($n = 67$), schizophreniform disorder ($n = 12$) and schizo-affective disorder ($n = 5$). There were no significant differences between subjects with a DUP measure and those without in sociodemographics, pre-morbid functioning, baseline symptom and cognitive measures, and treatment characteristics.

Table 1 summarizes sociodemographics, pre-morbid adjustment and treatment characteristics of the patient sample. Patients with a long DUP were significantly more likely to be male than those with a short DUP. Otherwise, no significant differences between the two groups among other variables were observed.

As shown in Table 2, there were no significant differences between patients and healthy controls in age, sex and educational level. Patients performed

Table 1. *Demographics, pre-morbid adjustment, baseline and treatment characteristics of patients with first-episode schizophrenia-spectrum disorder*

Variable of interest	Subjects with DUP <180 days ($n=41$)	Subjects with DUP ⩾180 days ($n=43$)	Statistics: χ^2 or t (df)	p
Baseline sociodemographic and clinical characteristics				
Mean age at entry, years (S.D.)	31.5 (10.2)	31.5 (8.9)	−0.023 (82)	0.98
Male sex, n (%)	13 (31.7)	23 (53.5)	4.1	0.044
Mean duration of education, years (S.D.)	10.5 (3.6)	10.5 (2.4)	−0.001 (82)	0.99
Mean PAS total score (S.D.)	0.34 (0.1)	0.36 (0.1)	−0.4 (78)	0.67
Mean DUP, days (S.D.)	49 (42.7)	878.6 (936.1)	5.8 (82)	<0.0001
Treatment characteristics				
Mean CPZ equivalence at intake, mg/day (S.D.)	219.4 (615.4)	139.3 (195.5)	0.8 (82)	0.42
Mean CPZ equivalence at clinical stabilization, mg/day (S.D.)	405.4 (427.9)	304.9 (317.6)	1.2 (82)	0.22
Mean CPZ equivalence at year 1, mg/day (S.D.)	264.3 (391.6)	274.8 (242.5)	0.2 (82)	0.88
Mean CPZ equivalence at year 2, mg/day (S.D.)	293.9 (452.9)	245.0 (249.7)	0.6 (82)	0.54
Mean CPZ equivalence at year 3, mg/day (S.D.)	233.3 (346.4)	228.8 (233.8)	0.07 (82)	0.94
Mean anticholinergic dose[a] at intake, mg/day (S.D.)	0.7 (1.7)	1.2 (2.1)	−1.3 (82)	0.21
Mean anticholinergic dose[a] at clinical stabilization, mg/day (S.D.)	3.2 (3.4)	3.6 (3.5)	−0.6 (82)	0.55
Mean anticholinergic dose[a] at year 1, mg/day (S.D.)	2.2 (2.9)	2.9 (2.8)	−1.1 (82)	0.29
Mean anticholinergic dose[a] at year 2, mg/day (S.D.)	2.1 (2.9)	2.1 (2.5)	−0.08 (82)	0.94
Mean anticholinergic dose[a] at year 3, mg/day (S.D.)	2.2 (2.8)	2.0 (2.6)	0.4 (82)	0.68
On SGA at clinical stabilization[b,c], n (%)	1 (2.4)	1 (2.3)	0.001	0.99
On SGA at year 1[b,d], n (%)	4 (9.8)	3 (7.0)	0.2	0.71
On SGA at year 2[b,e], n (%)	5 (12.2)	8 (18.6)	0.7	0.55
On SGA at year 3[b,f], n (%)	7 (17.1)	8 (18.6)	0.3	0.86

DUP, Duration of untreated psychosis; df, degrees of freedom; S.D., standard deviation; PAS, Premorbid Adjustment Scale; CPZ, chlorpromazine; SGA, second-generation antipsychotic; FGA, first-generation antipsychotic.

[a] Anticholinergic medication refers to benzhexol.

[b] Fisher's exact test was applied.

[c] Out of the 84 subjects, two took SGA medication at clinical stabilization, with all on risperidone. The remaining subjects were treated with a FGA.

[d] Out of the 84 subjects, seven took SGA medication at year 1, with five on risperidone and two on olanzapine. The remaining subjects were treated with FGA medication.

[e] Out of the 84 subjects, 13 took SGA medication at year 2, with 10 on risperidone, two on olanzapine and one on clozapine. The remaining subjects were treated with FGA medication.

[f] Out of the 84 subjects, 15 took SGA medication at year 3, with 11 on risperidone, three on olanzapine and one on clozapine. The remaining subjects were treated with FGA medication.

significantly worse than controls in all cognitive tests, with a range from 0.4 (forward digit span) to 1.0 (logical memory, delayed recall) standard deviations below those of controls with the exception of the visual reproduction test which yielded no significant differences between the two groups. Thus, our results were comparable with the findings in the literature on cognitive impairment in patients presenting with first-episode schizophrenia (Mesholam-Gately *et al.* 2009).

Comparison between short and long DUP groups at each assessment time point

As the long DUP group was found to be significantly associated with male sex in the current analysis, while pre-morbid adjustment was shown by previous studies to be related to the severity of negative symptoms (Harris *et al.* 2005; Jeppesen *et al.* 2009) and cognitive impairment (Silverstein *et al.* 2002), a series of ANCOVAs were performed with sex and pre-morbid functioning as covariates to control their potential confounding effects on clinical and cognitive outcomes.

Symptom outcomes

The long DUP group had significantly more negative symptoms than the short DUP group at the end of the 3-year follow-up ($F_{1,78}=4.1$, $p<0.05$). There were no significant differences in negative symptom levels

Table 2. *Comparison of sociodemographics and baseline cognitive functions between patients and healthy controls*

Variable of interest	Patients (*n* = 93)	Controls (*n* = 114)	Statistics: χ^2 or *t* (df)	*p*
Sociodemographic characteristics				
Mean age at entry, years (S.D.)	31.2 (9.6)	33.4 (10.0)	1.6 (205)	0.11
Male sex, *n* (%)	42 (45.2)	47 (41.2)	0.3	0.57
Mean duration of education, years (S.D.)	10.5 (2.9)	11.1 (2.2)	1.6 (205)	0.11
Baseline cognitive functions				
Mean WAIS-R-HK information subset (S.D.)	14.6 (5.4)	17.1 (4.7)	3.5 (205)	0.001
Mean WAIS-R-HK digit span forward (S.D.)	11.4 (1.9)	12.1 (1.7)	2.5 (205)	0.013
Mean WMS-R-HK logical memory, immediate recall (S.D.)	35.1 (17.0)	50.6 (18.9)	6.1 (205)	<0.0001
Mean WMS-R-HK logical memory, delayed recall (S.D.)	28.3 (17.5)	45.2 (19.6)	6.4 (205)	<0.0001
Mean WMS-HK visual reproduction, immediate recall (S.D.)	20.2 (3.4)	20.7 (3.2)	1.2 (205)	0.232
Mean WMS-HK visual reproduction, delayed recall (S.D.)	19.6 (3.7)	19.9 (4.1)	0.7 (205)	0.203
Mean semantic category fluency (S.D.)	17.0 (4.6)	20.0 (5.8)	4.0 (205)	<0.0001
Mean MWCST categories completed (S.D.)	4.1 (2.2)	5.0 (1.5)	3.5 (204)	0.001
Mean MWCST perseverative errors (S.D.)	6.0 (7.9)	3.3 (3.4)	−2.9 (204)	0.005

df, Degrees of freedom; S.D., standard deviation; WAIS-R-HK, Wechsler Adult Intelligence Scale Revised (Hong Kong version); WMS-R-HK, Wechsler Memory Scale Revised (Hong Kong version); MWCST, Modified Wisconsin Card Sorting Test.

Table 3. *Symptom ratings of patients with first-episode schizophrenia-spectrum disorder across 3 years of follow-up[a]*

Assessment time point	Patients categorized as short *v*. long DUP group	PANSS positive symptom score	HEN total score
Intake evaluation	DUP <180 days	20 (6.2)	12.2 (11.5)
	DUP ≥180 days	19.8 (4.7)	14.6 (11.8)
Clinical stabilization	DUP <180 days	9.0 (2.5)	10.8 (9.9)
	DUP ≥180 days	9.4 (2.7)	10.7 (9.4)
Year 1 assessment	DUP <180 days	8.7 (3.6)	8.5 (8.6)
	DUP ≥180 days	9.3 (3.1)	12.8 (10.5)
Year 2 assessment	DUP <180 days	8.8 (3.1)	10.0 (10.9)
	DUP ≥180 days	9.1 (3.3)	13.3 (11.2)
Year 3 assessment	DUP <180 days	8.9 (3.9)	7.7 (10.0)
	DUP ≥180 days	9.3 (3.0)	12.0 (13.1)*

DUP, Duration of untreated psychosis; PANSS, Positive and Negative Syndrome Scale; HEN, High Royds Evaluation of Negativity Scale.

Data are given as mean (standard deviation).

[a] Analysis of covariance was conducted with sex and Premorbid Adjustment Scale total score as covariates.

*$p < 0.05$.

between the two groups at other time points although there was a trend indicating that patients with a long DUP exhibited a worse outcome on negative symptoms from 12 months onwards compared with those with a short DUP. The two groups did not differ in the severity of positive symptoms at all time points (Table 3).

Cognitive outcomes

There were no significant differences between the two groups in baseline cognitive measures with the exception that the short DUP group outperformed the long DUP group in the visual reproduction test (delayed recall) ($F_{1,76} = 60.3$, $p < 0.05$). Subjects with a

Table 4. *Scores on cognitive measures of patients with first-episode schizophrenia-spectrum disorder across 3 years of follow-up*

Cognitive function[a]	Clinical stabilization		Year 1		Year 2		Year 3	
	DUP <180 days	DUP ≥180 days	DUP <180 days	DUP ≥180 days	DUP <180 days	DUP ≥180 days	DUP <180 days	DUP ≥180 days
Information subset	14.5 (5.8)	14.9 (5.2)						
Digit span forward	11.5 (2.2)	11.4 (1.9)	12.1 (2.3)	12.1 (1.4)	12.0 (2.0)	12.1 (1.4)	11.7 (2.2)	12.2 (1.3)
Logical memory, immediate recall	39.0 (17.0)	32.7 (17.2)	37.2 (16.0)	34.7 (16.1)	42.5 (16.0)	31.8 (16.2)**	45.1 (17.3)	35.3 (14.6)**
Logical memory, delayed recall	32.4 (18.0)	25.4 (16.6)	33.0 (16.6)	29.7 (14.4)	38.1 (17.9)	26.4 (16.8)***	42.8 (17.8)	30.7 (16.7)**
Visual reproduction, immediate recall	20.8 (3.3)	19.5 (3.7)	20.6 (3.8)	19.6 (3.4)	20.4 (3.6)	19.3 (3.2)	21.3 (3.8)	20.6 (2.8)
Visual reproduction, delayed recall	20.5 (3.0)	18.8 (4.1)*	20.3 (3.4)	18.8 (3.5)	20.4 (3.9)	19.3 (2.9)	21.2 (3.8)	20.5 (2.7)
Semantic category fluency	17.2 (4.4)	17.2 (4.8)	17.9 (5.1)	17.3 (5.1)	18.2 (6.5)	17.7 (5.1)	18.6 (5.7)	18.0 (4.8)
MWCST categories completed	4.5 (2.1)	4.1 (1.9)	5.2 (1.8)	5.1 (1.5)	5.3 (1.7)	5.2 (1.8)	5.3 (1.8)	5.4 (1.4)
MWCST perseverative errors	4.3 (4.8)	5.0 (6.2)	1.7 (2.2)	3.0 (4.7)	1.6 (3.2)	3.0 (6.9)	1.1 (2.5)	1.8 (4.6)

DUP, Duration of untreated psychosis; MWCST, Modified Wisconsin Card Sorting Test.

Data are given as mean (standard deviation).

[a] Analysis of covariance was conducted with sex and Premorbid Adjustment Scale total score as covariates.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

short DUP scored significantly higher in the logical memory test (both immediate and delayed recall) than those with a long DUP at 24 months (immediate recall: $F_{1,77} = 12.5$, $p = 0.001$; delayed recall: $F_{1,77} = 13.5$, $p < 0.001$) and 36 months (immediate recall: $F_{1,77} = 11.0$, $p = 0.001$; delayed recall: $F_{1,77} = 13.3$, $p = 0.001$). No significant differences were found in other cognitive measures at subsequent follow-ups (Table 4).

Comparison between short and long DUP groups across the 3-year follow-up period

Symptom outcomes

Results from a repeated-measures ANCOVA, controlling for the effects of sex and pre-morbid adjustment, showed that the main between-subject effect of DUP on negative symptoms was significant ($F_{1,73} = 4.2$, $p < 0.05$). This indicates that the short DUP group had fewer negative symptoms than the long DUP group across the 3-year follow-up period. The within-subject effect and time × group interaction did not reach statistical significance. No significant results were found for positive symptom scores for all main effect and interaction analyses.

Cognitive outcomes

The longitudinal analysis revealed a significant main between-subject effect of DUP on both immediate and delayed recall of logical memory (immediate recall: $F_{1,71} = 7.4$, $p < 0.05$; delayed recall: $F_{1,71} = 8.5$, $p < 0.05$). The results thus suggest that the short DUP group scored higher than the long DUP group in both immediate and delayed recall of logical memory across all time points. The interactions between DUP and logical memory were significant (immediate recall: $F_{3,213} = 3.6$, $p < 0.01$; delayed recall: $F_{2.7,190.9} = 4.4$, $p < 0.01$), with the within-subject contrast test showing a significant change between 12 and 24 months after intake assessment (immediate recall: $F_{1,71} = 12.4$, $p = 0.001$; delayed recall: $F_{1,71} = 15.4$, $p < 0.001$). There was no significant within-subject effect of logical memory observed. No significant main between-subject effect of DUP on other cognitive measures or group × time interaction effect was found.

Impact of DUP on cognition when negative symptoms were taken into consideration

As our results indicated that DUP was significantly associated with the severity of both negative symptoms and logical memory impairment at 36 months, and the literature suggested that cognitive functions were correlated with negative symptoms in schizophrenia particularly on a cross-sectional basis (Harvey

et al. 2006), Pearson correlation analysis was thus conducted to examine the relationship between logical memory and negative symptoms at 36 months. Negative symptom level was found to be significantly correlated to both immediate ($r = -0.35$, $p = 0.001$) and delayed ($r = -0.36$, $p < 0.001$) recall of logical memory. To control for the potential confounding effect of negative symptoms on memory functions, we repeated cross-sectional (ANCOVA at 36 months) and longitudinal (repeated-measures ANCOVA) analyses with logical memory as the dependent variable and negative symptom rating at 36 months as a covariate along with sex and pre-morbid adjustment. The short DUP group was found to perform significantly better than the long DUP group in logical memory at the end of the 3-year follow-up (immediate recall: $F_{1,77} = 7.7$, $p < 0.01$; delayed recall: $F_{1,77} = 9.7$, $p < 0.01$). Repeated-measures ANCOVA revealed a significant main between-subject effect of DUP on logical memory (immediate recall: $F_{1,71} = 4.2$, $p < 0.05$; delayed recall: $F_{1,71} = 5.2$, $p < 0.05$) and significant group × time interactions (immediate recall: $F_{3,207} = 3.9$, $p < 0.01$; delayed recall: $F_{2.7,185.2} = 4.3$, $p < 0.01$) with significant change lying between 12 and 24 months after intake assessment. Thus, associations between DUP and logical memory remained significant even when negative symptoms were taken into consideration.

Discussion

The aim of the present study was to evaluate prospectively the impact of DUP on clinical and cognitive outcomes in patients presenting with first-episode schizophrenia. Our findings indicated that patients with a short DUP showed fewer negative symptoms and more improvement in verbal memory over the 3-year follow-up period.

While the literature mostly suggests a lack of an association between DUP and negative symptoms at initial presentation in patients experiencing first-episode schizophrenia (Addington *et al.* 2004; Harris *et al.* 2005; Jeppesen *et al.* 2009), results with regard to the impact of DUP on negative symptoms at follow-up are less consistent. Some investigators have posited that the observed relationship between DUP and negative symptoms may be partly spurious and confounded by pre-morbid functioning which has been shown to predict the severity of negative symptoms (Harris *et al.* 2005; Jeppesen *et al.* 2009). Our results, which are in agreement with two meta-analyses (Marshall *et al.* 2005; Perkins *et al.* 2005) and several past reports (Scully *et al.* 1997; Harrigan *et al.* 2003; Melle *et al.* 2008), showed that DUP predicts outcome on negative symptoms when the effect of pre-morbid adjustment is adjusted. Further, our findings revealed

differential trajectories of negative symptoms in two DUP groups. We found similar levels of negative symptoms between the two groups at intake and at the time when their first psychotic episodes were stabilized with treatment. However, by the end of the first year of follow-up, there was a trend suggesting a further decrease in negative symptoms in the short DUP group and an accumulation of negative symptoms in the long DUP group, with difference in symptom severity between the two groups reaching significance at the end of the 3-year follow-up. Thus, our results provide further support to an independent contribution of DUP to clinical outcome in which schizophrenia patients with longer DUP tend to exhibit an accrual of negative symptoms over the initial 3 years after treatment initiation. In fact, some researchers have suggested that a prolonged DUP may predict the subsequent development of persistent negative symptoms (Edwards *et al.* 2002; Malla *et al.* 2004).

Consistent with previous studies (Mesholam-Gately *et al.* 2009), our results showed that patients with first-episode schizophrenia had prominent cognitive impairment at baseline when compared with healthy controls. In line with most (Hoff *et al.* 2000; Norman *et al.* 2001; Ho *et al.* 2003; Addington *et al.* 2004), but not all prior reports (Joyce *et al.* 2002; Lappin *et al.* 2007), we found no significant association between DUP and most baseline cognitive functions. Two intriguing findings emerged in this study regarding the impact of DUP on longitudinal cognitive outcomes. First, among various cognitive functions, patients with a longer DUP were significantly more impaired in two specific areas, namely verbal and visual memory. Second, the effects of DUP on temporal evolution of these two memory deficits were different. A significant difference between the short and long DUP groups on visual memory was observed only at the time of clinical stabilization, with the former outperforming the latter. Conversely, patients with a longer DUP were found to have greater verbal memory impairment than those with a short DUP at the end of the second and the third years of follow-up. Thus, our findings indicate that among various cognitive domains, DUP may have a specific effect on memory function. In addition, DUP may impose short-term adverse effects on visual memory in the early phase of recovery from the first psychotic episode, while it may cause longer-term effects on verbal memory at a later stage of the recovery process. In this regard, our results were consistent with some earlier studies (Scully *et al.* 1997; Amminger *et al.* 2002) that prolonged DUP was related to worse cognitive outcomes.

It is important to note that thus far very few prospective first-episode studies have been conducted to

examine the influence of DUP on longitudinal cognitive outcomes, and, contrary to our results, most failed to find an inverse relationship between DUP and cognitive functions at follow-up (Townsend *et al.* 2002; Addington *et al.* 2004; Rund *et al.* 2007; Barnes *et al.* 2008; Goldberg *et al.* 2009). One possible reason for such discrepancy may relate to the timing of assessments and length of follow-up. Those few studies that revealed negative findings had a duration of follow-up that ranged from 4 months to 2 years only (Townsend *et al.* 2002; Addington *et al.* 2004; Rund *et al.* 2007; Barnes *et al.* 2008; Goldberg *et al.* 2009). In fact, their findings of no significant relationship between DUP and cognitive impairment at 1 year after treatment initiation were replicated by our study. Thus, it raises the possibility that previous research with short study periods may fail to detect the impact of DUP on cognitive function as such a relationship may become more evident only with a longer duration of follow-up. The inconsistent findings may also be attributable to the variation of diagnostic scope and DUP of the samples studied. In particular, for those two prospective studies that had a follow-up duration of up to 2 years, both recruited subjects with diagnoses encompassing a wider spectrum of functional psychoses such as affective disorders (Rund *et al.* 2007) and other non-affective psychoses including delusional disorder and brief psychotic disorder (Addington *et al.* 2004; Rund *et al.* 2007) in comparison with a more narrowly defined schizophrenia-spectrum disorder that was examined in our study. In addition, a cohort of one study had a relatively short median DUP [8 weeks in Rund *et al.* (2007) *v.* 26 weeks in Addington *et al.* (2004) and 180 days in this study], which may minimize the likelihood of observing an association between DUP and cognitive outcomes.

Concerning the relationship of prolonged DUP to worse cognitive outcomes, one possible explanation is that DUP may be biologically deleterious to the brain (Wyatt, 1991). There is evidence that indicates that a longer DUP is linked to greater grey matter volume reductions (Keshavan *et al.* 1998; Lappin *et al.* 2006; Bangalore *et al.* 2009; Malla *et al.* 2011), including the hippocampus (Ebdrup *et al.* 2010; Penttila *et al.* 2010), a brain region that is critically involved in the memory system (Tulving & Markowitsch, 1998). Thus, it is plausible that a prolonged DUP may result in greater brain structural deficits with consequently more pronounced cognitive dysfunction. Nonetheless, it should be noted that results regarding the impact of DUP on brain morphology remain unclear, with some studies failing to find such a relationship (Hoff *et al.* 2000; Ho *et al.* 2003; Boonstra *et al.* 2011). More research should therefore be conducted to clarify the relationship between DUP and brain structural abnormalities.

Alternatively, DUP may be an epiphenomenon of prognostic factors and a marker of a subset of schizophrenia patients having poor clinical and cognitive outcomes (McGlashan, 1999). However, in the current analysis, potential confounding effects of pre-morbid adjustment and sex were adjusted and the two DUP groups showed no significant difference in current intelligence quotient (IQ) estimate. Further, the postulation that greater cognitive impairment may lead to protracted DUP via delayed effective help-seeking (Lappin *et al.* 2007) could not account for our findings of significant association between DUP and longitudinal cognitive outcome as the two DUP groups did not differ in most cognitive measures at baseline.

The study results have to be interpreted considering the following methodological limitations. First, measurement of DUP is inherently retrospective, with potential recall bias. We employed a structured interview incorporating multiple sources of information from patients, relatives and medical records to improve the reliability of DUP assessment. Second, cumulative active positive symptoms after treatment initiation were not measured in this study. However, unresolved positive symptoms may contribute to worse outcomes on negative symptoms and cognition, as recent studies have revealed that a longer duration of active psychosis (including both DUP and length of active psychotic state during treatment) is associated with larger grey matter volume reduction and ventricular enlargement (Cahn *et al.* 2009). Third, our final sample comprised slightly more females than males, which was contrary to many (Marshall *et al.* 2005), but not all first-episode studies (Oosthuizen *et al.* 2005; Ucok *et al.* 2006) showing male preponderance, and thus may limit the generalizability of our results. One possible reason was that we recruited patients aged from 18 to 55 years with a relatively older mean age of entry (31.2 years); therefore it may be more likely for female schizophrenia patients to be included in our study as the literature shows that females have an older age of illness onset than males and a second (though smaller) peak age of onset in their 40s (Häfner *et al.* 1993; Castle *et al.* 1998). Fourth, healthy controls were assessed once at baseline without being followed up in parallel with schizophrenia patients for 3 years; thus the magnitude of practice effect on trajectories of cognitive functions could not be addressed in this study. Fifth, the number of subjects included in this study was modest and the drop-out rate of 29% may compromise the validity of our results. The potential attrition bias may partly be minimized by the lack of significant differences between completers and non-completers with regard to sociodemographics, psychopathological scores and cognitive functions at baseline. Our drop-out rate was also comparable with

that of several previous longitudinal first-episode studies (approximately 25–35% within 1 to 4 years of follow-up; Harrigan *et al.* 2003; Clarke *et al.* 2006; Jeppensen *et al.* 2008). Nonetheless, replication by further studies with a larger sample size is warranted to confirm our findings of an independent contribution of DUP to cognitive outcome.

In conclusion, our results provided further supportive evidence that prolonged DUP is associated with worse outcomes on cognition and negative symptoms in the early phase of schizophrenia even when potential confounders including pre-morbid adjustment are controlled for. Length of untreated initial psychosis was found to exert differential effects on various cognitive domains, with deficits in memory function being most related to DUP. The impact of DUP on memory dysfunction, particularly verbal memory impairment, may only become evident at a later stage of recovery from the first psychotic episode. Owing to limited data on the relationship between DUP and cognitive impairment, more prospective research with longer follow-up duration should be conducted to clarify whether treatment delay in the first psychotic episode independently predicts longitudinal cognitive outcomes.

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