European Psychiatry 44 (2017) 17–23

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Review

A meta-analysis of neurocognition in youth with familial high risk for bipolar disorder

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ARTICLE INFO

Article history:
Received 31 December 2016
Received in revised form 11 February 2017
Accepted 12 February 2017
Available online 3 March 2017

Keywords:
Bipolar disorder
High-risk
Familial
Cognition

ABSTRACT

Objective: Neuropsychological impairment, including deficits in social cognition is evident in subjects at genetic high-risk for psychosis. However, findings in youth at genetic risk to bipolar disorder (BP) have been suggested to be less supportive of premorbid deficits. We aimed to conduct a meta-analysis of cognitive deficits in youth with familiar risk for bipolar disorder (FHR-BD).
Methods: A novel meta-analysis of FHR-BD (mean age 10–25), including 18 studies (786 offsprings/siblings of patients with BD and 794 healthy controls), was conducted.
Results: Both general cognition (d = 0.29, CI = 0.15–0.44) and social cognition (d = 0.23, CI = 0–0.45) were impaired in FHR-BD. In comparison to controls, FHR-BD had significant deficits in several cognitive domains, including visual memory (d = 0.35), verbal memory (d = 0.21), processing speed (d = 0.26) and sustained attention (d = 0.36). There was no significant difference between FHR-BD and controls in planning and working memory.
Conclusions: Cognitive deficits are evident in individuals who are at genetic high-risk for developing BD. Neurodevelopmental abnormalities are likely playing a role not only in schizophrenia but also in BD.

1. Introduction

Bipolar disorder (BD) is associated with neurocognitive impairment which persists in remission phase of the illness [1,2]. Meta-analytical studies in remitted BD found deficits with medium to large effect sizes (Cohen d = 0.5–0.8) in a number of cognitive domains, including executive functions, processing speed, sustained attention and verbal memory [1,3]. In BD, cognitive deficits are already evident following the first episode of mania [4,5]. However, it was argued that premorbid cognitive functioning in BD, unlike in schizophrenia might be preserved [6]. Furthermore, some evidence suggests that above-average scholastic achievement and good premorbid cognitive functioning might be associated with increased risk for developing BD [7]. Therefore, it has been proposed that development of cognitive functions might be normal in BD and patients with BD only develop cognitive deficits during the course of illness [8,9].

On the other hand, other evidence suggests that neurodevelopmental factors also play a role in BD. BD and schizophrenia are associated with a number of common susceptibility genes which have a role in neurodevelopment [10]. Some studies also suggested a link between prenatal/perinatal abnormalities and BD [11]. Neurological soft signs might also be more common in BD than healthy controls [12]. Other studies found a significant relationship between BD and increased minor physical abnormalities, perinatal oxytocin use, abnormal cortical folding and abnormal olfactory sulcus morphology [13–18]. These findings suggest that developmental cognitive deficits might be evident at least in a subset of patients with BD [19].

Genetic (“familial”) high-risk studies in offsprings and young siblings of affected individuals have been particularly useful in defining cognitive vulnerability markers of adult onset disorders such as schizophrenia [20]. The findings of these studies found that cognitive deficits are evident in young first-degree relatives of patients with schizophrenia [21,22]. In recent years, a number of studies have also investigated cognitive functions in adolescents or young adults with familial high risk for BD (FHR-BD). Some of these studies found that youth with FHR-BD have underperformed healthy controls in cognitive abilities [23,24], but others have not found significant between-group difference [25,26]. The

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http://dx.doi.org/10.1016/j.eurpsy.2017.02.483
0924-9338/

inconsistent findings of studies investigating cognitive deficits in youth with FHR-BD might be related to low statistical power of individual studies as most of the available studies have small sample sizes. A meta-analysis can be helpful to increase statistical power to establish whether FHR-BD is associated with cognitive deficits.

Our goal was to conduct a meta-analysis of cognitive abilities in youth with FHR-BD in comparison to healthy controls and estimate the effect size for different aspects of potential cognitive deficits in youth with FHR-BD. We also aimed to explore the effects of variables which can potentially affect cognitive functioning in youth with FHR-BD..

2. Material and methods

2.1. Study selection

PRISMA guidelines were used in conducting this meta-analysis [27]. A literature search was conducted using the databases Pubmed, PsycINFO and Scopus to identify the relevant studies (January 1980 to November 2016) using the combination of keywords as follows: (bipolar disorder) AND (relatives OR high-risk) AND (“cognition” OR “neuropsychol*”). Reference lists of published reports and systematic reviews were also searched for additional studies. Inclusion criteria for the qualitative part of the review were studies that:

- compared cognitive abilities in young (mean age between 10 and 25) first-degree relatives of patients with bipolar disorder (type I or II) and healthy or community controls;
- reported sufficient data to calculate the effect size and standard error of the neuropsychological measure including results of parametric statistics (i.e. *t* and *F* values).

The studies in which age of FHR-BD and healthy controls were statistically different were not included as cognitive abilities continue to develop within adolescence and young adults. Literature search was conducted by both authors and final selection of articles meeting inclusion criteria were decided in a joint meeting including both authors.

2.2. Statistical analyses

Effect size for cognitive domains were calculated by averaging effect size of individual cognitive tests in each domain. Cognitive domains included in the current review were the IQ, verbal memory, visual memory, processing speed, sustained attention, executive functions, working memory. Also, an effect size for social cognition was calculated based on ToM and emotion recognition performances (See eTable-1 in the supplement for cognitive tests under each domain). An average effect size for neurocognition was calculated by 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 list learning and delayed recall, Stroop interference, Wisconsin card sorting test (WCST) perseverative errors and the number of categories achieved.

Meta-analyses were performed using packages in R environment (OpenMetaAnalyst, Metafor) [28,29]. 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. 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.

The Q_{bet} test was used to compare the severity of deficits in neurocognition between subgroups that did or did not exclude co-morbid depression. Meta-regression analyses were conducted for investigating the relationship between cognitive impairment in FHR-BD and mean age of FHR-BD, the percentage of FHR-BD individuals with mood disorder and ADHD co-morbidity. Meta-regression analyses were only conducted when a minimum of 10 studies reported required information. 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. Two reports based on a single sample were excluded as FHR-BD and healthy control groups were not statistically matched for age. Another study was excluded as it included a FHR-BD group, unlike other studies, coming from multigenerational bipolar disorder families. A total of 18 studies consisting of 786 FHR-BD (48.4% females) and 794 (50.9% females) healthy (including community controls) controls were included in the meta-analysis (Table 1) [23–26,30–43]. There was no significant between-group difference for age ($d = -0.03$, CI = −0.13–0.07, $Z = 0.52$, $P = 0.60$). The diagnosis of bipolar disorder in FHR-BD was an exclusion criterion in all studies. In nine out of 18 studies, history of other mood disorders in FHR-BD group was excluded. In other studies, 3 to 30% of youth with FHR-BD had a history of depressive disorders (mainly, major depression). Eleven of the studies reported information regarding the history of ADHD and 15 to 36% of youth with FHR-BD had co-morbidity with ADHD.

Global cognition (IQ) ($d = 0.29$, CI = 0.15–0.44) (Fig. 2) and social cognition ($d = 0.23$, CI = 0.01–0.45) (Fig. 3) were significantly impaired in youth with FHR-BD in comparison to healthy controls (Table 2). In meta-analyses of individual cognitive domains, youth with FHR-BD performed significantly worse than healthy controls in visual and verbal memory, processing speed and sustained attention ($d = 0.21$–0.35) but not in executive functions and working memory. The distribution of effect sizes was significantly heterogeneous only for sustained attention ($I^2 = 72\%$, $\tau^2 = 0.09$). Inspection of funnel plots and Egger’s tests found no evidence of publication bias for any cognitive measure.

In individual task analyses, youth with deficit FHR-BD were significantly impaired in list learning, delayed recall and Stroop interference ($d = 0.23$–0.32) but not in WCST measures. There was heterogeneity in the distribution of effect sizes only in WCST measures ($I^2 = 72\%$, $\tau^2 = 0.09$).

The group difference between youth with FHR-BD and healthy controls was not significantly different when depression was or was not excluded ($Q_{bet} = 0.64$, $P = 0.42$). Meta-regression analyses found no significant effect of age of FHR-BD ($P = 0.33$), the percentage of individuals with depression ($P = 0.96$) and percentage of individuals with ADHD ($P = 0.70$) within FHR-BD samples of individuals studies on FHR-BD vs healthy control differences.

4. Discussion

The current meta-analysis investigated cognitive deficits in FHR-BD in comparison with healthy controls. Current findings showed that youth with FHR-BD significantly underperformed healthy controls in neurocognition and social cognition.

FHR-BD in youth (age 10–25) was associated with modest sized cognitive deficits in several domains including processing speed, sustained attention, visual and verbal memory ($d = 0.21$–0.36). However, the performance of FHR-BD and healthy controls were not different in executive functions and working memory. The