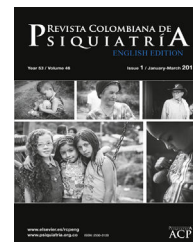




REVISTA COLOMBIANA DE PSIQUIATRÍA

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Original article

Comparison of the neurocognitive profile of the children of parents with bipolar disorder and controls: A transnational cross-sectional study



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ARTICLE INFO

Article history:

Received 28 June 2021

Accepted 13 July 2021

Available online 18 November 2023

Keywords:

Child of impaired parents

Bipolar disorder

Cognition

High risk

Endophenotypes

ABSTRACT

Introduction: Studies that have compared the cognitive alterations of the children of parents with bipolar disorder (CPBD) versus the children of control parents (CCP), present heterogeneous results due to the studies' methodological differences, the age of the population studied, and the lack of standardisation of the measures used for the different neurocognitive domains. The objective was to compare the neurocognitive profile of CPBD versus CCP to observe if there are differences that could be proposed as possible endophenotypes of BD. **Results:** A total of 107 individuals (51 CPBD, and 56 CCP) with ages between 6 and 16 (mean, 12.2 ± 2.80) years of age were evaluated. Seventy-four point five percent of the CPBD group had some disorder compared to 67.9% of the CCP group. Tests such as letter-F phonemic verbal fluency, letter-S phonemic verbal fluency, overall F-A-S phonemic verbal fluency, story recall and retrieval, and Wisconsin perseverative errors showed a difference with a small effect size, but with a high degree of uncertainty.

Conclusions: The CPBD did not have differences in their neurocognitive profile in comparison with CCP. Both groups have a high prevalence of psychopathology, which is a factor that could explain the lack of differences in neurocognitive performance.

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Comparación del Perfil Neurocognitivo de los Hijos de padres con Trastorno Bipolar y Controles: un Estudio de Corte Transversal

R E S U M E N

Palabras clave:

Hijo de padre discapacitado
Trastorno bipolar
Cognición
Alto riesgo
Endofenotipos

Introducción: Los estudios que han comparado las alteraciones cognitivas de los hijos de padres con trastorno bipolar (HPB) con las de los hijos de padres de control (HPC) presentan resultados heterogéneos debido a las diferencias metodológicas de los estudios, la edad de la población estudiada y la falta de estandarización de las medidas utilizadas para los diferentes dominios neurocognitivos. El objetivo es comparar los perfiles neurocognitivos de los HPB y los HPC para observar si existen diferencias que puedan llegar a proponerse como posibles endofenotipos del trastorno bipolar.

Resultados: Se evaluó a un total de 107 individuos (51 HPB y 56 HPC) de 616 (media, $12,2 \pm 2,80$) años de edad. El 74,5% del grupo de HPB presentó algún trastorno en comparación con el 67,9% del grupo de HPC. Las pruebas de fluidez verbal fonológica-letra efe, fluidez verbal fonológica-letra ese, fluidez fonológica F-A-S total, recuerdo y recuperación de una historia y errores perseverativos del Wisconsin mostraron una diferencia con un tamaño del efecto pequeño, pero con alto grado de incertidumbre.

Conclusiones: Los HPB no presentaron diferencias en el perfil neurocognitivo en comparación con los HPC. Los 2 grupos presentaron una alta prevalencia de psicopatología, lo cual es un factor que puede explicar la falta de diferencias en el desempeño neurocognitivo.

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Introduction

Bipolar disorder (BD) affects 0.6%–2.4% of the general population and 1%–3% of children and adolescents. It is characterised by episodes of mania and depression, with periods of intercritical recovery and impaired interpersonal, social and occupational functioning, and is considered to be very disabling.¹ In addition, cognitive disturbances manifest even in exacerbation-free periods, which further impedes functionality. Impairments in executive function, episodic and working memory, sustained attention, processing speed and theory of mind have been reported most frequently^{2–5}; the greatest cognitive impairment is exhibited in bipolar I disorder.⁶

Offspring of parents with BD (OPBD) have a high probability of having the disorder, with heritability estimated at 56%–93%.^{7,8} In addition, they are four times more likely than the offspring of control parents (OCP) to develop a psychiatric disorder, such as major depressive disorder, attention disorders and other externalising disorders.^{9,10} Of the heritable factors of BD, neurobiological and neuropsychological variables have been studied in addition to psychopathological variables. It has been found that OPBD may manifest neurocognitive disorders even if they do not have affective episodes.^{11,12} Deficits have been seen in verbal learning, visual and spatial memory, retrieval function, attention and executive function, mainly in processing speed, although some results are heterogeneous. This has led to the proposal that some of these deficits may be a genetic marker for risk of the disorder.¹³

The sustained attention in school-aged OPBD and adolescents assessed by the continuous performance task (CPT) showed that some variants could detect deficits.¹⁴ De la Serna

et al.¹⁵ found that OPBD performed less well in sustained attention than OCP, but the difference was not statistically significant in any of the subtests of the assessment. In selective attention, a study of adolescents at familial risk of BD showed slower overall performance and greater variability in response time on the Flanker continuous performance test,¹⁶ a finding that was not repeated in a study with similar characteristics.¹⁷ Other authors who assessed psychomotor attention using the Trail Making Test-A (TMT-A) found no differences. Preliminary studies indicate that the tendency towards faster but more accurate responses to affective stimuli observed in OPBD may be a marker of attentional bias towards affective information and vulnerability to BD.¹⁸

In executive function, processing speed impairment has been found, although the effect size varies from small to moderate.^{18,19} In a multicentre cross-sectional study, De la Serna et al.²⁰ reported that OPBD scored significantly lower than OCP. Cognitive flexibility has also been reported to be impaired in OPBD, although this alteration is proposed as an endophenotype for psychosis in general.²¹

In a cross-sectional study of first-degree relatives of BD subjects and control subjects aged 18–50 years, they were found to have differences in digits backward recognition, spatial Cambridge Neuropsychological Test Automated Battery (CANTAB) and spatial recognition, tests assessing working memory and visual perception.²² In another study, the working memory of OPBD and OCP was not affected when assessed using a delayed spatial memory paradigm with two levels of delay.²³ Other studies have reported impairments in working memory with small effect sizes, but not in declarative memory.²⁴ It has been reported that on the Rey-Osterrieth complex figure test (ROCF), which assesses visual-spatial memory, OPBD

had worse organisation than OCP.²⁵ Some authors¹⁹ have also reported impaired spatial working memory. In general, studies show that OPBD have no differences in intellectual ability (IA) compared to healthy controls and that their performance is better than that of children of individuals with schizophrenia. Other authors who have explored functions such as theory of mind found no differences in emotion recognition tasks.²⁶ Some studies have also found no difference between groups in verbal learning tasks, sustained attention, speed and/or psychomotor attention or IA.²¹

A meta-analysis assessed the neurocognitive profile of BD patients (23 studies) and their unaffected relatives (28 studies). They found that both, but relatives to a lesser extent, showed impairments in attention, processing speed, learning, memory and verbal fluency, but consistent impairments in intelligence, working memory and visual-spatial learning/memory were not assessed.¹⁴ Previous studies in our population have reported statistically significant differences in the processing speed of OPBD.²⁷

Although all these studies show cognitive abnormalities in OPBD compared to OCP, the results vary due to methodological differences between the studies, the age of the population studied and the lack of standardisation of the measures used for the different neurocognitive domains. Taking into account the characteristics of the “paisa” population (people from the same region) and the high aggregation of BD in Antioquia, Colombia,²⁸ the aim of this study was to compare the neurocognitive profile of OPBD and OCP to identify any differences that could be proposed as possible endophenotypes of BD.

Methods

This was a descriptive cross-sectional study which took an OPBD and OCP sample evaluated by the Grupo de Investigación en Psiquiatría (GIPSI) [Psychiatry Research Group] of the University of Antioquia. Data were collected from July 2016 to September 2019.

Inclusion and exclusion criteria

All participating parents had to be over 18 years of age and have one or more children between the ages of six and 18. Control parents (CP) had to be natives and residents of Antioquia and not have a diagnosis of BD or psychotic disorder according to the Diagnostic Interview for Genetic Studies (DIGS). Parents with BD (PBD) had to have at least six ‘paisa’ great-grandparents (defined as subjects born in Antioquia, Caldas, Risaralda, Quindío, Norte del Valle or Norte del Tolima),^{28,29} have a diagnosis of bipolar I disorder according to DIGS and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and have had at least one documented psychiatric hospitalisation before the age of 50.

Children had to be between six and 18 years of age and have written parental consent to participate, and assent to participate in the study. All subjects had to be in good enough health to participate in a diagnostic interview and neuropsychological testing. OPBD had to have a biological parent with a diagnosis of bipolar I disorder. Both parents of OCP had to meet the criteria for CP. Children from the two groups were

excluded if they met criteria for cognitive disability or autism spectrum disorders, and also a history of hydrocephalus, central nervous system surgery or traumatic brain injury with loss of consciousness, a history of structural or degenerative neurological lesions or epilepsy.

Procedures

The researchers contacted the participants by telephone and invited them to participate in the study. After signing the informed consent form, the evaluations were conducted at the facilities of the University of Antioquia’s Department of Psychiatry, at Hospital San Vicente Fundación (HSVF). The psychiatric evaluation was performed by psychiatry residents and a child psychiatrist, and the neuropsychological evaluation by a psychologist with prior training in testing. All evaluators were blind to the parents’ diagnosis. The following instruments were used.

Measuring instruments

The Diagnostic Interview for Affective Disorders and Schizophrenia in School Children – Present and Lifetime version – Latin American version (K-SADS-PL) was used for the psychiatric evaluation of children under 18 years of age. This is a semi-structured diagnostic interview designed to assess current and past episodes of psychopathology according to DSM-5 criteria.³⁰ It identifies several clear psychiatric disorders and can identify symptoms below the threshold of different disorders. It has a good inter-evaluator performance in the Latin American version.³¹

The DIGS³² is a semi-structured diagnostic interview designed to assess psychiatric disorders in genetic studies and validated in Colombia. This instrument evaluates a range of disorders, including mood and psychotic disorders, substance use disorders, anxiety disorders and eating disorders, and was used to evaluate parents.

The Child Global Assessment Scale (CGAS)³³ provides a global measure of the functional level of children and adolescents. The measure provides an overall score from 0 to 100 on a hypothetical health-illness continuum. This instrument was used to evaluate the functionality of OPBD and OCP.

Cognitive functions traditionally reported to be most associated with bipolar I disorder, such as memory, executive function, attention and gnosis were assessed, as well as general intellectual ability. In children and adolescents, tests from the Evaluación Neuropsicológica Infantil (ENI) [Paediatric Neuropsychological Assessment] battery and the abbreviated version of the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) were used.

The entire protocol was applied by a neuropsychologist trained in the tests, in a standard order for all subjects, and was carried out in a sufficiently well-lit space with appropriate physical conditions to avoid possible bias due to distractibility. The entire assessment process of the children and adolescents lasted approximately 90 min.

This study complied with the standards for research in humans, according to the provisions of Resolution No. 008430 of 1993 of the Ministry of Health of Colombia and in the Declaration of Helsinki of 2013. It was considered to involve minimal

Table 1 – Sociodemographic data of the participating offspring.

	OPBD (n = 51)	OCP (n = 56)	Total (n = 107)
Female	24 (47.1)	29 (51.8)	53 (49.5)
Low socioeconomic level	34 (66.7)	46 (82.1)	80 (74.8)
Urban residence	41 (80.4)	41 (73.2)	82 (76.6)
Lives with bipolar parent	41 (80.4)	0 (0)	41 (38.3)
Age (years)	12.2 ± 2.87	12.3 ± 2.76	12.2 ± 2.80
Education	6.4 (2.68)	6.8 (2.70)	6.6 (2.69)
Repeated years	0 [0–1.00]	0	0 [0–1.00]
Mother's age at pregnancy (years)	27.0 [22.0–35.0]	28.5 [26.0–32.3]	28.0 [23.5–33.5]
Age of children at parents' separation (years)	3.00 [0.724–6.19]	3.46 [1.00–6.33]	3.00 [1.00–6.44]

OCP: offspring of control parents; OPBD: offspring of parents with bipolar disorder.
Values are expressed as n (%), mean ± standard deviation or median [interquartile range].

risk. The procedures were carried out by qualified and clinically competent individuals. Necessary measures were taken at all times to respect subject privacy by coding the information when it was systematized. The original forms, which are kept securely and confidentially, were carefully processed exclusively by the principal investigator.

The study was endorsed by the Independent Ethics Committee of the University of Antioquia and the committee of the Hospital San Vicente Fundación Psychiatry programme.

Statistical analysis

To describe the sociodemographic and clinical characteristics, as well as the cognitive testing scores of each group, the absolute and relative frequencies were calculated for categorical variables and the mean ± standard deviation or median [interquartile range] for quantitative variables.

To determine differences in cognitive performance, the standardised mean difference (SMD) was calculated, considering a large difference for (absolute) values >0.8, moderate 0.5–0.8 and low if <0.5.³⁴

For cognitive tasks where normality³⁵ as assessed by Q-Q plots or the Shapiro-Wilk test was not assumed, the SMD was calculated with the Mann-Whitney U r statistic, considering large differences with SMD > 0.5, moderate if 0.3–0.5 and low if <0.3.³⁴ In tasks where the normality assumption was met, we present the SMD adjusted for the presence of attention deficit hyperactivity disorder (ADHD) and depression. In each case, OCP were compared to OPBD using Student's t-test for independent samples or the Mann-Whitney U test, and p-values and S-values were calculated ($S = -\log_2(p)$ ³⁶), which represents the amount of information against the hypothesis that the groups are equal in cognitive performance assuming the assumptions of the model are correct. For all analyses, we used the R software environment³⁷ version 4.0.4, Rstudio Version 1.4.1106³⁸ and the esc package for calculating the SMD.³⁹

Results

A total sample of 107 individuals with a mean age of 12.2 ± 2.80 years (range, 6–16) was evaluated: 51 OPBD and 56 OCP. The socio-demographic characteristics of both groups are homogeneous (Table 1).

Overall, 71% of the participants had a psychiatric disorder. In total, 74.5% (n = 38) of the OPBD group had some disorder, compared to 67.9% (n = 38) of the OCP group. When exploring overall functionality at the worst time in the past, 66.7% (n = 34) of OPBD were found to have scores ≤ 70. In the population analysed, ADHD was found in a higher percentage of OCP than OPBD. When comparing cognitive performance, no significant effect size differences were found (Table 2).

When the results were adjusted for the variables depression and ADHD, there were no results with significant effect sizes. Phonological verbal fluency-letter F, phonological verbal fluency-letter S (direct score), total F–A–S phonological fluency, recall and retrieval of a story and Wisconsin perseverative errors showed a difference with low effect size, but with a high degree of uncertainty (Table 3).

Discussion

In our study, we found no significant differences between OPBD and OCP in cognitive performance in the applied tests. This contrasts with the majority of studies which have found impairments in response inhibition, set shifting, executive function, verbal memory, working memory and sustained attention in first-degree relatives of patients with BD.^{15,17,24,40} However, most of these studies have marked methodological heterogeneity and used small samples. Some studies in OPBD have found discrete differences in executive function and psychomotor performance speed, but as with our study, they did not report significant differences in simple attention and working memory tasks.⁴¹

Visual-spatial ability has been considered one of the affected functions in bipolar patients even in the euthymic phase, and its assessment in OPBD is of interest because of the possibility of predicting its course even before the onset of BD.⁴² One study found significant differences in visual-spatial ability, but the OPBD participants had a mean age of 22.2,⁴³ compared to 12.2 in our study. Some authors argue that one of the main reasons why longitudinal studies of OPBD are needed is to observe at what age the deficits postulated as cognitive endophenotypes of BD appear.¹⁴ It may be that the absence of significant differences in our group is related to the age of the OPBD.

Given the high variation and low standardisation of the tests used to analyse even the same cognitive dimension,

Table 2 – Clinical characteristics of the offspring of parents with bipolar disorder and the offspring of control parents.

	OPBD (n = 51)	OCP (n = 56)	Total (n = 107)
Major depressive disorder	15 (29.4)	7 (12.5)	22 (20.6)
Bipolar disorder	2 (3.9)	0	2 (1.9)
Bipolar spectrum disorder	8 (15.7)	3 (5.4)	11 (10.3)
Social anxiety disorder	14 (27.5)	13 (23.2)	27 (25.2)
Social phobia	12 (23.5)	9 (16.1)	21 (19.6)
Generalised anxiety disorder	6 (11.8)	7 (12.5)	13 (12.1)
ADHD	11 (21.6)	16 (28.6)	27 (25.2)
Oppositional defiant disorder	10 (19.6)	9 (16.1)	19 (17.8)
Antisocial personality disorder	2 (3.9)	3 (5.4)	5 (4.7)
Tobacco dependence	3 (5.9)	1 (1.8)	4 (3.7)
Alcohol dependence	1 (2.0)	0	1 (0.9)
Substance abuse/dependence	1 (2.0)	0	1 (0.9)

ADHD: attention deficit hyperactivity disorder; OCP: offspring of control parents; OPBD: offspring of parents with bipolar disorder. Values are expressed as n (%).

Table 3 – Cognitive performance of offspring of parents with bipolar disorder and offspring of control parents.

	OPBD (n = 51)	OCP (n = 56)	SMD	p	S	SMD ^a
Intellectual ability	87.0 [81.0–98.0]	88.0 [81.0–101]	–0.043	0.822	0.283	0.016
Attention						
Trail Making Test Part A ^b	54.0 [44.3–69.0]	56.0 [38.8–70.5]	–0.004	0.823	0.282	
STROOP word	76.0 [64.0–85.0]	75.0 [63.5–95.0]	–0.228	0.244	2.033	0.228
STROOP colour	50.0 [42.0–59.0]	49.0 [37.5–56.5]	0.157	0.422	1.243	0.163
Auditory performance ^b	15.0 [14.0–16.0]	15.0 [13.8–16.0]	–0.042	0.663	0.594	
Visual performance time ^b	38.0 [28.0–51.5]	41.0 [32.0–56.0]	0.086	0.431	1.214	
Auditory attention (ENI) ^b	20.0 [16.5–23.5]	20.0 [18.0–21.0]	0.024	0.804	0.315	
Visual performance correct answers ^b	16.0 [15.0–16.0]	16.0 [15.8–16.0]	0.087	0.371	1.427	
Executive function						
Trail Making Test part B ^b	113 [89.0–146]	100 [79.3–130]	–0.144	0.137	2.859	
Phonological fluency F	6.00 [4.00–9.00]	7.00 [5.00–9.00]	–0.296	0.126	2.988	–0.043
Phonological fluency A	7.00 [5.00–10.0]	7.00 [5.00–9.25]	–0.001	0.996	0.005	–0.082
Phonological fluency S	6.00 [4.00–8.00]	6.00 [4.00–9.00]	–0.225	0.243	2.038	–0.334
Phonological fluency F-A-S	20.5 [13.0–26.0]	20.0 [16.8–27.3]	–0.167	0.389	1.362	–0.294
Semantic fluency	27.0 [23.0–31.0]	27.5 [23.8–32.0]	0.0371	0.703	0.508	
STROOP conflict	28.0 [24.0–36.0]	29.0 [21.0–33.0]	0.116	0.551	0.858	0.077
Wisconsin errors ^b	21.5 [17.0–28.0]	19.0 [15.3–24.0]	0.182	0.398	1.328	0.199
Wisconsin perseverative errors	9.00 [3.75–13.0]	8.00 [4.00–11.0]	0.190	0.378	1.405	0.232
Wisconsin categories ^b	2.00 [1.00–3.00]	2.00 [1.00–3.00]	–0.022	0.824	0.279	
Gnosis						
Rey figure copy ^b	32.0 [25.6–35.0]	32.0 [27.5–34.3]	0.009	0.924	0.114	
Rey figure time copy	171 [138–195]	164 [143–208]	–0.087	0.991	0.012	0.039
Memory						
Story recall	8.00 [6.00–10.0]	8.00 [7.00–10.0]	–0.303	0.119	3.062	–0.305
Story retrieval	7.00 [6.00–9.00]	8.00 [6.50–9.50]	–0.281	0.148	2.754	–0.273
Rey figure evocation ^b	11.3 [6.63–21.4]	13.5 [7.88–17.6]	0.027	0.783	0.353	
Rey figure evocation time	103 [76.0–123]	94.0 [70.0–120]	–0.082	0.401	1.320	

OCP: offspring of control parents; OPBD: offspring of parents with bipolar disorder; SMD: standardised mean difference. Values are expressed as the median [interquartile range].

^a Secondary analysis controlling for the variables attention deficit hyperactivity disorder and major depressive disorder.

^b Variables that did not meet the assumption of normality.

differences in study performance may be related to other variables such as the age and educational level of the subjects tested, as well as the time at which the first symptoms begin to appear in OPBD. Therefore, longitudinal follow-up is essential to define whether or not there is a specific course that can be generalised to all offspring at risk of BD.⁴⁴

Previous studies in Colombia have reported impairment in the cognitive domains of attention, verbal fluency, work-

ing memory and information processing speed, and also lower than average scores in working memory and verbal comprehension.^{45,46} However, these studies did not compare with a control group, which limits the validity of their conclusions. We found a difference in sustained attention (STROOP: word) even when adjusting for the variables ADHD and depression. However, this was obtained with a low effect size and a high degree of uncertainty. Although our results do not

support the endophenotype hypothesis, some studies have concluded that working memory and sustained attention are endophenotypes or early manifestations of BD in OPBD.^{13,46}

Although the prevalence of mental disorders was high in both groups, it was higher in the OPBD group. This prevalence is also high when compared to previous local epidemiological studies in the general population⁴⁷ and similar to other studies in OPBD, which show high prevalences especially in affective disorders.^{48,49} Nonetheless, it differs from findings in a first study of OCP versus OPBD in the “paisa” population, which found high frequencies of substance use disorder, mainly alcohol dependence, in the OPBD. This difference could be due to the inclusion of subjects with a wider age range (6–30 years) in that study.⁵⁰

In particular, similar rates of some psychiatric disorders such as ADHD and major depressive disorder (MDD) were found in both groups, which could explain the lack of differences in cognitive profile. Several studies in subjects with ADHD, MDD and BD, as well as studies with OPBD, report poorer performance in inhibitory control, executive function and working memory.^{51,52} This may be a confounding factor when conducting studies in this high-risk population. Our selection of CP required them not to have BD or psychotic disorders, but did not exclude other illnesses. Nor was psychiatric disorder in the children established as an exclusion criterion. These criteria were intended to enhance the external validity of the study, but may have added confusion by affecting internal validity. However, contrary to the above, we believe that this situation allows performance on neuropsychological tests to be compared not only for the psychopathology of the children, but specifically the risk associated with being OPBD.

Another aspect to consider in OPBD studies is the high prevalence of affective disorders such as MDD and BD, as well as ADHD, and also the high comorbidity between BD and ADHD.⁴⁹ In other words, the origin of neuropsychological disturbances in this population may be confused. Some studies in OPBD that controlled for ADHD found that impairments in processing speed and task response time conflict (executive function) persisted even after removing the confounder from the analysis.⁴⁰ In our sample the results were similar.

One strength of our study is the clinical and neuropsychological assessment of children by evaluators blind to their parents' diagnosis. Another strength is that it has a control group of children of parents with no history of BD or psychotic disorders. However, given the high prevalence of psychopathology detected in this group, future studies should consider eligibility criteria in their designs to control for the influence of psychopathologies other than BD.

A possible limitation of our study for the assessment of executive function could be that we used the abbreviated version of the Wisconsin test. Although the size of the sample was adequate according to the original calculations of 42 subjects for each group,¹⁵ when estimating significant effect sizes on performance in the different tests, this size may have been insufficient.

Future studies in OPBD should consider longitudinal follow-up in order to correlate neurocognitive deficits with the risk of developing BD. Consideration should also be given to selecting larger sample sizes and a control group with characteristics similar to those of the general population.

Similarly, consideration should also be given to the standardization of the neuropsychological tests to be applied. Finally, comparisons of OPBD and OCP with and without concomitant diagnoses, such as ADHD, should be considered in order to remove the confounder. Structural and functional neuroanatomical studies report early changes and impairments in BD and in the prefrontal cortex, limbic system, striatum and parietal regions of OPBD; areas involved in the performance of cognitive tasks which have also been reported to differ even in the at-risk population, such as executive function, sustained attention, emotion recognition and processing speed.⁵³ The correlation and study of cognitive functions and functional studies in our population may be the key to confirming the hypothesis that OPBD manifest cognitive disturbances which can be postulated as possible endophenotypes of BD.

Conclusions

No differences were found when comparing the neurocognitive profile between OCP and OPBD in a sample of the Antioquia population. A high prevalence of psychopathology was found in both groups, which could explain the lack of differences in neurocognitive performance. Despite this, we consider it important to continue evaluating the paisa population in search of neurocognitive differences, in order to determine whether or not there are impairments which could be defined as cognitive endophenotypes of BD. This requires a stricter selection of controls to reduce confusion caused by psychopathology.

Funding

This study was supported by the Departamento Administrativo de Ciencia, Tecnología e Innovación (Colciencias) [Colombian Administrative Department of Science, Technology and Innovation] No. 99059634 “PRISMA U.T Phase II Programme: mental health programme with a focus on reducing the harm, burden and social expenditure of mental illness”, and the Faculty of Medicine of the University of Antioquia.

Conflicts of interest

The authors have no conflicts of interest to declare.

REFERENCES

- Vieta E, Berk M, Schulze TG, Carvalho AF, Suppes T, Calabrese JR, et al. Bipolar disorders. *Nat Rev Dis Prim.* 2018;4:18008.
- Bourne C, Aydemir O, Balanzá-Martínez V, Bora E, Brissos S, Cavanagh JTO, et al. Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. *Acta Psychiatr Scand.* 2013;128:149–62.
- Bora E, Hıdıroğlu C, Özerdem A, Kaçar ÖF, Sarısoy G, Civil Arslan F, et al. Executive dysfunction and cognitive subgroups in a large sample of euthymic patients with bipolar disorder. *Eur Neuropsychopharmacol.* 2016;26:1338–47.

4. Cullen B, Ward J, Graham NA, Deary IJ, Pell JP, Smith DJ, et al. Prevalence and correlates of cognitive impairment in euthymic adults with bipolar disorder: a systematic review. *J Affect Disord.* 2016;205:165–81.
5. Raucher-Chéné D, Achim AM, Kaladjian A, Besche-Richard C. Verbal fluency in bipolar disorders: a systematic review and meta-analysis. *J Affect Disord.* 2017;207:359–66.
6. Kessler U, Schoeyen HK, Andreassen OA, Eide GE, Hammar Å, Malt UF, et al. Neurocognitive profiles in treatment-resistant bipolar I and bipolar II disorder depression. *BMC Psychiatry.* 2013;13:245–55.
7. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. *Lancet.* 2016;387:1561–72.
8. Seifuddin F, Mahon PB, Judy J, Pirooznia M, Jancic D, Taylor J, et al. Meta-analysis of genetic association studies on bipolar disorder. *Am J Med Genet Part B Neuropsychiatr Genet.* 2012;159 B:508–18.
9. Ozerdem A, Ceylan D, Can G. Neurobiology of risk for bipolar disorder. *Curr Treat Options Psychiatry.* 2016;3:315–29.
10. Oquendo MA, Ellis SP, Chesin MS, Birmaher B, Zelazny J, Tin A, et al. Familial transmission of parental mood disorders: Unipolar and bipolar disorders in offspring. *Bipolar Disord.* 2013;15:764–73.
11. Goetz M, Sebel A, Mohaplova M, Ceresnakova S, Ptacek R, Novak T. Psychiatric disorders and quality of life in the offspring of parents with bipolar disorder. *J Child Adolesc Psychopharmacol.* 2017;27:483–93.
12. De La Serna E, Baeza I, Andrés S, Puig O, Sánchez-Guistau V, Romero S, et al. Comparison between young siblings and offspring of subjects with schizophrenia: clinical and neuropsychological characteristics. *Schizophr Res.* 2011;131:35–42.
13. Glahn DC, Almasy L, Barguil M, Hare E, Peralta JM, Kent JW, et al. Neurocognitive endophenotypes for bipolar disorder identified in multiplex multigenerational families. *Arch Gen Psychiatry.* 2010;67:168–77.
14. Cardenas SA, Kassem L, Brotman MA, Leibenluft E, McMahon FJ. Neurocognitive functioning in euthymic patients with bipolar disorder and unaffected relatives: a review of the literature. *Neurosci Biobehav Rev.* 2016;69:193–215.
15. De la Serna E, Vila M, Sanchez-Gistau V, Moreno D, Romero S, Sugranyes G, et al. Neuropsychological characteristics of child and adolescent offspring of patients with bipolar disorder. *Prog Neuro-Psychopharmacology Biol Psychiatry.* 2016;65:54–9.
16. Brotman MA, Rooney MH, Skup M, Pine DS, Leibenluft E. Increased intrasubject variability in response time in youths with bipolar disorder and at-risk family members. *J Am Acad Child Adolesc Psychiatry.* 2009;48:628–35.
17. Deveci E, Ozan E, Kirpınar I, Oral M, Daloğlu AG, Aydin N, et al. Neurocognitive functioning in young high-risk offspring having a parent with bipolar I disorder. *Turkish J Med Sci.* 2013;43:110–7.
18. Bauer IE, Wu MJ, Frazier TW, Mwangi B, Spiker D, Zunta-Soares GB, et al. Neurocognitive functioning in individuals with bipolar disorder and their healthy siblings: a preliminary study. *J Affect Disord.* 2016;201:51–6.
19. Calafiore D, Rossell SL, Van Rheenen TE. Cognitive abilities in first-degree relatives of individuals with bipolar disorder. *J Affect Disord.* 2018;225:147–52.
20. de la Serna E, Sugranyes G, Sanchez-Gistau V, Rodriguez-Toscano E, Baeza I, Vila M, et al. Neuropsychological characteristics of child and adolescent offspring of patients with schizophrenia or bipolar disorder. *Schizophr Res.* 2017;138:183.
21. Bora E, Vahip S, Akdeniz F, Ilerisoy H, Aldemir E, Alkan M. Executive and verbal working memory dysfunction in first-degree relatives of patients with bipolar disorder. *Psychiatry Res.* 2008;161:318–24.
22. Ferrier IN, Chowdhury R, Thompson JM, Watson S, Young AH. Neurocognitive function in unaffected first-degree relatives of patients with bipolar disorder: a preliminary report. *Bipolar Disord.* 2004;6:319–22.
23. Diwadkar VA, Goradia D, Hosanagar A, Mermon D, Montrose DM, Birmaher B, et al. Working memory and attention deficits in adolescent offspring of schizophrenia or bipolar patients: comparing vulnerability markers. *Prog Neuro-Psychopharmacology Biol Psychiatry.* 2011;35:1349–54.
24. Bora E, Yucel M, Pantelis C. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *J Affect Disord.* 2009;113:1–20.
25. Klimes-Dougan B, Ronsaville D, Wiggs EA, Martinez PE. Neuropsychological functioning in adolescent children of mothers with a history of bipolar or major depressive disorders. *Biol Psychiatry.* 2006;60:957–65.
26. Whitney J, Howe M, Shoemaker V, Li S, Marie Sanders E, Dijamco C, et al. Socio-emotional processing and functioning of youth at high risk for bipolar disorder. *J Affect Disord.* 2013;148:112–7.
27. Palacio JD, Zapata-Barco AM, Aguirre-Acevedo DC, Tamayo AL, Lopera-Vásquez JP, López MC, et al. Trastorno bipolar tipo I de una población paisa: perfil psicopatológico y neuropsicológico. *Rev Colomb Psiquiatr.* 2011;40:90–107.
28. Herzberg I, Jasinska A, García J, Jawaheer D, Service S, Kremeyer B, et al. Convergent linkage evidence from two Latin-American population isolates supports the presence of a susceptibility locus for bipolar disorder in 5q31-34. *Hum Mol Genet.* 2006;15:3146–53.
29. Carvajal-Carmona LG, Ophoff R, Service S, Hartiala J, Molina J, Leon P, et al. Genetic demography of Antioquia (Colombia) and the Central Valley of Costa Rica. *Hum Genet.* 2003;112:534–41.
30. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth ed. Arlington: American Psychiatric Publishing, Inc; 2013. p. 947.
31. De la Peña FR, Rosetti MF, Rodríguez-Delgado A, Villavicencio LR, Palacio JD, Montiel C, et al. Construct validity and parent-child agreement of the six new or modified disorders included in the Spanish version of the Kiddie Schedule for Affective Disorders and Schizophrenia present and Lifetime Version DSM-5 (K-SADS-PL-5). *J Psychiatr Res.* 2018;101:28–33.
32. Palacio CA, García J, Arbeláez MP, Sánchez R, Aguirre B, Garcés IC, et al. Validación de la entrevista diagnóstica para estudios genéticos (DIGS) en Colombia. *Biomédica.* 2004;24:56–62.
33. Lundh A, Kowalski J, Sundberg CJ, Gumpert C, Landén M. Children's Global Assessment Scale (CGAS) in a naturalistic clinical setting: inter-rater reliability and comparison with expert ratings. *Psychiatry Res.* 2010;177:206–10.
34. Fritz CO, Morris PE, Richler JJ. Effect size estimates: current use, calculations, and interpretation. *J Exp Psychol Gen.* 2012;141:2–18.
35. Chow ZR, Greenland S. Semantic and cognitive tools to aid statistical inference: replace confidence and significance by compatibility and surprise. *arXiv.* 2019;9:1–13.
36. Rafi Z, Greenland S. Semantic and cognitive tools to aid statistical science: replace confidence and significance by compatibility and surprise. *BMC Med Res Method.* 2020;2020:1–13.
37. R Core Team, Available from: R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2021 <https://www.R-project.org/>.
38. RStudio Team, Available from: RStudio: integrated development environment for R. Boston, MA: RStudio Team; 2015 <http://www.rstudio.com/>.

39. Lüdtke D (2019). *esc: Effect size computation for meta analysis* (Version 0.5.1). <https://doi.org/10.5281/zenodo.1249218>. Available from: <https://CRAN.R-project.org/package=esc>.
40. Patino LR, Adler CM, Mills NP, Strakowski SM, Fleck DE, Welge JA, et al. Conflict monitoring and adaptation in individuals at familial risk for developing bipolar disorder. *Bipolar Disord*. 2013;15:264-71.
41. Anttila M, Tuulio-Henriksson A, Kieseppä T, Eerola M, Tímo P, Lönnqvist J. Cognitive functioning in patients with familial bipolar I disorder and their unaffected relatives. *Psychol Med*. 2007;37:679-87.
42. Denicoff KD, Ali SO, Mirsky AF, Smith-Jackson EE, Leverich GS, Duncan CC, et al. Relationship between prior course of illness and neuropsychological functioning in patients with bipolar disorder. *J Affect Disord*. 1999;56:67-73.
43. MacQueen GM, Grof P, Alda M, Marriott M, Young LT, Duffy A. A pilot study of visual backward masking performance among affected versus unaffected offspring of parents with bipolar disorder. *Bipolar Disord*. 2004;6:374-8.
44. Birmaher B, Axelson D. Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. *Dev Psychopathol*. 2006;18:1023-35.
45. Palacio-Ortiz JD, Uribe-Villa E, Duque-Ríos P, Gutiérrez-Briceño P, Zapata-Henao V, Peña-Quintero CE, et al. Descripción de perfiles psicopatológicos y neurocognitivos de hijos de pacientes con trastorno bipolar tipo I dentro un programa de intervención multimodal: PRISMA. *Rev Colomb Psiquiatr*. 2015;44:150-8.
46. Bertieri Arcila HC, Julio De La Rosa A, Lemos Buitrago R. Funciones cognitivas en la descendencia de pacientes con trastorno bipolar I. *Rev Médica Risaralda*. 2020;26:110-22.
47. Zapata Vanegas MA, Montoya Velez LP, Garro Cossio GI, Hurtado Villegas G, Valencia ML. Segundo estudio de salud mental del adolescente – Medellín, 2009. *Rev Salud Pública Medellín*. 2010;4:23-40.
48. De la Serna E, Ilzarbe D, Sugranyes G, Baeza I, Moreno D, Rodríguez-Toscano E, et al. Lifetime psychopathology in child and adolescent offspring of parents diagnosed with schizophrenia or bipolar disorder: a 2-year follow-up study. *Eur Child Adolesc Psychiatry*. 2021;30:117-29.
49. Lau P, Hawes DJ, Hunt C, Frankland A, Roberts G, Mitchell PB. Prevalence of psychopathology in bipolar high-risk offspring and siblings: a meta-analysis. *Eur Child Adolesc Psychiatry*. 2018;27:823-37.
50. Palacio-Ortiz JD, Peña-Quintero CE, Gómez-Valero MA, Bustamante-Gómez PA, Arroyave-Sierra PH, Vargas-Upegui CD, et al. Trastornos psiquiátricos a través de la vida: un estudio de comparación de hijos de padres con trastorno afectivo bipolar tipo I frente a hijos de padres controles de la comunidad. *Rev Colomb Psiquiatr*. 2017;46:129-39.
51. Kebir O, Joob R. Neuropsychological endophenotypes in attention-deficit/hyperactivity disorder: a review of genetic association studies. *Eur Arch Psychiatry Clin Neurosci*. 2011;261:583-94.
52. Agha SS, Zammit S, Thapar A, Langley K. Maternal psychopathology and offspring clinical outcome : a four-year follow-up of boys with ADHD. *Eur Child Adolesc Psychiatry*. 2017;26:253-62.
53. Miskowiak KW, Kjørstad HL, Meluken I, Petersen JZ, Maciel BR, Köhler CA, et al. The search for neuroimaging and cognitive endophenotypes: a critical systematic review of studies involving unaffected first-degree relatives of individuals with bipolar disorder. *Neurosci Biobehav Rev*. 2017;73:1-22.