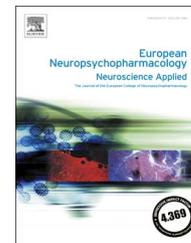




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## REVIEW

# Social cognition in first-degree relatives of patients with bipolar disorder: A meta-analysis

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## Abstract

Cognitive impairment is evident euthymic patients with bipolar disorder (BP) and in their first-degree relatives (BP-Rel). Increasing evidence suggests that BP is also associated with social cognitive impairment. It is important to establish whether social cognitive impairment is also evident in BP-Rel. A novel meta-analysis of theory of mind (ToM) and facial emotion recognition in BP-Rel including 16 studies (728 first-degree relatives of patients with BP and 865 healthy controls) was conducted. ToM ( $d=0.34$ ,  $CI=0.16-0.52$ ) was significantly impaired in BP-Rel. The effect size for the difference between BP-Rel and healthy controls was smaller for facial emotion recognition ( $d=0.17$ ,  $CI=0.16-0.29$ ) and could be nonsignificant after the effect of publication bias was taken into account. First-degree relatives of patients with BP underperform healthy subjects in social cognitive abilities, particularly in ToM. However, the effect size for between-group difference is small. ToM impairment might be a vulnerability marker of BP. © 2017 Elsevier B.V. and ECNP. All rights reserved.

## 1. Introduction

Bipolar disorder (BP) is associated with cognitive deficits in a number of domains including processing speed, executive functions, verbal memory and sustained attention (Arts et al., 2009; Balanzá-Martínez et al., 2010; Bora et al., 2009a; Cardenas et al., 2016; Cullen et al., 2016; Robinson and Ferrier, 2006; Solé et al., 2011; Torres et al., 2007; Vieta et al., 2013). Cognitive

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deficits are already evident following the first episode of mania (Daglas et al., 2015; Lee et al., 2014; Bora and Pantelis, 2015; Martino et al., 2015). First-degree relatives of probands with BP also underperform healthy subjects in cognitive abilities (Arts et al., 2009; Balanzá-Martínez et al., 2008; Bora et al., 2008; Cardenas et al., 2016; Hidroğlu et al., 2015; Miskowiak et al., 2017).

Another aspect of neuropsychological functioning is social cognition. Social cognitive abilities, including theory of mind (ToM) and recognition of emotions from facial cues, are crucial for effective interpersonal and occupational functioning. Facial emotion recognition and ToM, the ability to infer mental states of others, are impaired in schizophrenia and developmental disorders such as autism and ADHD (Bora et al., 2009b; Bora and Pantelis, 2016a; Senju, 2012). Some authors have proposed that social cognition might be relatively preserved in BP compared to schizophrenia (Lee et al., 2013). However, increasing evidence suggests that ToM and facial emotion recognition abilities are also impaired in BP (Bora et al. 2016a; Samamé et al., 2015). Social cognition might be already impaired following first-episode mania (Daros et al., 2014). BP is associated with an intermediate level of impairment both in neurocognition and social cognition compared to schizophrenia (Bora and Pantelis, 2016b).

Social cognition, like other aspects of neurocognition, might be potentially a vulnerability marker of major psychoses (Bora and Pantelis, 2013). The studies in remitted patients suggest that social cognitive impairment might be a trait-related feature of BP (Bora et al., 2005; Olley et al., 2005). However, it is not entirely possible to exclude the potential negative effects of subthreshold mood symptoms and medication on social cognition in patients with established BP. The studies in unaffected first-degree relatives of patients might be particularly important to differentiate social cognitive impairment related to vulnerability to BP from secondary deficits which might emerge as a result of medical co-morbidity (i.e. metabolic syndrome), iatrogenic and other nonspecific factors. In recent years, a number of studies have also investigated social cognition in first-degree relatives of probands with BP (BP-Rel). Some of these studies found that BP-Rel has underperformed healthy controls in facial emotion recognition and ToM (Seidel et al., 2012; Yücel et al., 2016) but others have not found significant between-group difference for social cognition (Ruocco et al., 2014; Sharma et al., 2016; Whitney et al., 2013).

The inconsistent findings of studies investigating deficits in ToM and facial emotion recognition in BP-Rel might be related to the low statistical power of most of the individual studies. Many of the available studies have small sample sizes. A meta-analysis can be helpful to increase the statistical power to establish whether BP-Rel is associated with social cognitive deficits and to reveal which aspects of social cognition are most impaired in BP-Rel. Our goal was to conduct a meta-analysis of ToM and facial emotion recognition in individuals with BP-Rel in comparison to healthy controls and estimate the effect size for different aspects of potential social cognitive deficits in these individuals.

## 2. Experimental procedures

### 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, PsycINFO and Scopus to identify the relevant studies (January 1980 to November 2016) using the combination of keywords as follows: ((bipolar disorder) AND (relatives) AND ("social cognition" OR "emotion recognition" OR "theory of mind")). 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: (1) Compared social cognition in BP-Rel and healthy controls; (2) Reported sufficient data to calculate the effect size and standard error of the social cognitive measure including results of parametric statistics (i.e.  $t$  and  $F$  values).

### 2.2. Social cognitive tasks

Several different ToM tasks have been utilized across studies, most commonly the reading the mind from the eyes test (RMET) (Baron-Cohen et al., 2001) and the Hinting task (Corcoran et al., 1995). In RMET, individuals are instructed to look at a series of photographs of just the eye region of the face, and picking which of four words best describe what the person in the photo is thinking or feeling. The Hinting task is a theory of mind (ToM) assessment that requires clients to make social judgments about the intentions of protagonists in 10 brief stories (Corcoran et al., 1995). Other ToM measures used in included studies were false belief tasks (stories and picture sequencing), Happe stories, Faux pas recognition, differentiation of sarcastic and sincere statements and referential communication task. Emotion recognition tasks included in this meta-analysis were measuring the accuracy of labeling emotions from facial cues.

### 2.3. Statistical analyses

The effect size for social cognitive domains (ToM and facial emotion recognition) were calculated by averaging effect size of individual cognitive tests under each domain. Also, an average effect size for social cognition was calculated based on ToM and emotion recognition performances. It was also possible to conduct individual task meta-analyses for several measures including the Hinting task, RMET, recognition of anger, fear, sadness and happiness.

Meta-analyses were performed using packages in R environment (OpenMetaAnalyst, Metafor) (Viechtbauer, 2010; Wallace et al., 2012). 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 ( $\tau^2$ ), 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, Egger's test and trim and fill method.

The  $Q_{bet}$  test was used to compare the severity of deficits in social cognition between older (age  $>18$ ) and younger (age  $<18$ ) BP-Rel subgroups. Meta-regression analyses were conducted for investigating the relationship between social cognitive impairment in BP-Rel and group differences in age, gender, IQ and duration of education between BP-Rel and healthy control. Meta-regression analyses were only conducted when a minimum of 8 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 Figure 1. One report based on a sample of individuals in late childhood/early adolescence was excluded as patients in BP-Rel were much younger than the control group. A total of 16 studies consisting

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