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Duration of untreated psychosis and neurocognition in first-episode psychosis: A meta-analysis

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ABSTRACT

Neurocognitive impairment is a well-established feature of first-episode psychosis (FEP). Neurotoxicity hypothesis of psychosis suggests that untreated psychosis before the initiation of first effective treatment is associated with loss of acquired cognitive abilities. However, the outcome of the studies investigating the relationship between duration of untreated psychosis (DUP) and cognitive impairment in FEP remains inconclusive. No previous meta-analysis investigating the relationship between DUP and cognitive impairment in FEP has been published. Following the systematic review of FEP studies, a random-effects meta-analysis of the relationship between DUP and neurocognition in schizophrenia was conducted. Current meta-analysis included 27 studies including 3127 patients with first-episode psychosis. Overall, DUP and cognitive abilities were not significantly related, with the exception of evidence for a weak relationship with a single cognitive domain. There was a very small but significant association between longer DUP and reduced performance in planning/problem-solving ability ($r = -0.09$, $CI = -0.14$ to -0.03). Current findings do not provide support for the neurotoxicity hypothesis of psychosis.

1. Introduction

Schizophrenia is associated with significant cognitive impairment (Heinrichs and Zakzanis, 1998; Bora et al., 2009; Mesholam-Gately et al., 2009; Schaefer et al., 2013; Bora, 2016). Cognitive impairment in schizophrenia has a significant effect on the level of functioning in individuals with schizophrenia (Fett et al., 2011; Hoe et al., 2012).

Cognitive deficits in schizophrenia are evident not only in chronic patients but also at first-episode (Mesholam-Gately et al., 2009; Bora and Pantelis, 2013; Aas et al., 2014; McCleery et al., 2014; Bora and Pantelis, 2015).

Several models have been proposed to explain the pronounced cognitive deficits which are evident from the beginning of the illness in schizophrenia. Neurodevelopmental model suggests that cognitive deficits in schizophrenia are mostly a consequence of problems in acquisition of cognitive abilities (developmental lag or arrest) during development (Weinberger, 1986; Murray and Lewis, 1987; Bora, 2015; Testa and Pantelis, 2009). It is widely accepted that neurodevelopmental factors play a significant role in cognitive impairment in schizophrenia. Also, emergence of psychotic symptoms might interfere with normal maturation of advanced cognitive abilities (i.e planning/problem-solving) which are complete until late adolescence/early adulthood. However, neurotoxicity hypothesis of psychosis suggests that cognitive deficits might also emerge as a consequence of untreated active psychosis in early years of the illness (Lieberman et al., 1993; Sheitman and Lieberman, 1998;Wyatt, 1991). There is usually a delay between the emergence of first psychotic symptoms and initiation of treatment. The time elapsing between onset of first psychotic symptoms and initiation of first effective intervention has been defined as the duration of untreated psychosis (DUP) (Marshall et al., 2005; Polari et al., 2011). The neurotoxicity hypothesis suggests that longer DUP can lead to structural brain changes and cognitive deficits in FEP.

Available evidence suggests that there is a modest but significant relationship between longer DUP and poor symptomatic and functional outcomes in FEP (Harrigan et al., 2003; Penttila et al., 2014). However, the studies investigating the relationship between DUP and cognitive deficits in FEP provided a weaker support for neurotoxicity hypothesis (Rund et al., 2004). While some studies found a positive association between longer DUP and cognitive impairment, most studies found no significant relationship between DUP and neurocognition in FEP (Rund, 2014).

The negative findings in studies investigating the relationship between DUP and neurocognition in FEP might be related to a number of factors including the low statistical power of the individual studies and heterogeneity of cognitive impairment in psychotic disorders (Reser et al., 2015; Bora et al., 2016; Bora, 2016). A meta-analysis might be

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beneficial in improving the statistical power by increasing sample size. To our knowledge, no previous meta-analysis investigating the relationship between DUP and neurocognition has been published. In this paper, a meta-analysis of the relationship between cognitive impairment and DUP in FEP was conducted for providing a reliable estimate of the strength of the potential relationship. We also aimed to investigate the effect of potential factors including diagnosis and demographic factors on the strength of the relationship between DUP and neurocognition. The primary hypothesis of the current meta-analysis was that there would be a significant relationship between longer DUP and cognitive impairment in FEP. We also hypothesized that the relationship between DUP and neurocognition would be particularly evident for advanced cognitive abilities which still continue to develop in late adolescence and early adulthood.

2. Methods

2.1. Study selection

PRISMA guidelines were used in conducting this meta-analysis (Moher et al., 2009). A literature search was conducted using the databases Pubmed and Scopus to identify the relevant studies (January 1980 to February 2017) using the combination of keywords as follows: ("duration of untreated psychosis" and "cogn*"). Reference lists of published reports were also searched for additional studies. Literature search was conducted independently by E.B and BY and final selection of articles were decided in a joint meeting of authors. Inclusion criteria for the studies were: (1) Relationship between DUP and cognitive functions were investigated in a sample of patients with first-episode psychosis; (2) Reported sufficient data to calculate the effect size and standard error for the strength of relationship between DUP and cognitive impairment. DUP was defined as the number of weeks between first psychotic symptoms to date of initiation of first effective treatment. To obtain unreported data and information, we contacted to authors of the included studies (See Acknowledgment). The quality of studies included was assessed using the selection and quality of outcome ascertainment sections (maximum score = 8) of a modified (for cross-sectional studies) version of the Newcastle-Ottawa Scale (Wells et al., 2000).

2.2. Statistical analyses

The effect size for neurocognition-DUP correlations (Pearson and Spearman's r coefficients) for each cognitive domain were pooled to calculate a single effect size for each study when more than one cognitive tests were available for a cognitive domain. A problem in the meta-analysis of correlation coefficients concerns the handling of the missing value owing to some studies reporting that a result was non-significant without providing exact statistics. We were able to obtain exact statistics of non-significant findings from authors for a number of studies (See acknowledgement). For the missing values in a few remaining studies (0 to 3 missing values for each cognitive domain (median number of missing values is 1)), we assigned the mean effect size of the studies that report an insignificant effect size. In the case of finding a significant correlation between DUP and particular cognitive domain, we also repeated the analysis with a highly conservative method in which values of $r = 0$ was given to missing values.

Cognitive domains included in the current review were the IQ, verbal memory, visual memory, working memory, processing speed, sustained attention, speed based executive functions (EF-speed), planning/problem solving and verbal fluency (See eTable 1 in the supplement for cognitive tests under each domain). An average effect size for global cognition was calculated by averaging all available cognitive domains. It was also possible to conduct individual task meta-analyses for several measures including digit symbol test, trail making A (TMT-A) and B (TMT-B) tests, category fluency, Wisconsin card sorting test (WCST) perseverative errors and the number of categories achieved.

Meta-analyses were performed using packages in R environment (Metafor) (Viechtbauer, 2010). Pearson r correlations were analyzed after Fisher's Z transformation was applied (Hedges and Olkin, 1985). Effect sizes were weighted using the inverse variance method and a random effects model (DerSimonian–Laird estimate) (p-value for significance <0.05). Homogeneity of the distribution of weighted effect sizes was tested with the Q-test and I^2 test. I^2 values of 25%, 50%, and 75%, correspond to small, moderate, and large heterogeneity. Tau-squared (τ^2), an estimate of between-study variance, was used as a measure of the magnitude of heterogeneity in the random effects model. The possibility of publication bias was assessed by trim and fill method and inspection of the funnel plot of Fisher's Z-transformed correlation coefficient and standard error. For analyses including at least 10 studies, Egger's test was also used to assess asymmetry of funnel plots.

Meta-regression analyses were conducted to investigate the effect of demographic (age, sex (ratio of males), duration of education), quality score and percentage of schizophrenia patients within FEP sample on the strength of the association between global cognition and DUP. If a significant relationship was found between a reduced performance in a cognitive domain and longer DUP, a subgroup analysis investigating the effect of diagnosis in FEP (schizophrenia only vs mixed) on this relationship was also conducted. Meta-regression analyses performed with a random-effects model were conducted using the restricted-information maximum likelihood method with a significance level set at $p < 0.05$.

3. Results

The selection process is summarized in Fig. 1. A total of 27 studies were included in the meta-analysis (Table 1). Twenty-five of these studies, including 3127 patients with FEP (61.7% males, mean age = 26.6) were selected as main studies and 2 overlapping studies (Leeson et al., 2010; Malla et al., 2011) included only for the outcome of cognitive variables not reported in two of the main studies. Six of these FEP studies included only schizophrenia patients and 19 studies also included some patients with schizophreniform disorder and other schizophrenia-spectrum disorders. Six of these studies also included some patients with affective psychoses.

In meta-analyses of global cognition and cognitive domains, the distribution of effect sizes was homogeneous for all but processing speed ($Q = 18.5$, $p = 0.03$) (Table 2). The magnitude of the heterogeneity for processing speed was modest ($I^2 = 51\%$, $\tau^2 = 0.01$). There was no significant correlation between DUP and global cognition ($r = -0.03$, $p = 0.14$) (Fig. 2; Table 2). For studies that used samples only consisting of patients with FE schizophrenia, the mean weighted correlation coefficient between DUP and global cognition was not significant either ($r = -0.05$, $p = 0.17$). There was no significant correlation between DUP and IQ (Table 2). The only cognitive domain that was significantly correlated with DUP was planning/problem-solving ability (Fig. 3). Low performance in planning/problem-solving was significantly associated with longer DUP ($r = -0.09$, $p = 0.003$). When we repeated this analysis with a more conservative approach (assigning $r = 0$ to the single study with missing value for planning/problem solving), longer DUP and low performance in planning/problem-solving were remained to be significantly correlated ($r = -0.08$, $CI = -0.14$ to -0.03, $z = 2.86$, $p = 0.004$). DUP was not significantly associated with other cognitive domains including verbal memory, visual memory, working memory, sustained attention, fluency, EF-speed and processing speed (Table 2). In individual task meta-analyses, longer DUP was associated with poor performance in both WCST measures ($r = -0.10$ and -0.13), but other cognitive measures including TMT-A, TMT—B, digit symbol and category fluency were not significantly related to DUP (Table 2). The distribution of effect sizes was modestly heterogeneous for category fluency ($I^2 = 68\%$, $\tau^2 = 0.02$) and TMT-A ($I^2 = 67\%$, $\tau^2 = 0.02$).

There was evidence of publication bias for two cognitive domains (processing speed and fluency) in funnel plots (inspection and Egger's test for asymmetry). The strength of trend-level correlations between

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