



## Psychiatric disorders in child and adolescent offspring of patients with schizophrenia and bipolar disorder: A controlled study



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### ABSTRACT

**Background:** Early clinical manifestations predating schizophrenia (SZ) and bipolar disorder (BP) have not been fully characterized. Child offspring studies are a valuable opportunity to study the natural history of the illness from its earliest stages. However, there is limited evidence assessing young offspring of SZ and BP simultaneously. We set out to assess rates of psychiatric disorders in child and adolescent offspring of SZ and BP, relative to offspring of community controls, so as to characterize the early phenotype of the disorders comparatively.

**Methods:** SZ and BP parents with offspring aged 7–17 years were recruited through adult mental health services of two tertiary hospitals. Community control (CC) parents were recruited from the same geographical area. Ninety BP-offspring, 41 SZ-offspring and 107 CC-offspring were assessed using the K-SADS-PL by child psychiatrists blinded to parental status. Differences in prevalence of psychiatric disorders between groups were adjusted for confounders and for sibling correlation using generalised estimating equations.

**Results:** We found a gradient of clinical severity and social disadvantage between SZ, BP and CC-offspring. After adjusting for socio-demographic confounders, SZ and BP-offspring presented higher rates of attention deficit hyperactivity disorder (ADHD) than CC-offspring. ADHD was more prevalent in SZ-offspring than BP-offspring, and BP-offspring presented a higher prevalence of depression than CC-offspring.

**Conclusions:** The higher rates of ADHD in SZ-offspring suggest that abnormal neurodevelopmental processes may exert a stronger influence in SZ than BP. Follow-up of these children will help elucidate the role of ADHD and depression phenotypes in predicting future transition to SZ or BP.

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## 1. Introduction

The notion that schizophrenia (SZ) and bipolar disorders (BP) share a common pathophysiological basis has gained growing support over the last three decades. This is largely due to advances in the field of molecular genetics, which have yielded overlapping findings between the two disorders (Moskvina et al., 2009; Tammimga et al., 2014). A number of unspecific behavioural, emotional and cognitive manifestations dating back to childhood have been reported to precede the full-blown onset of both disorders (Cornblatt et al., 2003; Conus et al., 2010). This has turned efforts towards identification and treatment of individuals

at early stages of the illness, when first clinical manifestations emerge. However, while early recognition and intervention during the prodromal phase of the disorder have been subjected to extensive research in the field of SZ (Fusar-Poli et al., 2013), research into valid prodromal criteria for BP is still at an early stage (Bechdolf et al., 2012). Retrospective studies combining subjects with early-onset mania and early-onset first-episode psychosis have reported a similar pattern of neurodevelopmental and psychopathological features predating the appearance of more specific prodromal symptoms in both disorders (Correll et al., 2007; Sanchez-Gistau et al., 2014). Therefore, the substantial overlap of symptoms in the initial phases suggests that early identification programmes should be aimed at detecting both the pre-psychotic and the pre-manic phases of SZ and BP (Correll et al., 2010).

SZ and BP are characterized by high inheritance rates; a positive first-degree family history is the strongest risk factor for developing the disorder identified so far (Gottesman et al., 2010). Therefore, the

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study of genetic high-risk children prevails as a powerful approach towards understanding the ethiopathogenesis and clinical course of major psychiatric diseases from its earliest stages.

Studies in child and adolescent BP-offspring have demonstrated that, prior to the age of peak incidence of mania, these youth suffer from higher rates of a range of psychiatric disorders relative to offspring of community controls (Lapalme et al., 1997; DelBello and Geller, 2001). Despite methodological disparity between studies (Duffy et al., 2011), elevated rates of attention deficit hyperactivity disorder (ADHD), anxiety and mood disorders have been consistently reported (Henin et al., 2005; Singh et al., 2007; Birmaher et al., 2009; Duffy et al., 2009; Garcia-Amador et al., 2012). By contrast, controlled SZ-offspring studies designed to assess the prevalence of psychopathology other than psychosis during childhood and adolescence are more limited. The few studies employing semi-structured DSM-IV interviews in young SZ-offspring have reported rates of 60 to 80% of any Axis I disorder, ADHD being the most common diagnosis (Ross and Compagnon, 2001; Keshavan et al., 2008; de la Serna et al., 2011).

A recent meta-analysis (Rasic et al., 2014) has reported a 55% rate of psychiatric disorders in offspring of patients with SZ, BP, or major depressive disorders, and has found substantial overlap between disorders, with little differences according to parental diagnoses. Of note, the authors highlighted the limited number of available studies in child offspring of parents with SZ, and the lack of studies comparing SZ and BP offspring. One of these studies in SZ offspring, which compared offspring of patients with SZ and with affective disorders, is the New York High Risk Project (Erlenmeyer-Kimling and Cornblatt, 1987). This study reported that both offspring groups had similar rates of DSM-III non-psychotic Axis I disorders in adulthood, after a 25 year follow-up (Erlenmeyer-Kimling et al., 1997). However, only one research group to date has evaluated child and adolescent offspring of parents with SZ and BP comparatively, employing the KD-SADS-PL interview for assessing DSM-IV psychiatric disorders in childhood. Maziade et al. (2008) assessed 28 SZ and 26 BP-offspring from families densely affected by SZ or BP; however, no community control group was included, which precluded the comparison of psychopathology rates. Around 60% of both offspring groups presented a non-psychotic disorder; however the authors did not find any significant differences in rates of psychiatric diagnoses between groups, suggesting a similar clinical phenotype at an early age.

Given the lack of studies assessing child offspring of SZ and BP patients comparatively, whether offspring of these patients share a similar risk of suffering premorbid psychopathology, and whether there is specificity in the rates of Axis I disorders between groups, remains unresolved.

In this context, the Bipolar And Schizophrenia Young offspring Study (BASYS) was set up to longitudinally assess clinical, neuropsychological and neurobiological measures in child and adolescent offspring of parents with BP or SZ. In the current article we aim to determine the lifetime prevalence of DSM-IV Axis I psychiatric disorders at study intake in SZ and BP offspring compared to a community control offspring group.

## 2. Methods

### 2.1. Participants

The study was conducted in two child and adolescent psychiatry departments in Spain; the Hospital Clinic of Barcelona and Hospital Gregorio Marañón of Madrid, and was approved by the ethical review board of each hospital. The recruitment period was January 2008–September 2012.

#### 2.1.1. Schizophrenia and bipolar disorder families

The fact that both hospitals have adult and child and adolescent psychiatry departments facilitated the interaction between mental health

professionals, aiding recruitment and assessment of patients. Psychiatrists of adult units were asked to identify BP and SZ probands with offspring aged 6–17 years, and to enquire whether they agreed to be contacted for the study. Exclusion criteria of high-risk offspring included intellectual disability, head injury with loss of consciousness or severe neurological conditions.

One hundred and two proband parents with children within this age range (60 BP and 42 SZ) were initially contacted, 10 of whom declined to participate (5 BP and 5 SZ), and 4 (3 SZ and 1 BP) failed to attend the initial interview. The final sample consisted of 88 families (98% unilineal families for BP or SZ), of which 54 BP (72.2% BP I and 27.8% BP II) and 34 SZ, including 41 SZ-offspring and 90 BP-offspring, respectively. All proband parents were outpatients at the time of recruitment, with the exception of 2 SZ mothers who were in chronic inpatient units. 69.3% of biological co-parents were assessed, 18 (52.9%) SZ co-parents and 43 (79.6%) BP co-parents.

#### 2.1.2. Community control families

Community control (CC) parents were recruited through advertisements posted in primary health care centres and other community locations within the same geographical area as the patients. Exclusion criteria for CC parents were personal or 1st degree family history of BP or SZ spectrum disorders, intellectual disability or severe neurological illness. In order to reduce selection bias, parents who stated to be specifically motivated to participate due to concerns about school performance or emotional or behavioural problems in their children were also excluded. The exclusion criteria for CC-offspring were the same as for high risk subjects.

Out of the 85 control families who contacted the team, 5 declined to participate and 15 did not meet inclusion criteria; 65 control families, including 107 CC-offspring, were finally enrolled. Both parents were assessed with the exception of 12 fathers who could not attend the assessment due to work commitments. The parent who contacted with the team was considered the proband community control parent.

### 2.2. Assessment

Written informed consent was provided by all parents or legal guardians and subjects over 12 years of age; assent was sought in younger children. The assessment of the participating family was carried out at the child and adolescent outpatient department of each hospital. The families received compensation for their time and travel expenses.

All research team members were clinically experienced psychiatrists or psychologists. The team member who had initially contacted the family assessed psychopathology of the proband parent and biological co-parent using the Spanish version of Structured Interview for DSM-IV; SCID-I (Kaufman et al., 1997). Psychopathology in children was ascertained by child psychiatrists or psychologists blinded to parental status using the Spanish version of The Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime version (K-SADS-PL) (Kaufman et al., 1997) administered separately to parents and children by the same interviewer. The parent interview was conducted first in pre-adolescent subjects, while in adolescents, the child interview was administered to them first. Finally the summary ratings were achieved by integrating both sources of information aided by clinical judgement. Pubertal development was estimated using The Petersen Pubertal Developmental Scale (Petersen et al., 1988), and respective Tanner Stages, which consist of five developmental stages for genitals (boys), breasts (girls), and pubic hair (boys and girls). Subjects in Tanner Stages I, II or III were considered to be pre-pubertal or pre-adolescents, while stages IV and V were considered to be post-pubertal or adolescents. Finally, parental socioeconomic status (SES) was estimated using the Hollingshead Scale (Hollingshead and Redlich, 2007); the highest SES among the two parents was included.

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