Characterizing offspring of bipolar parents: a review of the literature

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Offspring of parents with bipolar disorder (O-BP) is a high-risk cohort for mental illness in general and bipolar disorder (BD) specifically. This review aims to delineate the main clinical features of O-BP, including the psychopathology, interpersonal functioning, temperamental and personality features, neurocognitive deficits and neurobiological dysfunctions. Evidence indicates that several internalizing and externalizing symptoms/disorders are more prevalent in O-BP than in offspring of healthy control parents (O-HC). Furthermore, O-BP exhibits poorer interpersonal functioning than O-HC. Moreover, O-BP also endorses higher activity level, emotionality and behavioral disinhibition compared to O-HC. Besides, O-BP displays greater deficits on memory, cognitive flexibility and social cognition compared to O-HC. Finally, O-BP exhibits dysfunctional modulation in cortico-subcortical areas, more white matter abnormalities and higher cortisol basal levels compared to O-HC. Overall, these findings are discussed regarding the natural course and potential risk factors or endophenotypes for major mood disorders in general and BD specifically.

Keywords: Offspring, Bipolar disorder, Symptomatology, Neurocognition, Neuroanatomy

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Caracterización de los descendientes de padres con trastorno bipolar: Una revisión de la literatura

Los descendientes de padres con trastorno bipolar (O-BP *offspring of parents with bipolar disorder*) son una cohorte de alto riesgo para la enfermedad mental en general y el trastorno bipolar en particular. Esta Review tiene como objetivo delimitar las principales características clínicas de los O-BP, incluyendo su psicopatología, funcionamiento interpersonal, características temperamentales y de personalidad, los déficits neurocognitivos y las disfunciones neurobiológicas. La evidencia indica que varios síntomas/trastornos internalizantes y externalizantes son más frecuentes en O-BP que en hijos de padres sanos (O-HC *offspring of healthy control parents*). Por otra parte, los O-BP exhiben peor funcionamiento interpersonal que los O-HC. Por otra parte, los O-BP también presentan mayor nivel de actividad, emotividad y desinhibición conductual en comparación con los O-HC. Además, los O-BP muestra mayores déficits de memoria, flexibilidad cognitiva y cognición social en comparación con los O-HC. Por último, los O-BP exhiben una modulación disfuncional de áreas córtico-subcorticales, anomalías de la sustancia blanca y niveles de cortisol basal más elevados en comparación con los O-HC. En general, estos resultados son discutidos en relación a los factores de riesgo, curso natural y potenciales endofenotipos para los trastornos del estado de ánimo en general y el trastorno bipolar específicamente.

Palabras clave: Descendencia, Trastorno bipolar, Sintomatología, Neurocognición, Neuroanatomía

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INTRODUCTION

Offspring of parents with bipolar disorder (O-BP) is a high-risk cohort for mental illness in general and BD specifically[1]. Within this sample, prevalence rates for BD across childhood and adolescence range from 8.5% to 16%, with an odds ratio (OR) of up to 16.0 compared to offspring of healthy control parents (O-HC)[2-5].

Overall, the increased risk for early-onset BD among O-BP has suggested that the subset of O-BP might be a suitable sample for addressing some intriguing and unresolved issues in BD, namely: prodromal symptoms, psychosocial, psychopathological risk factors and potential endophenotypes[6]. Moreover, by clarifying these concerns, clinicians would be able to deliver early interventions aimed at delaying or preventing the onset of BD as well as ameliorating its course in the long-term[7,8].

Therefore, despite being a target sample that has been neglected over the past century[9,10], a burgeoning literature has emerged during the last 15 years which shed some light on long-standing queries. Thus, since previous systematic reviews have been able to include results from limited time period[11,12], we considered the need to integrate new findings into an up-to-date systematic review. Our primary goal was to comprehensively characterize O-BP by displaying the main findings regarding the (i) psychopathology, (ii) interpersonal functioning, (iii) temperamental and personality features, (iv) neurocognitive characteristics and (v) neurobiological profile.

METHOD

Search strategy

A literature search was carried out on the PsycINFO and PubMed databases from 1990 to June 2014. The terms employed included indexing terms (e.g., MeSH) and free texts: ((offspring OR relative OR family OR high-risk) AND (youth OR pediatric OR child OR adolescent) AND (bipolar disorder)).

Selection criteria

Inclusion criteria included youth that were the offspring of at least one parent diagnosed with type I BD or type II BD according to DSM-IV-TR criteria (APA, 2000). Treatment studies on O-BP were excluded because they went beyond the scope of this systematic review. Thus, 112 manuscripts fulfilled the inclusion criteria. Six of them were partial reviews and other 3 were full reviews. The remaining texts were original papers. We should underscore that O-BP from these studies were usually aged 2-20, although 5 studies recruited young adults as well (up to age 30).

Data extraction

The following variables were recorded for all the manuscripts: i) type of methodology (cross-sectional vs. prospective study); ii) instruments used (diagnostic interviews, psychometric/neuropsychological tests or medical equipment); iii) comparative groups used (offspring of healthy control parents, O-HC; offspring of parents with schizophrenia, O-SzP; offspring of parents with unipolar depression, O-DP; youth with pediatric bipolar disorder, PBD); and iv) outcome measures (symptomatology, interpersonal functioning, temperamental and personality features, neurocognitive findings and neurobiological results).

RESULTS

Psychopathology in offspring of bipolar parents

The first goal of our systematic review was to determine which symptoms and mental disorders were displayed by O-BP. The main findings related to these issues were arranged in both dimensional and categorical psychopathology, respectively (see Table 1 and Table 2).

Dimensional psychopathology

Psychophysiological symptoms

Concerning sleep disturbances and somatic complaints, a cross-sectional study comprising preschool children found greater severity of these symptoms among O-BP compared to O-HC through the Child Behavior Checklist (CBCL) as well as the Early Childhood Inventory (ECI-4)[13]. Similarly, three prospective studies carried out within the same cohort sample (Amish children) over 7, 10 and 16 years showed that O-BP who developed BD I had displayed more sleep disturbances and somatic complaints from childhood to adolescence compared to O-HC[14-16]. It should be pointed out that the psychophysiological symptoms identified in these studies were mostly evidenced in childhood rather than in adolescence samples.

Mood psychopathology

Regarding mood psychopathology, several cross-sectional studies comprising either children or adolescents obtained higher mood lability among O-BP compared to O-HC

Table 1 Overview of main evidence regarding dimensional psychopathology in O-BP

Psychopathology	Authors	Type of study	Main finding
Sleep disturbances	Egeland et al., 2003	Prospective (7 years)	Higher in O-BP than in O-HC
	Shaw et al., 2005	Prospective (10 years)	Higher in O-BP than in O-HC
	Egeland et al., 2013	Prospective (16 years)	Increased risk for BD in O-BP
	Maoz et al., 2014	Cross-sectional	Higher in O-BP than in O-HC
Somatic complaints	Egeland et al., 2003	Prospective (7 years)	Higher in O-BP than in O-HC
	Shaw et al., 2005	Prospective (10 years)	Higher in O-BP than in O-HC
	Egeland et al., 2013	Prospective (16 years)	Increased risk for BD in O-BP
	Maoz et al., 2014	Cross-sectional	Higher in O-BP than in O-HC
Mood lability	Egeland et al., 2003	Prospective (7 years)	Higher in O-BP than in O-HC
	Findling et al., 2005	Cross-sectional	Higher in O-BP than in O-HC
	Shaw et al., 2005	Prospective (10 years)	Higher in O-BP than in O-HC
	Diler et al., 2011	Cross-sectional	Higher in O-BP than in O-HC
	Birmaher et al., 2013	Cross-sectional	Higher in O-BP than in O-HC
	Maoz et al., 2014	Cross-sectional	Higher in O-BP than in O-HC
Depressive /	Dienes et al., 2002	Cross-sectional	Higher in O-BP than in O-HC
anxiety symptoms	Egeland et al., 2003	Prospective (7 years)	Higher in O-BP than in O-HC
	Shaw et al., 2005	Prospective (10 years)	Higher in O-BP than in O-HC
	Giles et al., 2007	Cross-sectional	Higher in O-BP than in O-HC
	Petresco et al., 2009	Cross-sectional	Higher in O-BP than in O-HC
	Simeonova et al., 2009	Cross-sectional	Higher in O-BP than in O-HC
	Diler et al., 2011	Cross-sectional	Higher in O-BP than in O-HC
	Egeland et al., 2012	Prospective (16 years)	Increased risk for BD in O-BP
	Birmaher el al., 2013	Cross-sectional	Higher in O-BP than in O-HC
Irritability	Dienes et al., 2002	Cross-sectional	Higher in O-BP than in O-HC
	Findling et al., 2005	Cross-sectional	Higher in O-BP than in O-HC
	Farchione et al., 2007	Cross-sectional	Higher in O-BP than in O-HC
	Giles et al., 2007	Cross-sectional	Higher in O-BP than in O-HC
	Diler et al., 2011	Cross-sectional	Higher in O-BP than in O-HC
	Birmaher et el., 2013	Cross-sectional	Higher in O-BP than in O-HC
	Maoz et al., 2014	Cross-sectional	Higher in O-BP than in O-HC
Inattention	Egeland et al., 2003	Prospective (7 years)	Higher in O-BP than in O-HC
	Shaw et al., 2005	Prospective (10 years)	Higher in O-BP than in O-HC
	Giles et al., 2007	Cross-sectional	Higher in O-BP than in O-HC
Thought problems	Petresco et al., 2009	Cross-sectional	Higher in O-BP than in O-HC
	Klimes et al., 2012	Prospective (15 years)	Increased risk for non-specific mental disorders in O-BP
	Narayan et al., 2012	Review	Higher in O-BP than in O-HC

BD, bipolar disorder; O-HC, offspring of healthy control parents; O-BP, offspring of bipolar parents; O-DP, offspring of parents with unipolar depression

using both the Children's Affective Lability Scale (CALS)[17] and the CBCL-Dysregulation Profile (CBCL-DP)[13,18,19]. It should underscore that the study using the CALS recruited the largest sample size included in this first section. Likewise, two prospective studies carried out over 7 and 10 years within the aforementioned Amish children found greater mood lability in O-BP than in O-HC in prepubertal stage[15,16]. Moreover, several cross-sectional studies found greater de-

Table 2 BD, bipolar disorder; O-HC, offspring of healthy control parents; O-BP, offspring of bipolar parents; O-DP, offspring of parents with unipolar depression

Mental disorders	Authors	Type of study	Main finding
MMD	Lapalme et al., 1997	Review	Higher in O-BP than in O-HC
	Duffy et al., 2007	Prospective (4 years)	Increased risk for BD in O-BP with prior MDE
Anxiety disorders	Akdemir et al., 2008	Cross-sectional	Higher in O-BP than in O-HC
	Birmaher et al., 2009	Cross-sectional	Higher in O-BP than in O-HC
	Duffy et al., 2009	Prospective (15 years) without control group	Increased risk for BD in O-BP with prior MDE
	Duffy et al., 2010	Prospective (15 years)	Increased risk for BD in O-BP with prior MDE
	Duffy et al., 2012	Prospective (4 years) without control group	Increased risk for substance misuse in O-BP with prior MMD
	Vandeleur et al., 2012	Cross-sectional	Higher in O-BP than in O-HC/O-DP
	García et al., 2013	Cross-sectional	Higher in O-BP than in O-HC
	Mesman et al., 2013	Prospective (12 years) without control group	Increased risk for BD in O-BP with prior MDE
	Sparks et al., 2014	Cross-sectional	Higher in O-BP than in O-HC
	Henin et al., 2005	Cross-sectional	Higher in O-BP than in O-HC
	Hirshfeld et al., 2006	Cross-sectional	Higher in O-BP than in O-HC y O-DP
	Duffy et al., 2007	Prospective (4 years)	Increased risk for BP in O-BP with prior anxiety disorder
	Birmaher et al., 2009	Cross-sectional	Higher in O-BP than in O-HC
	Duffy et al., 2010	Prospective (15 years)	Increased risk for MMD in O-BP with prior anxiety disorder
	Vandeleur et al., 2012	Cross-sectional	Higher in O-BP than in O-HC. No significant differences between O-BP and O-DP.
	Duffy et al., 2013	Prospective (15 years)	Increased risk for MMD in O-BP with prior anxiety disorderHigher in O-BP than in O-HC
	García et al., 2013	Cross-sectional	Higher in O-BP than in O-HC
ADHD and DBD	Henin et al., 2005	Cross-sectional	Higher DBD rates in O-BP than in O-HC
	Hirshfeld et al., 2006	Cross-sectional	Higher ADHD/DBD rates in O-BP than in O-HC/ O-DP
	Duffy et al., 2007	Prospective (4 years)	Increased risk for BD in O-BP with prior ADHD
	Akdemir et al., 2008	Cross-sectional	Higher DBD rates in O-BP than in O-HC
	Birmaher et al., 2010	Cross-sectional	Higher ADHD rates in O-BP than in O-HC
	Duffy et al., 2012	Review (prospective studies)	No consistent evidence concerning ADHD as a risk factor for BD
	García et al., 2013	Cross-sectional	Higher ADHD rates in O-BP than in O-HC

ADHD, attention deficit and hyperactivity disorder; BD, bipolar disorder; DBD, disruptive behavior disorder; MMD, major mood disorder; MDE, major depressive episode; O-HC, offspring of healthy control parents; O-BP, offspring of bipolar parents; O-DP, offspring of parents with unipolar depression

pressed mood and anxiety symptoms among O-BP compared to O-HC, mainly using the CBCL and the Youth Self-Report (YSR)[17,18,20-23]. These results were replicated in the aforementioned prospective studies undertaken with Amish youth. Hence, O-BP who ultimately developed BD had exhibited higher anxiety and depressed mood from childhood to adolescence compared to O-HC[14-16]. Finally, most cross-sectional studies also found greater irritability symptoms (including aggressiveness) in O-BP compared to O-HC using several psychometric tests, namely the CBCL and/or Teachers' Re-

port Forms (TRF)[13,18-21], the CALS[17] and the Children's Hostility Inventory (CHI)[24].

Cognitive psychopathology

Concerning cognitive psychopathology, most cross-sectional and prospective studies have found more distractibility in O-BP compared to O-HC, mainly among childhood samples[15,16,21,25]. These findings were obtained using psychometric instruments such as the CBCL instead of neuropsychological tests. Regarding thought disturbances as measured by psychometric tests (e.g., CBCL), studies usually included a third group of O-DP in order to determine whether or not these deficits are specifically related to O-BP. Following this methodology, most cross-sectional and prospective research showed greater thought disturbances among O-BP and O-DP than among O-HC[22,26], without consistent differences between the first two groups. Similarly, one prospective study over 15 years indicated that this higher deficit among O-BP increased the risk for non-specific mental disorders across early adulthood rather than the risk for BD exclusively[27].

Categorical psychopathology

Major mood disorders (MMD)

Overall, several cross-sectional studies have pointed out a greater percentage of MMD among O-BP compared to O-HC[28-32] and O-DP[32] as measured by the Schedule for Affective Disorders and Schizophrenia for School Aged Children (K-SADS). Rates within this targeted sample ranged from 10% to 34.5% and are on average 4 times higher than expected in O-HC[33]. Similarly, prospective studies over 12-15 years have found elevated MMD among O-BP (up to 54%)[25,34-36], although comparative groups were not always included in these studies[34,35]. Specifically, the presence of MMD among O-BP increased the risk of subsequently developing substance use disorders, reaching an odds ratio of 2.4[36,37]. Likewise, prospective studies have shown that a majority of O-BP who met BD criteria had previously been diagnosed with major depressive disorder (MDD)[25,34-36].

Anxiety disorders

Regarding anxiety disorders, cross-sectional research has agreed on a higher percentage of anxiety disorder among O-BP than O-HC[29,30,32,38,39] as ascertained by the K-SADS. For the former group, rates range from 14% to 42.5% and the odds ratio reached was as high as 2.3[29]. Conversely, comparative data including a third group of O-DP yielded no consistent differences between both clinical groups[32,39]. Furthermore, several prospective studies up to 15 years have also shown higher rates of anxiety disorders among O-BP compared to O-HC[25,36,40], in some cases predicting an increased risk for MMD[36,40] as well as specifically for BD[25].

Attention deficit hyperactivity disorder (ADHD) and disruptive behavior disorder

Concerning ADHD, cross-sectional studies found higher rates of this mental disorder among O-BP compared to O-HC[30,39] and O-DP[39]. These findings were replicated even in samples of preschool children[41]. Conversely, prospective studies yielded inconsistent findings regarding whether ADHD predicted BD among O-BP[42]. For instance, one study showed that ADHD was an antecedent condition to BD among the offspring of lithium non-responders only[25].

Regarding disruptive behavior disorder, several cross-sectional studies have found higher rates of this mental disorder among O-BP compared to O-HC[28,38,39].

Interpersonal functioning in offspring of bipolar parents

Concerning this issue, a majority of cross-sectional studies undertaken during last years pointed out lower interpersonal functioning among O-BP compared to O-HC, mainly using the Adolescent Longitudinal Interval Follow-Up Evaluation (A-LIFE)[43,44]. However, these results have been more consistent in samples of children than of adolescents[45,46].

Several mediating variables have been suggested to explain this main result. Regarding this issue, a single prospective study[47] and many other cross-sectional studies[43,48-54] have postulated that both the parents' personality traits (higher neuroticism and lower agreeableness) and the children's psychopathology could account for an inadequate family environment (lower cohesion) and dysfunctional parenting style (more rejection) which, in turn, could lead to lower interpersonal functioning among O-BP.

Irrespective of their risk status (O-BP vs. O-HC), both cross-sectional and prospective studies have highlighted an increased risk of triggering MMD among youth who have suffered from interpersonal stress. This relationship is stronger among youth with prior anxiety or depressive symptoms[55,56].

Temperamental and personality features in offspring of bipolar parents

Affective temperaments such as hyperthymia or cyclothymia have been associated with bipolar disorder[57]. Hence,

a plethora of research has been focused on O-BP in order to determine whether some affective temperaments may be potential precursors for BD. Regarding temperamental variables, cross-sectional studies found greater "emotionality"[58], "activity level"[59] and "behavioral disinhibition"[60] among O-BP compared to O-HC. In addition, one prospective study showed increased risk for developing MMD among those O-BP who reported higher emotionality[61]. Conversely, no between-group differences were obtained in "sensation-seeking"[62], "sensitivity to reward and punishment"[62] and "hypomanic temperament"[63].

Concerning personality variables, cross-sectional research showed no significant differences between non-bipolar O-BP and O-HC in several variables, namely "rumination"[62], "attributional style"[63], "neuroticism"[64], "coping style"[62,65] and "self-esteem"[62,65]. However, poorer scores on some variables were found among affected (bipolar) O-BP compared to O-HC[62,65].

Neurocognitive profile in offspring of bipolar parents

Sustained attention

Concerning sustained attention, studies have yielded inconsistent results using the Continuous Performance Test (CPT) (see table 3). On the one hand, several studies showed poorer sustained attention among O-BP compared to O-HC[66,67]. On the other hand, no significant differences between O-BP and O-HC were found in other studies[68-70]. Besides, studies which included a third group of offspring of one parent with schizophrenia (O-SzP) showed no consistent differences between both clinical groups[67,69].

Verbal and visual-spatial memory

With respect to verbal and visual-spatial memory, studies found greater deficits among O-BP and O-SzP compared to O-HC through the California Verbal Memory Test (CVMT) and the Rey complex figure test, respectively[69,71].

Executive functions

Regarding executive functions, results concerning working memory (WM) were inconsistent. On the one hand, two inquiries found higher deficits among O-BP compared to O-HC using either the Attention Network Test-Short version (ANT-S)[72] or the Stroop Test[70]. On the other hand, more studies found no significant differences between O-BP and O-HC on this neurocognitive variable using the Stroop test[68], a delayed spatial memory test[67], the N-back WM task[73] and the digit span subtest[68]. Moreover, studies which included a third group of O-DP/O-SzP showed no conclusive differences between both clinical groups[67,69,72].

With respect to cognitive flexibility, studies found greater impairments among O-BP compared to O-HC and O-SzP using the Eriksen Flanker Task[74] and the Wisconsin Card Sorting Test (WCST)[68,69].

Finally, research focused on response inhibition also yielded mixed findings. Some studies found poorer performance in O-BP than in O-HC using the CPT[66,67] and a stop signal task[70]. Alternatively, other studies have not evidenced differences between O-BP and O-HC using both neuropsychological tests[68,69,75]. In addition, those studies that included a third group of O-SzP found no conclusive differences between both clinical groups[67,69].

Social cognition

Regarding social cognition, studies found greater impairment in non-bipolar O-BP compared to O-HC[76]. This finding was obtained using the Social Responsiveness Scale[77], the Emotional Expression Multimorph Task[78] and the Diagnostic Analysis of Nonverbal Accuracy (DANVA) scale[79]. Interestingly, studies which included a third group of affected (bipolar) O-BP or PBD youth found that the samples did not differ from each other[76,78,79].

Neurobiological profile in offspring of bipolar parents

To improve the readability of this section, we organized the findings within three categories, namely neurofunctional, neuroanatomical and neuroendocrine findings.

Neurofunctional findings

Regarding neurofunctional results using functional magnetic resonance imaging (fMRI), several studies found that O-BP and PBD youth, compared to their O-HC counterparts, showed dysfunctional modulation in the amygdala and/or inferior frontal gyrus in response to stimuli changes during facial emotion discrimination tasks[76,80]. Likewise, other study showed that O-BP and PBD youth displayed dysfunctional activation in the striatum during a motor response inhibition task compared to O-HC, although the specific regions implicated were different for the former groups[75]. Moreover, one study revealed that compared to O-HC, O-BP exhibited altered task-dependent modulation of frontopolar, cerebellar vermis and insula activity during the N-back WM task[73]. Furthermore, a recent fMRI study indicates that O-BP have less activation in the pregenual cingulate than O-HC when anticipate losses during a

Table 3 Overview of neurocognitive findings among unaffected O-BP

Neurocognitive domain	Authors	Neuropsychological task	Main finding
Sustained attention	Klimes-Dougan et al., 2006	CPT	Lower performance in O-BP than in O-HC
	Brotman et al., 2009	CPT	Similar lower performance in O-BP/PBD youth than in O-HC
	Maziade et al., 2009	CPT	No significant differences between O-BP and O-HC/O-SzP
	Singh et al., 2009	CPT	No significant differences between O-BP and O-HC
	Diwadkar et al., 2011	CPT	Lower performance in O-BP than in O-HC/O-SzP
	Karakurt et al., 2013	CPT	No significant differences between O-BP and O-HC. PBD youth performed poored than O-BP/O-HC
Verbal/visual-spatial memory	Klimes-Dougan et al., 2006	Rey complex figure test	Lower performance in O-BP than in O-HC
	Maziade et al., 2009	CVLT Rey complex figure test	Similar lower performance in O-BP/ O-SzP than in O-HC
	Maziade et al., 2011	CVLT Rey complex figure test	Similar lower performance in O-BP/ O-SzP than in O-HC
Working memory	Maziade et al., 2009	Digit span subtest	No significant differences between O-BP and O-HC/O-SzP
	Singh et al., 2009	Stroop test	Lower performance in O-BP than in O-HC
	Diwadkar et al., 2011	Delayed spatial memory test	No significant differences between O-BP and O-HC. O-SzP performed poorer than O-BP/O-HC
	Thermenos et al., 2011	N-back WM task	No significant differences between O-BP and O-HC
	Belleau et al., 2013	ANT-S	Similar lower performance in O-BP/ O-DP than in O-HC
	Karakurt et al., 2013	Stroop test	No significant differences between O-BP and O-HC. PBD youth performed poored than O-BP/O-HC
Cognitive flexibility	Klimes-Dougan et al., 2006	WCST	Lower performance in O-BP than in O-HC
	Maziade et al., 2009	WCST	Lower performance in O-BP than in O-HC/O-SzP
	Karakurt et al., 2013	WCST	Lower performance in O-BP than in O-HC. PBD youth performed poored than O-BP/O-HC
	Patino et al., 2013	Eriksen flanker task	Lower performance in O-BP than in O-HC

Table 3 Continuation

Neurocognitive domain	Authors	Neuropsychological task	Main finding
Response inhibition	Frangou et al., 2005	Hayling Sentence Completion Task	Lower performance in O-BP than in O-HC
	Brotman et al., 2009	CPT	Similar lower performance in O-BP/PBD youth than in O-HC
	Maziade et al., 2009	CPT	No significant differences between O-BP and O-HC/O-SzP
	Singh et al., 2009	Stop signal task	Lower performance in O-BP than in O-HC
	Diwadkar et al., 2011	CPT	Lower performance in O-BP than in O-HC/O-SzP
	Deveney et al., 2012	Stop signal task	No significant differences between O-BP and O-HC/PBD youth
	Karakurt et al., 2013	CPT	No significant differences between O-BP and O-HC. PBD youth performed poored than O-BP/O-HC
Social cognition	Brotman et al., 2008a	EEMT	Similar lower performance in O-BP/PBD youth than in O-HC
	Brotman et al., 2008b	DANVA	Similar lower performance in O-BP/PBD youth than in O-HC
	Whitney et al., 2013	Social responsiveness scale	Lower performance in O-BP than in O-HC
	Brotman et al., 2014	Facial emotion discrimination task	Similar lower performance in O-BP/PBD youth than in O-HC

ANT-S, Attention Network Test-Short version; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; DANVA, Diagnostic Analysis of Nonverbal Accuracy scale; EEMT, Emotional Expression Multimorph Task; O-BP, offspring of bipolar parents; O-DP, offspring of parents with unipolar depression; O-HC, offspring of healthy control parents; O-SzP, offspring of parents with schizophrenia; PBD, pediatric bipolar disorder; WCST, Wisconsin Card Sorting Test; WM, working memory.

monetary incentive delay task. Conversely, when receiving rewards, O-BP have greater activation in the left lateral orbitofrontal cortex[81]. Finally, other comparative study between O-BP and O-HC reveal that the former group has decreased connectivities between the left amygdala and pregenual cingulate, between the subgenual cingulate and supplementary motor cortex, and between the left ventrolateral prefrontal cortex (VLPFC) and left caudate[82].

Neuroanatomical findings

Concerning the amygdala volume as measured by structural MRI, studies concurred in finding no significant differences between O-BP and O-HC[83-87]. In addition, some studies also found amygdala volume reduction among affected (bipolar) O-BP youth compared to non-bipolar O-BP[85]. Similarly, the research focused on striatum showed no evidence suggesting caudate volume reduction in O-BP using the same methodology[87,88]. Finally, single studies aimed at assessing the thalamus, prefrontal cortex, pituitary and subgenual cingulate yielded no differences between O-BP and O-HC[87,89,90]. We should underscore that studies focused on neuroanatomy usually excluded or controlled for the effects of psychotropic medications.

Furthermore, with one exception[91], white matter abnormalities measured by both Diffusion Tensor (DT) and Fluid Attenuated Inversion Recovery (FLAIR) images tended to displayed abnormalities in the bilateral superior longitudinal fasciculus I[92] as well as in the corpus callosum and temporal associative tract[93] among O-BP compared to O-HP.

Neuroendocrine findings

Research aimed at addressing the hypothalamic-pituitary-adrenal (HPA) axis among O-BP studied both basal cortisol levels and stress cortisol reactivity[94] (see Table 4). First, a pilot study found that O-BP exhibited greater afternoon levels of cortisol than O-HC[95]. Similarly, other study showed that O-BP had higher daytime levels of cortisol at baseline than O-HC[96]. Conversely, no between-group differences in the cortisol response to a laboratory psychosocial

Table 4 Overview of neuroendocrine findings among unaffected O-BP

Neuroendocrine substance	Autores	Type of methodology	Main finding
Cortisol	Ellenbogen et al., 2004	Cross-sectional	O-BP exhibited higher afternoon levels than O-HC
	Ellenbogen et al., 2006	Cross-sectional	O-BP had higher daytime levels, but no differences in cortisol response, than O-HC
	Ellenbogen et al., 2009	Prospective (2 years)	O-BP showed higher afternoon levels than O-HC
	Ellenbogen et al., 2010	Cross-sectional	O-BP with high (vs. low) quarrelsomeness displayed lower afternoon levels
	Ostiguy et al., 2011	Cross-sectional	O-BP with high (vs. low) interpersonal stress displayed higher levels after awakening
	Ellenbogen et al., 2013	Prospective (8 years)	Overall, low structure by parents predicted higher levels after awakening and during a laboratory task
N-acetyl aspartate & myo-inositol	Gallelli et al., 2005	Cross-sectional	No different levels between non-bipolar O-BP and O-HC/PBD in DLPFC
	Hajek et al., 2008	Cross-sectional	No different levels between non-bipolar O-BP and O-HC/PBD in DLPFC
	Singh et al., 2011	Cross-sectional	Lower levels in O-BP than in O-HC in vermis
	Singh et al., 2013	Cross-sectional	No different levels between non-bipolar O-BP and O-HC/PBD in DLPFC
Glutamate	Singh et al., 2010	Prospective (5 years)	No differences between non-bipolar O-BP and O-HC. PBD youth displayed higher levels

DLPFC, dorsolateral prefrontal cortex; O-BP, offspring of bipolar parents; O-HC, offspring of healthy control parents; PBD, pediatric bipolar disorder.

stressor were found. Two years later, cortisol levels still remained higher in the afternoon among O-BP[97]. With respect to modulating variables, a study showed that O-BP with high levels of quarrelsomeness (measured by an event-contingent recording) displayed lower afternoon cortisol levels than O-BP with poor levels of quarrelsomeness and O-HC[98]. In addition, a study found that O-BP who experienced high interpersonal stress displayed a larger cortisol rise following awakening than the O-BP reporting low interpersonal stress[99]. Interestingly, this difference was not detected in O-HC. Finally, a prospective study showed that low levels of structure provided by parents in middle childhood were predictive of an elevated cortisol response following awakening and during a laboratory psychosocial stressor, irrespective of risk status (O-BP or O-HC)[100].

Concerning metabolites, cross-sectional and prospective research concurred in finding no significant differences between O-BP and O-HC in n-acetyl aspartate and myo-inositol concentrations in the dorsolateral prefrontal cortex (DLPFC) using proton magnetic resonance spectroscopy (H-MRS)[101-103]. Conversely, one study found that O-BP showed lower myo-inositol concentrations in the vermis than O-HC[104]. Finally, a single study following the same methodology evidenced that affected (bipolar) O-BP displayed lower glutamate concentrations in the anterior cingulate cortex compared to non-bipolar O-BP and O-HC[105]. We should underscore that some of these studies did not control exposure to medication as a confounding variable for the results obtained[103,104].

DISCUSSION

This systematic review has striven to delineate O-BP by displaying the main findings regarding the (i) psychopathology, (ii) interpersonal functioning, (iii) temperamental and personality features, (iv) neurocognitive characteristics and (v) neurobiological profile. First, the evidence indicates that

O-BP tends to exhibit higher rates of clinical problems compared to O-HC and, in most cases, relative to O-DP. With respect to dimensional psychopathology, O-BP displays more somatic complaints, sleep problems, anxiety/depressed mood and distractibility across childhood (vs. adolescence), whereas others appear mainly through adolescence (e.g., irritability, mood lability, thought disturbances). Of note, prospective studies among O-BP indicate that these unspecified symptoms in childhood increase the risk of BD long afterward. Regarding the categorical psychopathology, O-BP presents more MMD, anxiety disorders, disruptive behavior disorders and ADHD. Of interest, prospective studies among O-BP evidence that anxiety disorders tend to precede MMD`s, whereas MMD´s predate the onset of substance use disorders. Particularly, some O-BP diagnosed of major depressive episode are at particular risk of developing bipolar illness in late adolescence or early adulthood. Second, O-BP manifests poorer interpersonal functioning than O-HC due to a reciprocal influence between parents´ and youth´s psychopathology, especially across the childhood period (vs. adolescence). Of note, prospective studies reveal that a dysfunctional family environment increases the probability of MMD among youth, irrespective of their risk status (O-BP vs. O-HC). Third, with regard to temperamental and personality features, O-BP endorses higher activity level, emotionality and behavioral disinhibition compared to O-HC. In addition, prospective studies indicate that high emotionality enhances the risk of developing MMD among O-BP. Furthermore, only the subset of bipolar (vs. non-bipolar) O-BP displays lower self-esteem and worse coping strategies compared to O-HC. Fourth, concerning the neurocognitive deficits, O-BP shows poorer performance on visual/verbal memory, cognitive flexibility and social cognition compared to O-HC. However, greater deficits are only obtained in cognitive flexibility compared to O-SzP. In addition, social cognition deficits do not differ between non-bipolar and affected (bipolar) O-BP. Fifth, with regard to the neurobiological findings, O-BP exhibits dysfunctional modulation in cortico-subcortical areas, more white matter abnormalities and higher cortisol basal levels compared to O-HC. Moreover, neurofunctional deficits in subcortical structures are similar to those encountered in PBD youth. In addition, studies on amygdala volume and glutamate concentrations show reduction levels only among bipolar (vs. non-bipolar) O-BP.

LIMITATIONS AND DIRECTIONS FOR FUTURE RESEARCH

First, more and longer prospective follow-up studies are needed on O-BP samples in order to determine which symptoms and childhood mental disorders precede the onset of MMD in general and BP specifically in adulthood. Particularly, research efforts should be focused on delineating specific pathways between internalizing and externalizing problems in childhood and risk of subsequently developing different mental disorders in adulthood. Likewise, by comparing affected (BP/MDD) vs. non-affected O-BP we will be able to delineate some protective factors (resilience variables) for mood disorders among this high-risk cohort. Second, neurobiological research on O-BP samples usually fails to include a third group of O-SzP/O-DP. This constraint is remarkable as there is a plethora of research underscoring common genetic risk between BD and schizophrenia/MDD[106,107]. By resolving this flaw, we will be able to identify specific trait markers that help us to distinguish among those O-BP at higher risk for BD or schizophrenia/MMD[108]. Third, neurocognitive research on O-BP samples tends not to include a third group of PBD youth or otherwise comparative analysis between affected (bipolar) and non-bipolar O-BP. Accordingly, we cannot elucidate whether or not these neurocognitive deficits in non-bipolar O-BP represent endophenotypes for the bipolar illness. Fourth, since O-BP studies are based on parent diagnosis, methods of family ascertainment should always rely on best estimate procedures (structured assessments) rather than self-referral[109]. This requirement would enhance the reliability and validity of the results. Fifth, since data derived from O-BP research is somewhat limited and probably biased[110,111], we encourage researchers to perform comparative studies among O-BP, offspring of siblings with BD and/or offspring of second-degree relatives with BD.

CLINICAL IMPLICATIONS

O-BP suffers higher rates of internalizing and externalizing symptoms/disorders compared to O-HC and O-DP.

Prospective studies among O-BP indicate that initial internalizing symptoms/disorders, temperamental traits (high emotionality) and family´s dysfunctionality should be treated in order to reduce the risk of developing MMD in general and bipolar disorder specifically[112].

Prospective studies among O-BP also suggest that the presence of a major depressive episode may be an early stage of bipolar illness.

Comparative data between bipolar and non-bipolar O-BP indicate that some personality traits (e.g., self-esteem) and neuroanatomical structures (e.g., amygdala volume) are negatively affected by bipolar disorder rather than being a vulnerability factor for it.

Comparative data between bipolar and non-bipolar O-BP also stress that social cognition deficits and neurofunctional abnormalities in striatum and amygdala may be potential endophenotypes for BD.

O-BP and O-SzP share several neurocognitive deficits, suggesting common trait markers for both disorders

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