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Review

A comparative meta-analysis of neurocognition in first-degree relatives of patients with schizophrenia and bipolar disorder

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ABSTRACT

Objective: Cognitive impairment is a familial and heritable aspect of major psychoses and might be a shared vulnerability marker for schizophrenia and BP. However, it is not clear whether some aspects of cognitive deficits are uniquely associated with risk for specific diagnoses.
Methods: A novel meta-analysis of cognitive functions in first-degree relatives of probands with bipolar disorder (BP-Rel) and schizophrenia (Sch-Rel) was conducted. Current meta-analysis included 20 studies and compared cognitive functions of 1341 Sch-Rel, 939 BP-Rel and 1427 healthy controls.
Results: Sch-Rel was associated with cognitive deficits in all domains (d = 0.20–0.58) and BP-Rel underperformed healthy controls in processing speed, verbal fluency and speed based executive function tests (d = 0.33–0.41). Sch-Rel underperformed BP-Rel in general intellectual ability, working memory, verbal memory, planning, processing speed and fluency (d = 0.24–0.42).
Conclusions: Inefficiency in processing information and impaired processing speed might be common vulnerability factors for major psychoses. On the other hand, low performance in accuracy based tasks and deficits in general intellectual ability, verbal learning, planning and working memory might be more specifically associated with risk for schizophrenia.

1. Introduction

Schizophrenia and bipolar disorder (BP) show a partial but significant overlap of genetic risk factors and familial co-aggregation. The results of genome-wide association studies suggest that commonly occurring genetic risk variants are associated with shared but also unique contributions to schizophrenia and BP. On the other hand, rare chromosomal structural variants, (i.e., copy number variants), are more specifically associated with schizophrenia risk [1]. Shared and nonshared genetic risk factors of major psychoses (including schizophrenia and BP) might be associated with different abnormalities in neural networks. Neuropsychological studies have been widely used to investigate behavioral correlates of potential abnormalities in brain structure and function related to vulnerability to schizophrenia and BP. Cognitive deficits might be vulnerability factors for major psychoses in general but some aspects of cognitive impairment might be more specifically associated with specific diagnoses such as schizophrenia and BP.

Current evidence suggests that cognitive impairment, while more severe in schizophrenia, is a shared feature of both disorders [2]. Schizophrenia and BP are associated with cognitive impairment in a number of domains including memory, processing speed, sustained attention and executive functions [3–6]. Cognitive deficits are already evident in first-episode of schizophrenia and BP [7–9]. However, it is not possible to identify core cognitive deficits related to vulnerability to major psychoses in patients with established illness. The studies in unaffected first-degree relatives of patients might be particularly important to differentiate cognitive impairment related to vulnerability to major psychoses from secondary deficits which might emerge as a result of medical co-morbidity (i.e metabolic syndrome), stress, iatrogenic and other nonspecific factors [10–12].

Several meta-analyses found that cognitive deficits are evident in first-degree relatives of patients with schizophrenia [13–15]. While evidence is more mixed, first-degree relatives of probands with BP might also underperform healthy subjects in cognitive abilities [16,17]. Two meta-analyses found evidence for modest deficits in executive functions and verbal memory in

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first-degree relatives of patients with BP [5,18]. In recent years, increasing number of studies has directly compared cognitive functions in first-degree relatives of probands with schizophrenia (Sch-Rel) and BP (BP-Rel) [19–22]. The findings of these studies regarding the specificity of particular cognitive deficits to BP-Rel or Sch-Rel were largely inconsistent. Currently, it is not known which aspects of cognitive deficits are specific to vulnerability to schizophrenia and BP and which other aspects of cognitive deficits are shared among major psychoses. It is important to establish shared and specific cognitive factors for schizophrenia and BP as cognitive deficits might potentially be predictors of major psychoses in genetic and clinical high-risk subjects [13,23,24].

The inconsistent findings of studies comparing cognitive deficits in Sch-Rel and BP-Rel might be related to the low statistical power of most of the individual studies as many of the available studies have small sample sizes. A meta-analysis can be helpful to increase the statistical power and provide a reliable estimate of cognitive deficits in BP-Rel and Sch-Rel. No previous meta-analysis of studies directly comparing BP-Rel and Sch-Rel has been published before.

The main and novel goal of the current review was to conduct a meta-analysis of cognitive functions in individuals with BP-Rel in comparison to Sch-Rel. A secondary aim of the study was to estimate effect sizes for cognitive deficits in Sch-Rel and BP-Rel in comparison to healthy controls.

2. Materials and methods

2.1. Study selection

PRISMA guidelines were used in conducting this meta-analysis [25]. A literature search was conducted using the databases Pubmed and Scopus to identify the relevant studies (January 1980 to December 2016) using the combination of keywords as follows: (["bipolar disorder"] AND [schizophrenia] AND [relatives] AND ["cognition]). Reference lists of published reports and systematic reviews were also searched for additional studies. Inclusion criteria for the studies were: (1) Compared cognitive functions in BP-Rel and Sch-Rel; (2) Reported sufficient data to calculate the effect size and standard error of the cognitive measure including results of parametric statistics (i.e. t and F values). In addition to the effect size for cognitive difference between BP-Rel and Sch-Rel, the effect sizes for cognitive differences between relative groups and healthy control group were also coded. To avoid error in data extraction, every empirical study was coded twice. Studies investigating samples with very high genetic risk (twin and relatives from multiplex families) were excluded, as the number of these studies was too small for a meaningful analysis. Additional studies, which are based on, shared or overlapping samples with the selected study were also excluded.

2.2. Statistical analyses

The effect sizes (*Cohen d*) were calculated for each of the cognitive variables. Minimum number of studies required to conduct a meta-analysis for a particular cognitive variable was accepted as four in this current meta-analysis. When there were more than one cognitive variable for a cognitive domain, the effect sizes for cognitive domain was calculated by averaging effect sizes of individual cognitive tests. Cognitive domains included in the current review were the IQ, verbal memory, visual memory, processing speed, sustained attention, executive functions, working memory and verbal fluency (eTable 1 in the supplement for cognitive tests under each domain). Executive function tests were further divided as speed and accuracy based scores. Accuracy based tasks were measuring planning (and problem solving/reasoning) abilities. An average effect size for neurocognition (global cognition) was calculated by IQ or averaging all available cognitive domains to be used in subgroup and meta-regression analyses (See below). It was also possible to conduct individual task meta-analyses for several measures including trail making test (TMT) A and B, delayed recall score in list learning tasks, Stroop interference, Wisconsin card sorting test (WCST) perseverative errors and the number of categories achieved.

Meta-analyses were performed using packages in R environment (Open Meta Analyst, Metafor) [26,27]. Effect sizes were weighted using the inverse variance method and a random effects model (DerSimonian–Laird estimate) (P-value for significance < 0.05). Previous simulation studies suggested that use of inverse variance rather than sample size in weighting d values of studies in a meta-analysis leads to more accurate results [28]. Random-effects model was selected as heterogeneity for the distribution of effect sizes was expected for cognitive studies in relatives of patients with schizophrenia and BP. Random effects model, unlike fixed-effects approach, assumes not only within-study variance but also between-study variance. This approach is preferable in this meta-analysis as there is considerable heterogeneity of cognitive tasks used and characteristics of participants across available studies in neurocognitive research in psychotic and affective disorders. Homogeneity of the distribution of weighted effect sizes was tested with the Q-test and I^2 test. 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 inspection of funnel plots and Egger's test was also used to assess asymmetry when 8 or more studies were available.

Meta-regression analyses were conducted to investigate the effect of demographic variables on group differences in cognition between Sch-Rel and BP-Rel. The demographic measures included were age (age of Sch-Rel), gender (ratio of males in Sch-Rel) and duration of education (effect size of between-group difference). Meta-regression analyses performed with a random-effects model were conducted using the restricted-information maximum likelihood method with a significance level set at $P < 0.05$. It was possible to conduct these analyses for global cognition (age, gender, and education), IQ (age and gender), Working memory (age and gender) and executive functions (age and gender) but not for other variables that were reported by less than 10 studies.

3. Results

The selection process is summarized in Fig. 1. Three studies including twin or multiplex families were excluded. Three other studies were excluded as they were based on overlapping samples with other studies included. A total of 20 studies (21 reports) were included in the meta-analysis (Table 1) [19,20,29–47].

3.1. Sch-Rel vs healthy controls

A total of 19 studies consisting of 1314 Sch-Rel (58.1% women) and 1427 healthy controls (57.3% women) healthy controls were included in the meta-analysis. The groups were well matched for gender (RR = 1.01, CI = 0.94–1.08, $Z = 0.15$, $P = 0.88$). There was no significant between-group difference for age ($d = 0.05$, CI = −0.10–0.21, $Z = 0.66$, $P = 0.51$).

In meta-analyses of cognitive functions, distributions of effect sizes were heterogeneous in verbal and visual memory, IQ, processing speed and executive functions (Table 2). The level of heterogeneity was large for three domains (visual memory,

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