TEMPERAMENT IN CHILD AND ADOLESCENT OFFSPRING OF PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR DISORDER

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ABSTRACT

Shared vulnerability in offspring of individuals with schizophrenia (SzO) and bipolar disorder (BpO) might manifest early during development through common temperament traits. Temperament dimensions in child and adolescent BpO (N=80), SzO (N=34) and the offspring of community controls (CcO) (N=101) were assessed using the Revised Dimensions of Temperament Survey. The association between temperament dimensions and lifetime psychopathology (including threshold and subthreshold DSM-IV-TR diagnoses) and current socio-academic adjustment was assessed using logistic regression. Fully adjusted models showed that both BpO and SzO scored significantly lower in the positive mood dimension and in the adaptability factor than CcO, with small-medium effect sizes (Cohen's *d* ~0.3-0.5). BpO also scored lower in the activity factor and the activity dimensions than CcO (Cohen's *d* ~0.3). Lower scores in the positive mood dimension were associated with increased risk of impaired adjustment both in BpO (OR 2.30, 95% CI [1.18-4.46]) and in SzO (OR 2.87, 95%CI [1.07-7.66]). In BpO, lower scores in positive mood were also associated with increased likelihood of internalizing (OR 1.84, 95% CI [1.28-2.64]) and externalizing disorders (OR 1.48, 95% CI [1.01-2.18]); in SzO, higher scores in activity and flexibility were associated with increased likelihood of internalizing (OR 2.31, 95% CI [1.22-4.38]) and externalizing disorders (OR 3.28, 95% CI [1.2-9]), respectively. Early difficulties in emotion regulation might represent a shared vulnerability phenotype in BpO and SzO. The identification of extreme temperament traits could help characterize subgroups at greater risk of psychopathology and impaired adjustment, in which targeted interventions are warranted.

Keywords: Temperament, bipolar disorder, schizophrenia, high-risk, development.

INTRODUCTION

Growing evidence for a genetic, neurodevelopmental and clinical overlap between schizophrenia and bipolar disorder supports a dimensional approach to the psychosis phenotype [1,2]. The offspring of parents with schizophrenia and bipolar disorder have been found to be at increased risk for developing both disorders [3]. Although some difficulties such as deficits in neurocognition or social cognition might be more specific to the offspring of patients with schizophrenia (SzO) [4], both offspring groups show

some overlapping early manifestations of vulnerability during childhood and adolescence, with a higher degree of severity in SzO [5,6].

Temperament is defined as biologically rooted mood and behaviour traits that are present from the earliest stages of development and are moderately stable over time [7,8]. Some temperament dimensions seem to constitute developmental risk factors, increasing the odds of psychopathology and reduced academic and social adjustment later in life [9,10]. In the offspring of patients with severe mental disorders, individual temperamental differences might represent early manifestations of increased genetic vulnerability, which are identifiable from a very young age. Some of these traits might lead to a higher likelihood of exposure or suboptimal response to environmental stressors, thus favouring subsequent development of psychopathology [10,11].

Most studies indicate that offspring of patients with bipolar disorder (BpO), especially those with psychopathology, show a distinct temperamental pattern compared with community control offspring (CcO) [12]. Child and adolescent BpO show reduced positive mood (i.e. low characteristic manifestation of positive affect) or increased emotionality (i.e. tendency to show distress) [13-16] and reduced task orientation (i.e. ability to concentrate and stay focussed on a specific activity for a sustained period of time), while results regarding other temperament dimensions such as general activity (i.e. general level of energy and motor activity) are less consistent [15,17]. High emotionality and other temperament traits such as increased harm avoidance (i.e. the tendency to inhibit responses to aversive stimuli, acting with caution and apprehension) have been found to predict the onset or recurrence of mood disorders in BpO in longitudinal studies [18,19]. However, research on temperament traits in schizophrenia is still scarce. Increased harm avoidance has been described in adult patients with schizophrenia, their non-psychotic siblings and subjects at ultra-high risk for psychosis [20-22]. Increased rates of unstable emotional responses have been reported as a common behavioural trait in male and female SzO and in the female offspring of patients with affective psychosis, along with increased levels of shyness and withdrawal in the male offspring of patients with affective psychosis [23]. To our knowledge, no previous study has specifically assessed temperament dimensions in child and adolescent SzO and compared them with those of BpO.

In this study, we sought to compare temperament dimensions among BpO, SzO and CcO and to explore the impact of these dimensions on current adjustment and lifetime psychopathology (including

subthreshold manifestations) in the high-risk samples (i.e. BpO and SzO). We hypothesized that shared vulnerability would translate both in SzO and BpO into common temperamental manifestations, especially in the mood dimension, and that higher scores in specific temperament dimensions would be associated with poorer adjustment and increased lifetime rates of psychopathology.

METHODS

Participants

The complete methods of the "Bipolar and Schizophrenia Young Offspring Study" (BASYS) have been described elsewhere [5]. In brief, 90 child and adolescent offspring (aged 6-17 years) from 55 families with at least one parent with a DSM-IV-TR [24] diagnosis of bipolar disorder I or II, 41 offspring from 34 families with at least one parent with a diagnosis of schizophrenia and 107 offspring from 65 community control families were recruited in the departments of child and adolescent psychiatry of two hospitals in Spain. Psychiatrists of the adult units of both hospitals identified patients with bipolar disorder and schizophrenia with offspring aged 6–17 years and enquired whether they agreed to be contacted for the study. Community control families with children of a similar age were recruited using advertisements posted in general practices and other community locations such as schools from the same geographical areas as the patients. All parents underwent a diagnostic and clinical interview with experienced psychiatrists or psychologists using the Structured Clinical Interview for DSM-IV Axis I Disorders [25] to confirm the diagnosis of schizophrenia or bipolar disorder and establish comorbid diagnoses in the affected parents. The interviews also established psychiatric diagnoses in the non-affected parents of the high-risk families and the control parents. In the affected parents, additional clinical information was collected (e.g. age at onset, clinical characteristics, current treatment, number of episodes, history of inpatient admissions or suicidality). Except for two mothers (one mother with schizophrenia and one mother with bipolar disorder) who were inpatients in a chronic patient unit, all the affected parents were stabilized and outpatients at the time of the assessment. Exclusion criteria for control parents included personal or first-degree family history of bipolar disorder or schizophrenia, intellectual disability and severe neurological conditions. The exclusion criteria for high-risk and community control offspring were head injury with loss of consciousness, intellectual disability and severe neurological conditions. For the purposes of this study, we only included offspring with valid data on temperament (i.e. with at least 50

completed items in the temperament scale), yielding the final sample comprising 80 BpO of 50 families, 34 SzO of 26 families and 101 CcO of 63 families.

This research was approved by the Institutional Review Boards of the two centres. The parents or legal representatives of all participating children signed the informed consent; children aged twelve or older also provided assent.

Clinical assessment

Temperament was assessed using the Revised Dimensions of Temperament Survey (DOTS-R) [8], which is a 54-item questionnaire designed to identify usual emotional and behavioural patterns present from early childhood in children and adolescents. The factorial and predictive validity of the DOTS-R across time and its association with a wide range of mental health and competence measures have been reported in several studies [8,26,27]. In order to increase consistency, the parent report version of the scale was used for all participants. The DOTS-R comprises nine subscales measuring one temperament dimension each, as follows: 1) Activity level (assessing general levels of energy and motor activity); 2) Activity–Sleep (motor activity during sleep); 3) Approach (tendency to approach new objects and persons); 4) Flexibility (adaptability to changes in the environment); 5) Mood (quality of mood, higher scores reflect high characteristic manifestation of positive affect); 6) Rhythmicity–Sleep (regularity in sleep behaviour); 7) Rhythmicity–Eating (regularity in eating behaviour); 8) Rhythmicity–Daily Habits (regularity in performing daily habits) and 9) Task-orientation (higher scores reflect high persistence and low distractibility). Three second-order factors were also calculated, as follows [28]: task rhythmicity (composed of task-orientation, rhythmicity in eating, sleeping and daily habits), adaptability (flexibility, approach and mood) and activity (general and sleep activity). Both parents contributed to the assessment of each of their children. In families where only one parent was available for interview, this parent completed the questionnaire. Of these, 11 SzO families (10 mothers, 8 of whom were affected, and 1 father, who was not affected) completed the questionnaire. Of 10 BpO families, 10 mothers, all of them affected, completed the questionnaire. Of 12 CcO families, 12 mothers completed the questionnaire.

Offspring psychiatric diagnoses and adjustment were assessed by trained child psychiatrists or psychologists blinded to the parental diagnosis. DSM-IV-TR [24] diagnoses were established based on parent and child interview and child direct observation using the Spanish version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS–

PL) [29,30]. Broad diagnoses were taken into account to capture subclinical manifestations and included subthreshold and threshold diagnoses (i.e. scores of 2 [subthreshold diagnosis] or 3 [diagnosis present] in the K-SADS-PL for each of the diagnostic categories). Diagnoses were then divided into three general categories [31]: 1) externalizing disorders (including attention-deficit hyperactivity disorder [ADHD], disruptive behaviour disorders [oppositional defiant disorder and conduct disorder] and substance use disorders), 2) internalizing disorders (including anxiety and mood disorders) and 3) other (including eating disorders, tic disorders, enuresis/encopresis, autism spectrum disorders, learning disability).

Current socio-academic adjustment was measured using the Premorbid Adjustment Scale (PAS) [32], which assesses sociability, peer relationships, school performance and adaptation and ability to form socio-sexual relationships over the course of childhood and adolescence with high reliability and validity [33]. The PAS was completed by the clinician after parent and child interview. For each participant, the score corresponding to the current developmental period was considered. Given the different number of items comprising the childhood and adolescence scales, raw scores were converted to decimals ranging from 0.0 to 1.0, where lower numbers represent higher levels of functioning [32]. Using clinical criteria, scores <0.33 were considered to represent good adjustment [34], and participants with moderate or poor adjustment (scores ≥ 0.33) were considered to present impaired adjustment. Parental socio-economic status (SES) was estimated using the Hollingshead-Redlich Scale [35].

Statistical analysis

Only participants with at least 50 completed items in the DOTS-R were included in this study (i.e. 80 BpO, 34 SzO and 101 CcO). To avoid potential loss of valuable information due to missing values, subgroup mean imputation was used to treat single-item missing values within each particular dimension, i.e., the mean score for that item in the subject's offspring subgroup was assigned (applicable to 0 to 10 subjects per dimension). Only dimension scores with no or one imputed missing item were included in the analyses. We computed Z-scores based on the results in CcO with no lifetime threshold or subthreshold psychopathology (n=49) for the nine subscales and the three factors in all BpO, SzO and CcO participants. Outliers in the temperament dimension scores were identified by calculating the Mahalanobis distance and removed from the corresponding analysis (1 CcO for the mood dimension and 1 CcO and 1 BpO for the flexibility dimension).

Normality of continuous variables was tested using the Shapiro-Wilk test and skewness and kurtosis ratios. Demographic, clinical, temperament and adjustment variables were compared between the three offspring groups using ANOVA or a Kruskal-Wallis test with a Bonferroni or a Games Howell post-hoc test, and the chi-square or Fisher's exact tests, as appropriate. Mixed model analyses were performed to compare temperament dimensions and factors between the three offspring groups, while controlling for potential confounders, with "family" as a random effect (to control the potential covariance within members of the same family), and age, sex, SES (dichotomized into high [I-II levels in the Hollingshead-Redlich scale] and medium-low [III-V]) and a lifetime diagnosis as fixed effects. Effect sizes were reported as Cohen's *d*. We used bias corrected and accelerated bootstrap resampling (β=1,000 bootstrap samples) to test the robustness of the models. A Bonferroni correction was applied to the alpha value of the pairwise comparisons between offspring subgroups to account for the number of post hoc subgroup comparisons conducted for each variable. Considering the small and uneven sample sizes and the exploratory nature of this work, we did not apply any formal correction for the number of variables tested. Sensitivity analyses were conducted for each dimension and factor to restrict these models to those children with no missing data and to the child (age <12) and adolescent offspring groups separately. We also performed Student's t-tests and mixed model analyses to explore the effect of the affected parent's sex on scores in temperament dimensions and factors within BpO and SzO.

A logistic regression analysis was performed to identify the temperament dimensions most likely to differentiate the high-risk sample as a whole from CcO, with high-risk status as the dependent variable, temperament dimensions as independent variables and age, sex, SES and a lifetime diagnosis as covariates.

In the BpO and SzO samples, bivariate analyses were first conducted to assess the association between demographic variables and temperament dimensions and the presence of a lifetime diagnosis, lifetime internalizing or externalizing disorder and impaired current adjustment. Then, binary multiple logistic regression models were used to assess the association of temperament dimensions with the same outcomes in each offspring group, adjusting for age, sex, SES, parent affected and temperament dimensions showing an association with p<.200 in the bivariate analyses. In the case of impaired current adjustment, the presence of a K-SADS-PL current disorder was also included as a covariate. A linear regression analysis was used to confirm the association of temperament dimensions and current adjustment by including the PAS score as a continuous variable. Since the PAS score was not normally

distributed, it was rank-transformed using an ANOVA-type method [36]. The analyses assessing lifetime diagnoses were repeated using a more restrictive definition of diagnosis [including only lifetime threshold DSM-IV-TR diagnoses (i.e. scores of 3 in the corresponding items of the K-SADS) of internalizing and externalizing disorders]. The assumptions of multiple linear regression or logistic regression models were tested for all models, as appropriate.

Statistical analyses were performed using the Statistical Package for the Social Sciences Version 21 [37]. The alpha level was set at $p<.05$ (two-tailed).

RESULTS

Table 1 shows the demographic and clinical characteristics of the three offspring groups. Table 2 shows the results from the group comparisons in the temperament dimensions and factors between SzO, BpO and CcO. In the unadjusted analyses, both BpO and SzO scored significantly lower in positive mood and in the adaptability factor than CcO. BpO scored lower in the activity dimension than SzO and in the activity factor than both SzO and CcO (Table 2 and Figure 1). Differences in the mood dimension (Cohen's *d* ~0.4-0.5) and the adaptability factor (Cohen's *d* ~0.3-0.4) between both high-risk groups and CcO, and between BpO and CcO in the activity factor and activity dimensions (Cohen's *d* ~0.3) remained significant in the adjusted analyses (Table 2). SzO also showed reduced approach as compared with CcO at trend level (Cohen's *d* ~0.3). Sensitivity analyses for each temperament dimension and factor in children with no missing data revealed little change in the direction, magnitude and significance level of the aforementioned associations (Table S1, available online).

There was little difference between the child and adolescent subsamples in the direction and magnitude of the effect sizes for the differences between SzO and BpO and CcO in the mood dimension (adjusted Cohen's *d* ~0.4 in both age groups) (see Tables S2 and S3). In high-risk offspring, we found significant differences in the task rhythmicity factor depending on which parent was affected, with an opposite effect in BpO and SzO (i.e. lower scores in this factor were found in BpO when the affected parent was the mother and in SzO when the affected parent was the father) (see Table S4).

The dimensions mood (OR 1.61, 95% CI [1.27-2.0]) and rhythmicity–daily habits (OR 0.75, 95% CI [0.58-0.97]) were the most likely to differentiate between high-risk participants and CcO (χ^2 19.83, p<.001).

The results of the bivariate analyses assessing the association between demographic and temperament variables and the diagnosis and adjustment outcomes are shown in Tables S5 (for BpO) and S6 (for SzO). Table 3 shows the fully adjusted logistic regression models separately for BpO and SzO. In BpO, (i) lower scores in positive mood were associated with a lifetime psychiatric diagnosis and a lifetime diagnosis of internalizing disorders; (ii) male sex and lower scores in task orientation and positive mood were associated with a lifetime diagnosis of externalizing disorders; and (iii) lower scores in flexibility, positive mood, task-orientation and activity during sleep were associated with impaired current adjustment (Table 3). A confirmatory linear regression model identified a similar set of correlates of current adjustment considering the PAS as a continuous variable, with lower scores in positive mood as the main predictor of this outcome (Table S7).

In SzO, (i) male sex was the main predictor of a lifetime psychiatric diagnosis; (ii) a higher score in the activity level dimension was the only predictor of a lifetime internalizing disorder; (iii) male sex and higher scores in flexibility were predictors of a lifetime diagnosis of an externalizing disorder; and (iv) lower scores in the positive mood dimension and parent affected (father relative to mother) were predictors of impaired adjustment in SzO (Table 3). The same predictors were identified in the linear regression model (Table S7).

Using a more restrictive definition of diagnoses, we also identified reduced positive mood as the main predictor of any lifetime diagnosis and internalizing disorders in BpO, while externalizing disorders were significantly associated with lower task orientation. In SzO, higher scores in the activity dimension were associated with higher rates of psychopathology and externalizing and internalizing (at a non-significant trend) disorders (Tables S8, S9 and S10).

DISCUSSION

Temperament dimensions in high-risk offspring

To our knowledge, this is the first study to compare temperament dimensions in the offspring of patients with schizophrenia, patients with bipolar disorder and community controls and to assess their potential association with psychopathology risk and adjustment in both high-risk groups. BpO and SzO show significantly lower scores in the positive mood temperament dimension than CcO, even after controlling for potential confounders, including the presence of lifetime psychopathology. This dimension reflects the regular expression of positive affect or emotionality by the child or adolescent, which seems to constitute an early marker of adaptive emotion regulation [38]. Our finding is consistent with those of previous studies on temperament in child and adolescent BpO reporting reduced positive mood or increased emotionality [13-16,39] and is also consistent with findings from a previous study reporting unstable emotional responses as a common behavioural trait in the offspring of patients with affective psychosis and schizophrenia [23]. In both high-risk samples, these traits seem to be associated with impaired adjustment, which has been conceptualized as a marker of liability for psychotic and other mental disorders [1,40,41]. Both high-risk offspring groups also show reduced adaptability (as a joint measure of reduced flexibility, approach and positive mood). These traits reflect some of the characteristics of the psychosis prodrome [42] and could constitute a shared vulnerability phenotype.

The presence of early unspecific mood alterations and reduced adaptability in both SzO and BpO could provide further support for a psychosis continuum [2]. Along this continuum, SzO seem to present increased vulnerability, along the lines of clinical and neuroanatomical findings in this sample [4,45]. Even if the temperament profile in SzO and BpO largely overlaps, scores tend to be higher in SzO than in BpO. SzO score higher in the activity dimension than BpO in the unadjusted analyses, and this trait is significantly associated with a higher likelihood of psychopathology in this subgroup. Increased activity and ADHD traits seem to be early unspecific markers of neurodevelopmental deviance and can represent early developmental signs of psychosis proneness [43]. Previous studies suggest that there might be a degree of diagnostic specificity in the childhood precursors of bipolar disorder and schizophrenia [44]. In this concern, psychomotor, cognitive and social difficulties seem to be more specific predictors of schizophrenia, which could indicate differences in the pathophysiology and developmental trajectories of both disorders [45-47]. However, alterations in emotional development such as increased affective dysregulation and subclinical mood symptoms during childhood and adolescence have been described in patients who later develop schizophrenia and bipolar disorder [42,48] and constitute core shared features in their prodromal phases [42,49,50]. In children at high familial risk of psychosis unspecific

subthreshold mood manifestations such as those covered by the positive mood temperament dimension could be thus early manifestations of unspecific vulnerability. The presence of these traits, in interaction with environmental factors, could eventually lead to the development of psychosis or other psychiatric disorders, along the lines of current dynamic staging models of mental illness [51].

Overlapping temperament manifestations found in high-risk offspring can also be the result of growing up in a family where one of the parents has a major mental disorder. Twin and adoption studies suggest that temperament is genetically influenced, but new studies in behavioural genetics highlight the influence of environmental factors such as exposure to psychosocial stressors, attachment and educational styles, and home context, as well as of gene-environment interaction, in temperament [52]. In families with a parent with bipolar disorder or schizophrenia, the non-specific burden of parental social impairment and parenting difficulties may thus be associated with both the temperamental difficulties and increased rates of mental disorders found in their offspring [53]. Moreover, more extreme temperament traits might pose a challenge for parenting, especially in families with a parent with a major mental disorder, contributing to the subsequent development of psychopathology [54]. Parent support and training can be useful for improving outcomes in children with 'difficult' temperaments, and could be an appropriate early intervention strategy in high-risk offspring showing more extreme temperamental profiles.

Although hyperactivity and ADHD traits are common in young people who later develop bipolar disorder [55] and increased activity levels have been previously reported in BpO [17], we found lower scores in the activity dimensions and the activity factor in BpO than in CcO. This could be in part due to rates of approximately 25% of threshold and subthreshold ADHD found in our CcO sample (comparable to those reported in community samples), as opposed to previous studies using healthy controls as the comparison group, but it is nevertheless consistent with previous findings in healthy BpO [13,15]. Even if we did not replicate previous reports of reduced task orientation in BpO [15,17], we did find that reduced task orientation was significantly associated with externalizing psychopathology and impairment within this sample. Interestingly, the set of dimensions identified as significant predictors in the regression models for current adjustment in BpO (reduced flexibility, task orientation, sleep activity and positive mood) almost mirrored the temperamental pattern associated with syndromal bipolar disorder in BpO in a previous study [15].

Association of temperament dimensions with psychopathology

Despite the similar negative impact of reduced positive mood on current adjustment in both high-risk samples, the vulnerability pattern for psychopathology, including threshold and subthreshold manifestations, seems to differ between BpO and SzO. While reduced positive mood is also associated with an increased risk for psychopathology in BpO, hyperactivity and greater flexibility are the main correlates in SzO. We found a similar pattern in the regression models assessing the impact of temperament dimensions on lifetime psychopathology using a more restrictive definition of diagnoses. That finding suggests that reduced positive mood and increased activity are the most consistent correlates of diagnoses in BpO and SzO, respectively. It has been proposed that early temperamental differences in emotion regulation might constitute useful risk markers for bipolar disorder and precursors of mood disorders in BpO [18,56]. The association between reduced positive mood and increased risk for both internalizing and externalizing psychopathology in BpO during childhood and adolescence, which often precede the onset of mood episodes in patients who later develop bipolar disorder [57,58], would support the role of early difficulties in emotion regulation as an unspecific marker of vulnerability in this group. Within SzO, we found that higher scores in flexibility were significantly associated with a diagnosis of externalizing disorders. This finding is surprising to some extent, since higher scores in flexibility would be expected to reflect greater adaptability to changes in the environment. Nevertheless, SzO as a whole shows a trend towards lower flexibility than CcO, especially in older children. It could be that among SzO greater tendency to respond flexibly to change might be the result of difficulties to maintain focus or be associated with other externalizing traits such as increased novelty seeking and impulsive behaviour, characterizing a subgroup at higher risk for ADHD and other externalizing disorders. Since male sex was significantly associated with a lifetime diagnosis in SzO (especially of externalizing disorders, which have been associated with poorer longitudinal outcomes in young people at high risk for psychosis) [59], male SzO could constitute a more vulnerable subgroup.

Association of temperament with the parent affected and developmental stage in high-risk offspring

In the exploratory analyses assessing the impact of the affected parent's sex, we found that this factor was mostly associated with rhythmicity-related variables, with an opposite effect in both high-risk groups. In BpO, we found lower rhythmicity when the mother was affected, while in SzO we found lower rhythmicity when the father was affected. We found a similar pattern in the linear regression analyses assessing current adjustment as a continuous variable, with greater impairment in adjustment in BpO when the mother was affected and greater impairment in SzO when the father was affected. This is

consistent with recent evidence suggesting a differential effect of maternal and paternal diagnosis on some offspring outcomes [60] that merits further exploration in the future, accounting for factors such as the sex of the offspring, severity of parental psychopathology and the differential impact of a diagnosis of schizophrenia or bipolar disorder on parenting strategies within high-risk families. Although our study lacked the power to test the impact of developmental stage on the temperamental profiles in high-risk offspring, the sensitivity analyses performed in the child and adolescent subsamples suggest that some temperament traits (such as reduced positive mood and reduced adaptability) might be already present in SzO and BpO during childhood, while others, such as reduced activity in BpO and reduced flexibility in SzO become more apparent during adolescence.

Limitations and implications

A number of caveats should be borne in mind when interpreting our results. First, ours was a cross-sectional study, and we assessed temperament retrospectively using parental reports. While this temperament assessment method has shown good reliability and concurrent validity with other measures of temperament in previous studies [8,27,61], it is difficult to completely control the results of the temperament assessment for the impact of psychopathology, especially in older children and adolescents. Even if we adjusted the analyses comparing temperament dimensions between the offspring groups for the presence of a lifetime diagnosis using a broad definition that also included subthreshold diagnoses, we cannot rule out a confounding psychopathology effect. Despite its limitations, we decided to use the DOTS-R because it is one of the few instruments that have been validated for temperament assessment in both child and adolescent populations and it has been previously used in high-risk samples, facilitating the comparability of our results. Dimensional measures of temperament such as the DOTS-R can offer added value in the study of high-risk populations by providing information on usual emotional and behavioural patterns that do not completely overlap with clinical symptoms, so they may enable earlier detection of developmental deviance. Also, even if we tried that both parents participated in the assessment of their offspring, parental psychopathology could have affected temperament assessments in the high-risk families to some extent. Although there is some evidence suggesting that parents with mental disorders might not show a significant bias in providing parent-report assessments of emotional and behavioural disturbances in their offspring, especially when they are not experiencing active symptoms [62,63], there have been controversial results, questioning the validity of parental reports in these populations [64,65]. It is still unclear the extent to which a parental diagnosis of schizophrenia or

bipolar disorder exerts a meaningful effect on temperamental assessments in their offspring, highlighting the need for further research on the issue. Retrospective assessments of psychopathology can also show reduced validity in some contexts. Nonetheless, consultant child and adolescent psychiatrists conducted extensive interviews with both the parents and their children using the K-SADS-PL, which has shown good reliability and validity for the assessment of past and current diagnoses in children and adolescents [30], especially when conducted by trained specialists.

The wide age span of our sample constitutes another limitation of the study from a developmental psychopathological perspective. Manifestations of vulnerability might change through development, with more externalizing traits in early childhood and more emotional difficulties in late childhood and adolescence [66]. Indeed, the sensitivity analyses in the child and adolescent subsamples found some differences in the temperament profiles of SzO and BpO. Nevertheless, we adjusted all our models for age and sensitivity analyses showed a similar effect in direction and magnitude for the positive mood dimension in high-risk children and adolescents. This suggests that early differences in affect regulation in high-risk offspring relative to community control offspring might be already present from childhood. Future research should further explore the impact of developmental stage on temperament traits in high-risk offspring in larger samples. Furthermore, it should be noted that we tested three different models for each of the nine temperament dimensions and the three temperament factors. Considering the small and uneven sample sizes and the exploratory nature of this work, we did not apply any formal correction for the number of variables tested across the study. Our results should be interpreted with caution and warrant replication in larger samples. Moreover, we did not use child self-report in older offspring in this study, which is the customary method for assessing the DOTS-R in adolescent samples. Nevertheless, we decided to use only parental report–based results in order to increase consistency, and parental and child reports have been found to be comparable elsewhere, especially in adolescent samples [67]. Finally, the possibility of selection and ascertainment bias and the small sample size, especially of the SzO group, might have affected our results to some extent.

These limitations notwithstanding, this study represents a step forward towards integrating assessment of temperament in the dimensional study of BpO and SzO. Our findings suggest that schizophrenia and bipolar offspring show early difficulties in emotional regulation, which are associated with impaired socio-academic adjustment in childhood and adolescence in both groups. This temperament trait may be a vulnerability marker shared by both disorders, and in BpO it may also be associated with an increased

risk of psychopathology. Differences in temperamental profiles between SzO and BpO appear to be quantitative rather than qualitative in nature and could point to greater developmental vulnerability in the former. The study of temperament dimensions early during development can improve knowledge of the mediators between familial risk and the development of psychopathology in these populations. In order to further ascertain their role, it is recommended to perform studies complementing self-report or parent-report questionnaires such as the DOTS-R with clinician-based measures of temperament using longitudinal prospective designs and accounting for broad dimensional and categorical definitions of psychopathology. These studies could help to detect early manifestations of vulnerability and identify subgroups at higher risk within these high-risk samples, in which targeted interventions should be developed to improve outcomes.

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Table 1: Demographic and clinical characteristics of schizophrenia, bipolar and control offspring.

	SzO *N=34*	***BpO*** *N=80*	***CcO*** *N=101*	***F/X²***	***p***	***Post hoc[a]***
Sex, female	13 (38.2%)	33 (41.3%)	56 (55.4%)	4.98	.083	
Race, caucasian	33 (97.1%)	78 (97.5%)	98 (97%)	0.32[b]	>.999	
Age, years [range]	10.3 (3.45) [6, 17]	12.4 (3.14) [6, 17]	11.7 (3.2) [7, 17]	4.93	**.008**	*SzO<BpO***
SES, median (IQR)	32.2 (25)	56 (21)	53 (19)	36.07[c]	**<.001**	*SzO<CcO***, SzO<BpO****
Low-medium[d]	20 (58.8%)	16 (20%)	15 (14.9%)	28.2	**<.001**	*SzO<CcO***, SzO<BpO****
High[d]	14 (41.2%)	64 (80%)	86 (85.1%)			
Maternal age, years	47.47 (10.35)	47.69 (6.04)	46.45 (5.80)	0.41	.633	
Paternal age, years	42.09 (5.62)	43.18 (4.53)	44.11 (5.55)	1.33	.267	
Mother affected[e]	23 (67.6%)	39 (49.4%)	NA	3.21	.073	
Developmental delays[f]	11 (33.3%)	11 (13.8%)	14 (13.9%)	7.60	**.022**	*SzO>CcO**
Axis I diagnosis[g]	28 (82.4%)	53 (66.3%)	52 (51.5%)	11.31	**.003**	*SzO>CcO***
Comorbidity	15 (44.1%)	38 (47.5%)	15 (14.9%)	24.92	**<.001**	*SzO>CcO***, BpO>CcO***
Internalizing disorders	12 (35.3%)	41 (51.2%)	27 (26.7%)	11.55	**.003**	*BpO>CcO***
Mood disorders	2 (5.9%)	18 (22.5%)	9 (8.9%)	8.28	**.011**	*BpO>CcO**
Anxiety disorders	11 (32.4%)	30 (37.5%)	21 (20.8%)	6.32	**.043**	*BpO>CcO**
Externalizing disorders	21 (61.8%)	28 (35%)	26 (25.7%)	14.65	**.001**	*SzO>CcO***, SzO>BpO**,
ADHD	20 (58.8%)	24 (30%)	25 (24.8%)	13.81	**.001**	*SzO>CcO***, SzO>BpO**
Disruptive disorders	6 (17.6%)	8 (10%)	2 (2%)	10.28	**.006**	*SzO>CcO***
SUD	0 (0%)	2 (2.5%)	0 (0%)	2.515[b]	.280	
Comorbid internalizing and externalizing disorders	8 (23.5%)	17 (21.3%)	8 (7.9%)	8.18	**.017**	*SzO>CcO**, BpO>CcO**
Other disorders[h]	12 (35.3%)	16 (20%)	14 (13.9%)	7.45	**.024**	*SzO>CcO***
Current adjustment (PAS), median (IQR)[i]	0.28 (0.25)	0.167 (0.22)	0.1 (0.13)	2.03[c]	**<.001**	*SzO>CcO***, BpO>CcO***
Current impaired adjustment[i]	11 (34.4%)	15 (18.8%)	6 (6%)	16.85	**<.001**	*SzO>CcO***, BpO>CcO***

Abbreviations: ADHD: attention-deficit hyperactivity disorder; BpO: bipolar offspring; CcO: community control offspring, NA: not applicable; PAS: premorbid adjustment scale, SES: socio-economic status; SUD: substance use disorders; SzO: schizophrenia offspring.

*Qualitative variables shown as N (%), quantitative variables expressed as mean (SD) unless otherwise specified. *p<.05; **p<.01; ***p<.001. [a]Bonferroni post-hoc test; only significant differences are shown. [b]Fisher's exact test. [c]Kruskal-Wallis test. [d]High SES: scores of I-II in the Hollingshead-Redlich scale; medium-low: III-V. [e]Data on maternal diagnosis not available for one family. [f]Including psychomotor developmental delay, language acquisition delay and reading/writing acquisition delay. [g]Broad K-SADS-PL lifetime diagnoses including subthreshold diagnoses. [h]Including eating disorders, tic disorders, enuresis/encopresis, autism spectrum disorders, learning disability. [i]PAS available for 32 SzO, 74 BpO and 100 CcO. [i]PAS ≥0.33.*

Table 2: Temperament dimensions and factors in schizophrenia, bipolar and community control offspring

	SzO N=34	*BpO* N=80	*CcO* N=101	*Unadjusted model[a]* Effect size (Cohen's d)			*Model 1[a,c]* Effect size (Cohen's d)			*Model 2[a,d]* Effect size (Cohen's d)		
				F, p	*SzO vs CcO*	*BpO vs CcO*	*SzO vs BpO*	*SzO vs CcO*	*BpO vs CcO*	*SzO vs BpO*	*SzO vs CcO*	*BpO vs CcO*	*SzO vs BpO*
Dimensions													
Rhythmicity–sleep	-0.27 (1.11)	-0.18 (1.13)	0.02 (1.05)	F=1.20, p=.303	*d*=-0.27	*d*=-0.18,	*d*=-0.08	*d*=-0.16	*d*=-0.15	*d*=-0.01	*d*=-0.16	*d*=-0.16	*d*=-0.01
Rhythmicity–eating	0.01 (1.04)	0.05 (1.19)	0.10 (0.98)	F=0.11, p=.893	*d*=-0.09	*d*=-0.05	*d*=-0.04	*d*=0.08	*d*=-0.02	*d*=0.10	*d*=0.09	*d*=-0.01	*d*=0.10
Rhythmicity–daily habits	0.17 (1.26)	0.31 (1.23)	0.02 (0.93)	F=1.47, p=.232	[b]*d*=0.15	[b]*d*=0.27	*d*=-0.11[b]	*d*=0.22	*d*=-0.18	*d*=0.05	*d*=0.24	*d*=0.20	*d*=0.05
Activity–level	0.73 (1.51)	0.00 (1.38)	0.37 (1.26)	**F=3.75, p=.025**	*d*=0.27	*d*=-0.18	***d*=0.51**[*]	*d*=-0.06	***d*=-0.23**[*]	*d*=0.17	*d*=-0.12	***d*=-0.28**[*]	*d*=0.16
Activity Sleep[f]	0.15 (1.19)	-0.31 (1.11)	0.07 (1.10)	**F=3.24 p=.041**	*d*=0.07	***d*=-0.34**[*]	*d*=0.41	*d*=-0.01	***d*=-0.31**[*]	*d*=0.28	*d*=-0.01	***d*=-0.31**[*]	*d*=0.28
Task orientation	-0.43 (1.35)	-0.30 (1.51)	-0.15 (1.20)	F=0.64, p=.527	*d*=-0.23	*d*=-0.11	*d*=0.09	*d*=0.06	*d*=-0.07	*d*=-0.12	*d*=0.11	*d*=-0.03	*d*=0.15
Mood[g]	-0.71 (1.28)	-0.73 (1.51)	-0.03 (1.09)	**F=7.60, p=.001**	[b]***d*=-0.60**[*]	[b]***d*=-0.54**[**]	[b]*d*=0.01	***d*=-0.54**[**]	***d*=-0.43**[**]	*d*=-0.13	[c]***d*=-0.46**[**]	***d*=-0.38**[**]	*d*=-0.10
Approach	-0.43 (1.27)	-0.28 (1.12)	-0.03 (1.06)	F=2.07, p=.129	*d*=-0.36	*d*=-0.23	*d*=-0.13	***d*=-0.32**[*]	*d*=-0.20	*d*=-0.13	*d*=-0.27	*d*=-0.17	*d*=-0.11
Flexibility[h]	-0.51 (1.17)	-0.13 (1.06)	-0.17 (1.02)	F=1.69, p=.187	*d*=-0.32	*d*=-0.04	*d*=-0.35	*d*=-0.14	*d*=-0.06	*d*=-0.08	*d*=-0.09	*d*=-0.03	*d*=-0.09
Factors													
Task rhythmicity	-0.21 (1.09)	-0.08 (1.30)	-0.01 (0.98)	F=0.42, p=.658	[b]*d*=-0.20	[b]*d*=-0.06	[b]*d*=-0.10	*d*=0.08	*d*=-0.05	*d*=0.13	*d*=0.11	*d*=-0.03	*d*=0.11
Activity	0.54 (1.34)	-0.17 (1.19)	0.26 (1.13)	**F=5.14, p=.007**	*d*=0.23	***d*=-0.37**[*]	***d*=0.57**[*]	*d*=-0.03,	***d*=-0.31**[**]	*d*=0.26	*d*=-0.09	***d*=-0.35**[**]	*d*=0.25
Adaptability	-0.76 (1.31)	-0.58 (1.33)	-0.12 (1.08)	**F=5.10, p=.007**	***d*=-0.56**[*]	***d*=-0.38**[*]	*d*=-0.14	***d*=-0.47**[**]	***d*=-0.33**[**]	*d*=-0.16,	***d*=-0.39**[*]	***d*=-0.28**[*]	*d*=-0.13

Abbreviations: BpO: bipolar offspring, CcO: community control offspring, NS: not significant; SES: socio-economic status, SzO: schizophrenia offspring. Effect sizes are shown as Cohen's d. Significant results are shown in bold; [*]p<.05, [**]p<.01, [***]p<.001. [a]Significance level based on 95% confidence intervals calculated with bias-corrected and accelerated (BCa) bootstrapping (1000 bootstrap samples). [b]Games-Howell post-hoc test. [c]Covariates: family, age, sex, SES (high/medium-low). [d]Covariates: family, age, sex, SES (high/medium-low), lifetime diagnosis. [e]Differences between SzO and CcO remained significant after removing two children from the SzO group who also had a parent with bipolar disorder (d=0.44, p<.05). [f]N=79 in the BpO subgroup for these analyses. [g]N=100 in the CcO subgroup for these analyses. [h]N=100 in the CcO and N=79 in the BpO subgroups for these analyses.

Table 3: Logistic regression models exploring the association of temperament dimensions with lifetime psychopathology and current impaired adjustment in bipolar and schizophrenia offspring

		OR [95% CI]	*p*	AUC [95% CI]	R^2_N
Bipolar offspring					
Lifetime diagnosis[a]	Lower positive mood	2.31 [1.43-3.71]	.001	0.77 [0.66-0.88]	0.27
Lifetime internalizing disorder	Lower positive mood	1.84 [1.28-2.64]	.001	0.72 [0.61-0.83]	0.21
Lifetime externalizing disorder	Male sex	5.58 [1.59-19.6]	.007	0.82 [0.72-0.92]	0.37
	Lower positive mood	1.48 [1.01-2.18]	.042		
	Lower task orientation	1.69 [1.14-2.51]	.001		
Impaired current adjustment[b]	Lower positive mood	2.30 [1.18-4.46]	.014	0.93 [0.85-1]	0.65
	Lower task orientation	2.74 [1.41-5.32]	.003		
	Lower flexibility	4.90 [1.66-14.49]	.004		
	Lower activity sleep	4.78 [1.51-15.15]	.008		
Schizophrenia offspring					
Lifetime diagnosis[a]	Male sex	12.5 [1.25-124.46]	.031	0.74 [0.57-0.98]	0.28
Lifetime internalizing disorder	Higher activity	2.31 [1.22-4.38]	.011	0.79 [0.64-0.94]	0.32
Lifetime externalizing disorder	Male sex	10.66 [1.48-76.82]	.019	0.83 [0.70-0.97]	0.42
	Higher flexibility	3.28 [1.20-8.97]	.021		
Impaired current adjustment[b]	Lower positive mood	2.87 [1.07-7.66]	.035	0.89 [0.77-1]	0.57
	Parent affected (mother)	0.03 [0.001-0.532]	.018		
	Current diagnosis	42.23 [1.68-1058.6]	.023		

Abbreviations: AUC: area under the operating receiver characteristic curve, CI: confidence interval, OR: odds ratio, R^2_N: Nagelkerke's pseudo-R^2 statistic. [a]All diagnoses include threshold and subthreshold K-SADS-PL diagnoses. [b]Scores ≥0.33 in the Premorbid Adjustment Scale. Only significant covariates in the models are shown.

FIGURE 1

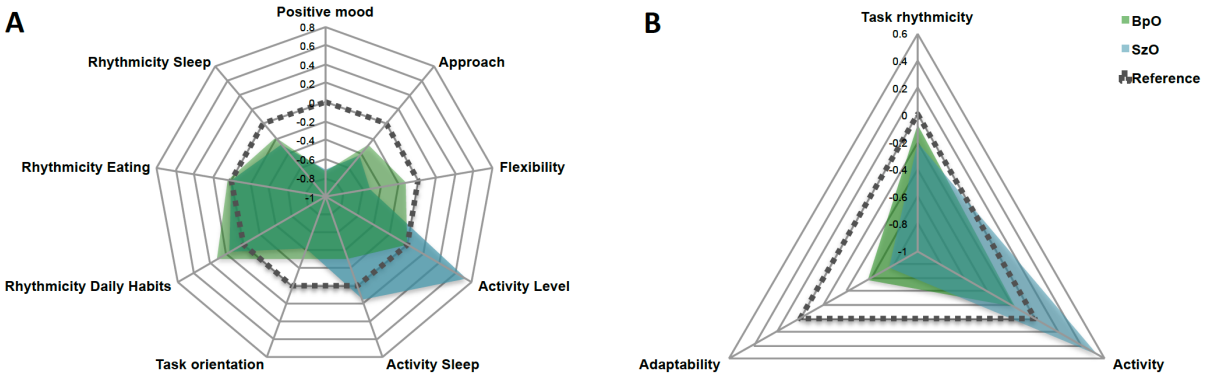

Fig. 1 Temperament dimensions (A) and factors (B) in schizophrenia and bipolar offspring

Reference: For illustration purposes, the scores from the community control offspring sample with no lifetime psychopathology are depicted as a reference. *Abbreviations: BpO: Bipolar Offspring, SzO: Schizophrenia Offspring*