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 predicating 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; Tamminga 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 (Correll 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 prepsychotic 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
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 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 the child and adolescent offspring of patients with SZ and BP comparatively, employing the KD-SADS-PL interview for assessing DSM-IV psychiatric disorders in childhood. Mazziade 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 Marañon 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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2.3. Statistical analysis

Chi-square statistics with Yates’ correction and Fisher’s exact test were used to compare percentages of discrete variables. One-way analysis of variance (ANOVA) and the Kruskal–Wallis non-parametric test were used to compare continuous variables, as appropriate. Post-hoc parametric (Chi-square or Student’s t) and non-parametric (Chi-square with Fisher’s exact test or Mann–Whitney U test) analyses were carried out when the three-group comparison was statistically significant (p<.05). In the present sample there were families with more than one offspring, that is to say, that each family cluster could contain various siblings. In order to account for the effects of sibling correlation, binary generalised estimating equations (GEE) were performed. GEE is a statistical technique which focuses on data which is correlated due to relatedness of the subjects within the same cluster (Burton et al., 1998 and Hanley et al., 2003). Socio-demographic variables showing statistical significance between-group differences at univariate level were included as covariates. In addition, in order to control for the intactness and overall burden of illness of the family, the variables “family intactness” and “both parents with any psychiatric disorder” were also added as covariates to the model. Significance was set at p<.05 and all p values were two-tailed.

3. Results

3.1. Parents

3.1.1. Socio-demographical and psychopathological features

As shown in Table 1, SZ probands had the lowest SES and were less likely to be married and employed than BP and CC probands. Both SZ and BP probands presented higher rates of psychopathology and comorbidity than CC probands. The most frequent comorbid diagnosis in SZ and BP were anxiety disorders, while adjustment disorders were the most common diagnosis in CC probands. No differences were found in the rates of comorbidity between BP and SZ probands. In co-parents, adjustment disorders were the most prevalent diagnoses; no significant differences were observed between the three groups.

3.2. Offspring

3.2.1. Socio-demographical and psychopathological features

As described in Table 2, there was a higher proportion of males in the SZ-offspring group relative to the CC-offspring group. BP-offspring were more likely to be in developmental Tanner Stage IV or V (post-pubertal) than SZ and CC-offspring, while SZ-offspring had lower SES and were less likely to be living in an intact family compared with BP and CC offspring. A higher proportion of both SZ and BP-offspring had “both parents with any psychiatric disorders” and had had prior contact with mental health services compared to CC-offspring. However, the mean age of first contact in SZ-offspring was significantly younger than BP and CC-offspring. With regards psychopathology, 58.5% of SZ-offspring, 36.7% of BP-offspring and 17.8% of CC-offspring had experienced a lifetime Axis I DSM-IV psychiatric disorder. ADHD was the most prevalent disorder in all groups, followed by disruptive behaviour disorders (DBDs) in SZ-offspring, mood disorders in BP-offspring and anxiety disorders in CC-offspring. The comparison of rates of Axis I psychiatric disorders between the three offspring groups is depicted in Table 2.

3.2.2. Multivariate analysis

Adjusted odd ratios of significant associations after controlling for sibling correlation and for differences in socio-demographical features and family burden are shown in Table 3.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>SZ proband parents</th>
<th>BP proband parents</th>
<th>Control proband parents</th>
<th>χ²/F</th>
<th>p-Value</th>
<th>Post-hoc paired analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: female, %</td>
<td>N=34</td>
<td>N=54</td>
<td>N=65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race: white, %</td>
<td>64.7</td>
<td>57.4</td>
<td>61.5</td>
<td>.49</td>
<td>.78</td>
<td></td>
</tr>
<tr>
<td>Age (mean/SD)</td>
<td>42.4 (5.7)</td>
<td>44.2 (5.5)</td>
<td>44.7 (5.6)</td>
<td>1.72</td>
<td>.18</td>
<td></td>
</tr>
<tr>
<td>SES (mean/SD)</td>
<td>26.4 (14.8)</td>
<td>41.4 (15.9)</td>
<td>46.1 (13.6)</td>
<td>15.1</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Partly or fully employed, %</td>
<td>17.9</td>
<td>50.0</td>
<td>80.0</td>
<td>32.6</td>
<td>.000</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (mean/SD)</td>
<td>28.6 (9.6)</td>
<td>34.4 (7.7)</td>
<td>2.90</td>
<td>.009</td>
<td>.005</td>
<td></td>
</tr>
<tr>
<td>Number offspring included (mean/SD)</td>
<td>1.3 (0.1)</td>
<td>1.7 (0.1)</td>
<td>1.7 (0.9)</td>
<td>4.65</td>
<td>.09</td>
<td></td>
</tr>
<tr>
<td>Lifetime Axis I disorders, %</td>
<td>100%</td>
<td>100%</td>
<td>26.2</td>
<td>92.30</td>
<td>.000</td>
<td></td>
</tr>
<tr>
<td>Mood disorders (excluding BP)</td>
<td>3.2</td>
<td>NA</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>12.9</td>
<td>13.0</td>
<td>7.7</td>
<td>1.06</td>
<td>.38</td>
<td></td>
</tr>
<tr>
<td>Adjustment disorders</td>
<td>6.5</td>
<td>7.4</td>
<td>13.8</td>
<td>1.9</td>
<td>.38</td>
<td></td>
</tr>
<tr>
<td>Any substance use disorder</td>
<td>6.5</td>
<td>11.1</td>
<td>0.8</td>
<td>7.30</td>
<td>.02</td>
<td>BP &gt; CCb</td>
</tr>
<tr>
<td>Others</td>
<td>6.5</td>
<td>7.4</td>
<td>1.5</td>
<td>7.56</td>
<td>.27</td>
<td></td>
</tr>
<tr>
<td>Axis I comorbidity, %</td>
<td>29.0</td>
<td>33.3</td>
<td>3.2</td>
<td>19.61</td>
<td>.000</td>
<td>SZ &gt; CC &gt; BP &gt; CC</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th></th>
<th>SZ co-parents</th>
<th>BP co-parents</th>
<th>Control co-parents</th>
<th>χ²/F</th>
<th>p-Value</th>
<th>Post-hoc paired analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: female, %</td>
<td>N=18</td>
<td>N=41</td>
<td>N=53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race: white, %</td>
<td>50</td>
<td>51.2</td>
<td>49.1</td>
<td>.42</td>
<td>.99</td>
<td></td>
</tr>
<tr>
<td>Age (mean/SD)</td>
<td>46.3 (10.1)</td>
<td>45.8 (5.5)</td>
<td>45.1 (6.2)</td>
<td>.31</td>
<td>.72</td>
<td></td>
</tr>
<tr>
<td>SES (mean/SD)</td>
<td>52.9</td>
<td>74.4</td>
<td>98.3</td>
<td>20.9</td>
<td>.000</td>
<td></td>
</tr>
<tr>
<td>Partly or fully employed, %</td>
<td>75.0</td>
<td>79.1</td>
<td>86.8</td>
<td>1.61</td>
<td>.44</td>
<td></td>
</tr>
<tr>
<td>Lifetime Axis I disorders, %</td>
<td>61.1</td>
<td>53.5</td>
<td>47.2</td>
<td>1.12</td>
<td>.56</td>
<td></td>
</tr>
<tr>
<td>Mood disorders (excluding BP)</td>
<td>5.6</td>
<td>14.0</td>
<td>5.7</td>
<td>2.31</td>
<td>.31</td>
<td></td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>11.3</td>
<td>16.3</td>
<td>15.1</td>
<td>.27</td>
<td>.27</td>
<td></td>
</tr>
<tr>
<td>Adjustment disorders</td>
<td>38.4</td>
<td>23.6</td>
<td>28.3</td>
<td>1.11</td>
<td>.57</td>
<td></td>
</tr>
<tr>
<td>Any substance use disorder</td>
<td>5.6</td>
<td>4.7</td>
<td>1.9</td>
<td>.80</td>
<td>.67</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>4.7</td>
<td>3.8</td>
<td>.83</td>
<td>.66</td>
<td></td>
</tr>
<tr>
<td>Axis I comorbidity, %</td>
<td>0</td>
<td>7.0</td>
<td>7.5</td>
<td>1.91</td>
<td>.49</td>
<td></td>
</tr>
</tbody>
</table>

χ²: Chi-square or Fisher’s test and F: One-way analyses of variance ANOVA or KW = Kruskal–Wallis;
p-Value of paired analysis (Chi-square or Fisher and t Student or Mann–Whitney U test): “p<.05,” “p<.01,” and “p<.001.
Note: SZ = schizophrenia; BP = bipolar disorder; CC = community control; SZc = schizophrenia co-parent; CCC = community control co-parent.

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When BP and SZ-offspring where directly compared, only the differences in the prevalence of ADHD remained significant after adjusting for confounders compared to CC-offspring. SZ-offspring continued to exhibit a higher prevalence of psychopathology, specifically ADHD and anxiety disorders, while differences in the prevalence of DBD did not remain significant. BP-offspring presented a higher prevalence of any Axis I psychiatric disorder, ADHD and any mood disorder than CC-offspring. However, there was a significant interaction between pubertal stage and mood disorders: post pubertal BP-offspring were more likely to suffer from mood disorders than post-pubertal CC-offspring (78.6% vs 20%, $\chi^2 = 5.4, p < .05$).

### 4. Discussion

To our knowledge, this is the first study to directly compare the lifetime prevalence of DSM-IV psychiatric disorders in child and adolescent offspring of BP and SZ patients relative to community controls. The New York High Risk Study (Erlenmeyer-Kimling et al., 1997) compared prevalence of psychiatric disorders in adulthood offspring of parents with SZ and affective disorders, while the single study to date (Maziade et al., 2008) which included adolescent SZ and BP-offspring, included only densely affected families and did not have a control group. Both previous studies failed to find any significant differences in rates of non-psychotic disorders between groups, thus contrasting with our own findings of a greater prevalence of ADHD in SZ relative to BP-offspring.

Consistent with previous evidence, this high risk group presented higher rates of psychopathology than CC-offspring. Specifically, SZ-offspring showed higher rates of any psychiatric disorder, greater
comorbidity and a younger age of first contact with mental health services than BP and CC-offspring. Our findings therefore suggest a gradient of clinical severity between offspring of SZ, BP and CC. SZ-offspring also lived in families with less intactness and lower SES relative to BP and CC-offspring, suggestive of greater social-disadvantage in SZ-offspring. Lower SES and less family intactness have been associated with a heightened risk of childhood psychopathology, especially externalizing disorders (McLaughlin et al., 2012). When adjusting for SES and family intactness, the higher prevalence of DBD in SZ-offspring compared with BP and CC-offspring was no longer significant, while ADHD continued to be more prevalent in BP and SZ-offspring relative to CC-offspring. Therefore, our results suggest that while DBD appears to be related to social-disadvantage, ADHD may be more closely associated with genetic risk status (Larsson et al., 2013).

The significance of the overrepresentation of ADHD in young offspring of SZ and BP (Keshavan et al., 2003; Duffy, 2012; Pallanti and Salerno, 2015) is subject to ongoing debate. There is also substantial co-occurrence of ADHD in patients with early-onset SZ and early-onset BP (Ross et al., 2006; Frias et al., 2015), and symptoms of inattention appear in both SZ and BP, especially in early-onset presentations. Whether ADHD is an early risk phenotype, a comorbid condition, or an early expression of the disorder is still unresolved. Recent genetic and molecular findings (Larsson et al., 2013) have demonstrated that the three disorders share genetic factors, suggesting a similar etiological basis rather than a purely comorbid relationship. Furthermore, hyperactivity and irritability symptoms in childhood are often present in both ADHD and internalizing disorders, which suggests that, rather than indexing separate conditions, these symptoms could be early manifestations of a major psychiatric condition (Duffy, 2012). Another possible explanation is that since ADHD is considered to be a neurodevelopmental disorder (American Psychiatric Association, 2013), the expression of ADHD symptoms in high risk children could be a manifestation of neurodevelopmental deviance. Our findings suggest that the elevated rates of ADHD in SZ-offspring compared to BP-offspring and CC-offspring may reflect abnormal neurodevelopmental processes which, according to some authors, may exert a stronger effect in SZ than in BP (Peralta et al., 2011; Arango et al., 2014). In concordance with this assumption, a history of ADHD and neurodevelopmental abnormalities during childhood has been commonly reported in subjects who later develop schizophrenia in adulthood (Rho et al., 2015; Kim-Cohen et al., 2003). Conversely, longitudinal studies in BP-offspring have revealed that ADHD does not appear to be a reliable antecedent of BP, with the exception of a subgroup of youth with a high familial load for psychosis spectrum disorders and more neurodevelopmental impairment (Duffy, 2012).

We report a lower prevalence of both externalizing and internalizing disorders in our BP-offspring in comparison with other similarly aged samples (Chang et al., 2000; Henin et al., 2005; Singh et al., 2007; Birmaher et al., 2009). When interpreting offspring psychopathology it is important to take into account the clinical characteristics of the parents (Duffy et al., 2011). In the present study, proband parents were identified systematically and in a clinical setting, and their diagnoses and comorbidities were confirmed by clinical psychiatrists in order to guarantee an accurate and stable diagnosis. Our BP proband parents presented a lower prevalence of comorbidity with substance use disorders, and a more homogeneous gender and SES distribution than samples of self-referred parents (Chang et al., 2000; Birmaher et al., 2009), in which offspring presented substantially higher rates of psychopathology than the ones reported here. Similar to a previous study in BP-offspring (Birmaher et al., 2009), the influence of having both parents with an Axis I disorder was also controlled for in multivariate analysis.

As expected, we found that BP-offspring presented a higher prevalence of mood disorders compared to CC-offspring, specifically major depressive disorders. However, we did not identify any case of mania or hypomania: this is also at odds with the elevated rates of BP (between 10 and 38%) reported in some similarly aged BP-offspring samples (Chang et al., 2000; Henin et al., 2005; Singh et al., 2007; Birmaher et al., 2009). In contrast, in other BP-offspring studies, mainly comprised of adolescents, rates of diagnosable BP did not reach 6% (Wals et al., 2001; Duffy et al., 2009). In addition to differences in the recruitment strategy, clinical assessment and demographic features of the samples, a possible explanation for the divergent rates may be the criteria employed for diagnosis of BP. In the studies showing elevated rates of BP, a broad bipolar phenotype spectrum was considered, while in ours and in the other studies showing lower rates of BP, patients needed to fulfill narrow DSM-IV criteria for mania or hypomania in order to be considered Bipolar I or II. We only found an increased rate of depressive disorders in post-pubertal BP-offspring compared to CC-offspring. This finding concurs with a number of longitudinal BP-offspring studies (Shaw et al., 2005; Mesman et al., 2013) which suggest that, in early adolescence, prior to the age of peak incidence of mania, predominant symptoms are those related to depression, while unspecific psychopathology such as ADHD and anxiety are more commonly reported during childhood. In this regard, depressive disorders may be a reliable precursor of BP in adolescent high risk individuals, and have been recently associated with a specific clinical stage within the clinical staging model of BP (Berk et al., 2014; Duffy, 2015).

4.1. Study strengths and weaknesses

A number of factors need to be considered when interpreting the current findings. First, the sample size limited our capacity to analyse specific diagnoses separately, therefore diagnoses of main categories were considered together. Despite sizeable efforts invested in recruiting SZ-offspring, the low reproductive rates of SZ patients (Bundy et al., 2011) restricted the number of SZ-offspring participants included. Second, ascertainment bias of affected and control parents cannot be entirely ruled out. Nevertheless, we endeavoured to minimize selection bias of the community control group by rejecting families who stated that their sole motivation for participating in the study were their children’s difficulties. The rate of psychopathology in the CC-offspring group is in the range of rates reported by previous population-based studies conducted locally (Gómez-Beneyto et al., 1994; Canals et al., 1997). Finally, the SCID-I does not include an assessment of ADHD, therefore, in parents, diagnoses of ADHD were not evaluated, and the influence of parental ADHD on offspring psychopathology can not be entirely ruled out.

This study has a number of strengths which sets it apart from previous investigations. On one hand, the study includes a direct comparison of psychiatric disorders between child and adolescent offspring of SZ, BP and CC. On the other, the methodology is particularly robust, as all participants, children and parents, underwent face-to-face assessments by experienced adult and child and adolescent psychiatrists and psychologists blinded to parental status, employing standardized DSM-IV interviews. Moreover, in contrast with some previous offspring studies, where there is a lack of data on co-parents (Wals et al., 2001; Henin et al., 2005; Maziade et al., 2008), we were able to directly assess 75% of biological co-parents. Finally, the results were controlled for the effect of sibling correlation and were adjusted for socio-demographic confounders and psychopathology of both parents.

5. Conclusions

In summary, we have found that both SZ and BP-offspring present a high percentage of psychopathology in comparison with CC-offspring. However, SZ-offspring exhibited greater clinical and substantial over-representation of ADHD, whereas there was some specificity for the association between mood disorders in offspring of parents with BP. Whether carrying genetic risk for SZ plus exhibiting an ADHD phenotype during childhood, or carrying genetic risk for BP plus presenting a depressive phenotype during adolescence, are the early clinical stages of a later full-blown SZ or BP syndrome will be elucidated after follow-

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