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Effects of risk for bipolar disorder on brain function: A twin and family study

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Abstract
Bipolar disorder (BPD) is associated with altered regional brain function during the performance of cognitive tasks. The relative contribution of genetic and environmental risk factors for BPD to these changes has not yet been quantified. We sought to address this issue in a functional neuroimaging study of people who varied in their risk for BPD. Functional magnetic resonance imaging was used to study 124 subjects (29 twin and 9 sibling pairs with at least one member with BPD, and 24 healthy twin pairs) performing a working memory task. We assessed the influence of risk for BPD on regional brain function during the task in a two stage process. Firstly, we identified areas where there were group differences in activation. Secondly, we estimated the heritability and phenotypic correlation of activation and BPD using genetic modeling. BPD was associated with increased activation in the anterior cingulate, orbitofrontal, medial prefrontal, and left precentral cortices, and in the precuneus. Within these regions, activation in the orbitofrontal cortex rendered the most significant heritability estimate (h^2=0.40), and was significantly correlated with BPD phenotype (r_{ph}=0.29). A moderate proportion of the genetic influences (r_g=0.69) acting on both BPD and on the degree of orbitofrontal activation were shared. These findings suggest that genetic factors that confer vulnerability to BPD alter brain function in BPD.

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1. Introduction

Bipolar disorder (BPD) has a strong genetic etiological component (Muller-Oerlinghausen et al., 2002). Clinically, patients experience core mood pathology but also altered cognitive function, including impairments in working memory (Arts et al., 2008). Working memory deficits are also seen in patients' unaffected relatives (Arts et al., 2008). Functional magnetic resonance imaging (fMRI) studies suggest that patients performing working memory tasks, show altered activation in several frontal and parietal cortical regions (Adler et al., 2004; Drapier et al., 2008; Monks et al., 2004; Townsend et al., 2010). Altered frontal activation is also seen in fMRI studies of working memory tasks in unaffected relatives, who are at familial (i.e., genetic and shared environmental) risk (Drapier et al., 2008; Thermenos et al., 2010), and in healthy people with a genetic risk allele for BPD (Bigos et al., 2010). Because working memory-related activation in healthy subjects is partially genetically influenced (Blokland et al., 2011), a key question emerges as whether altered working memory activation in bipolar patients and their relatives is linked to the genetic risk for the disorder, and could thus serve as an intermediate phenotype marker for BPD (Preston and Weinberger, 2005).

Twin studies are the best means of investigating the relationship between genetic and environmental risk and candidate intermediate phenotypes. They permit firstly the quantification of the relative influence of genetic and environmental factors on the candidate intermediate phenotype, and then on the phenotypic correlation between the intermediate phenotype and the disorder. This approach has identified significant relationships between the risk for BPD and alterations in white matter volume (van der Schot et al., 2009), frontal grey matter concentration (van der Schot et al., 2010), event-related potentials (Hall et al., 2009), and cognition such as working memory and IQ (Georgiades et al., 2016), with genetic factors the main source of these associations. Environmental risk for BPD has been linked to alterations in global grey matter volume (van der Schot et al., 2009) and peripheral inflammatory markers (Padmos et al., 2009).

The present study had two aims, firstly to investigate familial influences on differential regional activation in BPD during a working memory task. Secondly, to quantify the common genetic and environmental origins with BPD. On the basis of the existing literature, we hypothesized: (1) familial risk for BPD would be associated with altered activation in frontal and parietal regions; and (2) these alterations would be more related to genetic than to environmental factors. To test these hypotheses, we examined a sample of twin and sibling pairs with BPD, their unaffected co-twins and siblings, and healthy twin pairs. We used fMRI to assess signal change during a working memory task. In regions showing group differences in activation, genetic modeling was then used to quantify the impact of genetic and environmental sources of variation on activation, and the extent to which the covariation between BPD risk and activation was due to genetic, common environmental, and unique environmental effects.

2. Experimental procedures

2.1. Participants and assessments

Probands with BPD and their relatives were recruited nationally from clinical services, patient support groups, national media and a study website. Healthy control twins were recruited from the Institute of Psychiatry, Psychology and Neuroscience Volunteer Twin Register and national media. One hundred and twenty-four individuals participated in the study; 7 monozygotic (MZ) twin pairs concordant for BPD, 14 MZ and 8 dizygotic (DZ) discordant twin pairs (BPD patients and their unaffected co-twins), 9 discordant sibling pairs (BPD patients and their unaffected siblings), and 18 MZ and 6 DZ healthy control twin pairs. In concordant twin pairs both members, and in discordant pairs only one member met DSM-IV criteria for BPD, while their co-twin or sibling was unaffected by BPD. Diagnoses were determined by a post-graduate qualified psychiatrist using a structured clinical interview, augmented with a systematic review of the medical records. Forty three patients had bipolar I, and two bipolar II. Twenty-eight patients with BPD had experienced psychotic episodes. Two patients from MZ concordant pairs and 1 from an MZ discordant pair had a previous history of alcohol dependence, and one patient met DSM-IV criteria for panic disorder. Healthy controls and unaffected twins and siblings were screened for mental disorders using the Schedules for Clinical Assessment in Neuropsychiatry (Wing et al., 1990). Control subjects who met criteria for an Axis I disorder at the time of assessment or had a personal or family history of BPD were excluded. Among unaffected co-twins, 4 met lifetime criteria for major depressive disorder, 2 for an anxiety disorder, and 1 for a history of alcohol dependence, but all were clinically well at assessment, and included. The probability that any discordant pair would subsequently become concordant for BPD was low, as an average of 17.4 (standard deviation [SD]=11.7) years in the MZ, and 19.8 (10.2) years in the DZ/sibling pairs had elapsed since the probands illness began. Exclusion criteria for all subjects included organic brain disease, significant head trauma, and drug or alcohol dependence in the 12 months before participation. Zygosity was confirmed by DNA analysis of blood or cheek swab samples. Full-scale IQ was assessed using Wechsler Adult Intelligence Scale-R (Wechsler, 1981) or Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999), and standardized using the mean and SD of the control sample. Handedness and parental socio-economic status were assessed using the Annett Handedness Questionnaire (Annett, 1970) and the Standard Occupational Classification (Great Britain, 1995) respectively, and current mood using the Beck Depression Inventory (BDI) (Beck et al., 1961) and the Altman Self-Rated Mania Scale (ASRM) (Altman et al., 1997). All patients were clinically stable and had been taking regular medication for at least one month before participation. After ethics committee approval, written informed consent was obtained from all participants.

2.2. Demographic, clinical, and behavioral data analysis

Group effects were analyzed using a regression model with standard errors that are robust against familial correlations (Binder, 1983; Picchioni et al., 2010). Regression and logistic regression with the Huber–White sandwich standard error were used to compare demographic, clinical, and behavioral variables while taking account of family clusters. We carried out overall group comparisons followed by *post-hoc* pair-wise comparisons where the initial test was significant using established testing models (Picchioni et al., 2006, 2010) in STATA 10.1.