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RESEARCH ARTICLE

# Functional Impairment and Clinical Correlates in Adolescents with Bipolar Disorder Compared to Healthy Controls. A Case-control Study

**Iria Mendez MD[1]; Josefina Castro-Fornieles PhD, MD[1-3]; Sara Lera-Miguel PhD[1]; Marisol Picado PhD[1]; Roger Borras MS[2]; Sandra Cosi PhD4; Marc Valenti PhD, MD[3,5]; Pilar Santamarina PhD[1]; Elena Font PsyA[1]; Soledad Romero PhD, MD[1,3]**

## Abstract:

**Background:** Evidence shows that most adolescents with bipolar disorder (BD) achieve syndromic recovery after being referred to specialized treatment. However, functional recovery is reached in less than 50% of those cases. **Method:** Descriptive cross-sectional case-control study, based on a clinical sample of 44 BD patients aged 12–19, matched by age and sex with 44 healthy controls (HC). Psychopathology was ascertained using the KSADS-PL, in addition to the clinical scales. Information about previous academic performance was included, as well as functional outcome based on the Children's Global Assessment Functioning Scale (CGAS). Previous exposure to stressful experiences was assessed using the Schedule for Stressful Life Events (SLES). All analyses were performed using either conditional or stepwise logistic regression models. **Results:** Once they have become stabilized, and even after controlling for socio-demographic differences, BD patients were associated with lower levels of functionality [OR 0.65 (0.46, 0.93), p=0.02], and worse performance at school [OR 0.03 (0.01, 0.67), p=0.03] compared with HC. Persistent sub-syndromal psychosis showed the strongest negative correlation with functionality (rho=-0.65, -0.57 for BD and HC respectively; p<0.001). Although BD was associated with more stressful life events, this association did not remain significant in the multivariate models. **Limitations:** The small sample size limits our ability to detect differences between groups, and between BD subtypes. **Conclusions:** Even when early detection and intervention is provided, BD has a significant impact on functioning and academic performance. It is important to address persistent sub-threshold symptoms and to emphasize the social and rehabilitative components of treatment.

***Key Words:*** *bipolar disorder, adolescents, functionality, clinical*

## Résumé

**Contexte:** Les données probantes indiquent que la plupart des adolescents souffrant de trouble bipolaire (TB) obtiennent un rétablissement syndromique après avoir été adressés à un traitement spécialisé. Cependant, le rétablissement fonctionnel n'est réalisé que dans moins de 50 % de ces cas. **Méthode:** Une étude

[1]Department of Child and Adolescent Psychiatry and Psychology, Clinic Hospital, Barcelona, Spain
[2]Institute d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
[3]CIBERSAM, Institute Carlos III, Spain
[4]Research Center for Behavior Assessment, Department of Psychology, Universitat Rovira i Virgili, Tarragona, Spain
[5]Department of Adult Psychiatry and Psychology, Clínic Hospital, Barcelona, Spain

Corresponding E-Mail: imendez@clinic.cat

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cas-témoins transversale descriptive, basée sur un échantillon clinique de 44 patients de TB âgés de 12 à 19 ans, appariés selon l'âge et le sexe avec 44 témoins en santé (TS). La psychopathologie a été déterminée à l'aide de KSADS-PL, en plus des échelles cliniques. L'information sur le rendement scolaire antérieur était incluse de même que le résultat fonctionnel basé sur l'échelle d'évaluation globale du fonctionnement pour les enfants (CGAS). L'exposition précédente à des expériences stressantes a été évaluée à l'aide de l'échelle des événements stressants de la vie (SLES). Toutes les analyses ont été menées à l'aide de modèles de régression logistique conditionnelle ou séquentielle. **Résultats**: Une fois stabilisés, et même après contrôle des différences sociodémographiques, les patients de TB ont été associés à des niveaux plus faibles de fonctionnalité [RC 0,65 (0,46, 0,93), p = 0,02], et à un rendement scolaire plus mauvais [RC 0,03 (0,01, 0,67), p = 0,03] comparé aux TS. Une psychose sous-syndromale persistante présentait la corrélation négative la plus forte avec la fonctionnalité (rho =-0,65, -0,57 pour TB et TS respectivement; p < 0,001). Bien que le TB soit associé à des événements plus stressants, cette association ne demeurait pas significative dans les modèles multivariés. **Limitations:** La taille modeste de l'échantillon limite notre capacité de détecter les différences entre les groupes, et entre les sous-types de TB. **Conclusions:** Même lorsque la détection et l'intervention précoces sont fournies, le TB a un effet significatif sur le fonctionnement et sur le rendement scolaire. Il est important de prendre en compte les symptômes de sous-seuil persistants et de mettre l'accent sur les composantes sociale et de rétablissement du traitement.

***Mots clés:*** *trouble bipolaire, adolescents, fonctionnalité, clinique*

## Introduction

It has been confirmed that most cases of bipolar disorder (BD) have their onset during adolescence or early adulthood, with only a quarter of cases outside the 12-30 age range (Baldessarini et al., 2012; Joslyn, Hawes, Hunt, & Mitchell, 2016; Perlis et al., 2004; Post et al., 2017). The available evidence also confirms a uniform phenomenology, which strengthens the validity of current diagnostic criteria for all ages (Goldstein et al., 2017; Grande, Berk, Birmaher, & Vieta, 2016). However, some variations have been observed. Family history and comorbidity has been strongly linked to childhood onset (Birmaher et al., 2009; Strober, 1992; Wozniak, Faraone, Martelon, Mckillop, & Biederman, 2012), whereas onset during ages 12-18 is more closely associated with negative life events (Romero et al., 2009, 2010; Rucklidge, 2006; Tillman et al., 2003). There is also a greater prevalence of psychotic symptoms (Baldessarini et al., 2012; Hur, Cherny, & Sham, 2012; Tillman et al., 2008) and suicidal behaviors (Cate-Carter, Mundo, Parikh, & Kennedy, 2003; Hauser, Galling, & Correll, 2013; Joslyn et al., 2016; Perlis et al., 2004) in this age group.

Longitudinal studies corroborate that the course of the illness is episodic in all age groups. Distinct inter-episodes of full syndromic remission can be identified in 80% of subjects, although they continue to experience persistent subsyndromic depressive or mixed symptoms, or irritability in the youngest patients (Birmaher et al., 2006; Delbello, Hanseman, Adler, Fleck, & Strakowski, 2007; Geller, Tillman, & Bolhofner, 2008; Hunt et al., 2009; Tohen et al., 2000; Wozniak et al., 2011). Moreover, only half of all subjects return to the level of functioning prior to onset (Birmaher et al., 2009; Carlson, Kotov, Chang, Ruggero, & Bromet, 2012; Geller, Tillman, Bolhofner, & Zimerman, 2008; Jansen, Magalhaes, Tavares-Pinheiro, Kapczinski, & SIlva, 2012; Judd et al., 2002; Tohen et al., 2003), with some differences in degree of impairment depending on age (Baldessarini et al., 2012; Perlis et al., 2004). Baldessarini and colleagues (Baldessarini et al., 2012), based on a retrospective analysis of a STEP-adult BD sample (n=1665), found a significantly lower level of general functioning (including employment and marital status) among BD patients with onset during childhood, compared with adolescent or adult onset. When children and adolescents were considered together, successful functional outcome was 41% lower than in the adult-onset group. Furthermore, the ability to perform well academically was maintained in the majority of BD adult-onset samples (Martinez-Aran et al., 2007; Torres et al., 2017), in contrast to the lower performance observed in the majority of BD studies with child or adolescent-onset (Geller et al., 2000; Lewinsohn et al., 2000). Significantly, two studies have found greater social and academic impairment in adolescent BD patients than child BD patients, regardless of the age of onset, with a decrease in the level of satisfaction and recreational skills only in the adolescent group (Biederman et al., 2005; Goldstein et al., 2009). The interaction of persistent symptoms during adolescence and the dramatic change in social demands and autonomy may explain these differences, whereas very early-onset BD may not be as damaging due the protective aspect of the family.

To reduce the impact of the illness during the early phases, new treatments and approaches have been developed over the past decade, and tested in several randomized clinical trials (Alvaro & Romero, 2011; Goodwin et al., 2016). However, there is a lack of information concerning their impact on functional recovery in naturalistic settings. In this paper, we will compare the level of daily general

functioning in a group of adolescents with BD (12–18 years old, in euthymia) to a group of healthy controls of the same age and sex.

In line with previous studies, we hypothesized that low levels of general functioning, including academic performance and level of education, will be associated with the BD group. Other variables indirectly associated with functionality, such as socio-economic status, family loading for mental disorders, or exposure to stressful life events, will be more closely associated with the BD group. The presence of comorbidity or past/ current history of alcohol and drug abuse will be associated with a lower level of functioning, and will be more specifically associated with the BD group as well. Finally, lower levels of functionality will be correlated with the persistence of psychiatric symptoms, such as mania, depression, suicidality and psychosis.

## Methods

### *Participants*

Forty-four (44) adolescents diagnosed with BD type I or II aged 12–19 years old and forty-four (44) age- and sex-matched healthy controls (HC) were recruited from January 2012 to September 2016. BD patients were recruited at the Department of Child and Adolescent Psychiatry and Psychology of the Clinic Hospital in Barcelona, either after being discharged from the inpatient care unit (32, 72.7%) or directly from the outpatient unit (12, 27.3%). HC were recruited from advertisements from the same geographical area. Similar gender and age, and being healthy without any past or current history of a psychiatric disorder were the inclusion criteria. Exclusion criteria were intellectual disability, major medical illness, and serious head injuries. None of the controls and one of the eligible participants with BD refused to participate in the study.

### *Procedures*

After obtaining permission from the institutional review board (IRB), families were explicitly informed about the rights, procedures, risks, benefits, and the voluntary nature of the study. A written consent form was required from all parents and those adolescents older than 14 years old.

### *Assessments and measures*

The interview package included basic demographic information from each BD and control, and their family, including socioeconomic status (SES) based on the Hollingshead scale (Hollingshead, 1982), perinatal history from the Lewis scale (Lewis, Owen, & Murray, 1989), and early developmental milestones. Both adolescents and their parents directly informed us about the patient's past medical and psychiatric history, as well as the pubertal status, considered as Tunner IV-V in the Peterson Pubertal Stage (Petersen, Crockett, Richards, & Boxer, 1988). Parents completed psychiatric history using the Family History Screening (Weissman, 2000). The information was confirmed wherever possible using available medical records.

All adolescents and their parents were interviewed face-to-face using the Spanish version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL) (Puig-Antich & Ryan, 1986). Two child psychiatrists and one research psychologist conducted the assessments. Information was completed wherever possible using medical records. The final diagnosis was established by consensus and based on DSM-5 criteria (APA: American Psychiatric Association, 2013). BD patients were required to be euthymic, defined as depressive symptoms rated lower than 8 on the short version of the Hamilton Depression Scale (HDRS-17) (Hamilton, 1967), and manic symptoms rated as 12 or lower on both the Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978) and the Parents-YMRS (Gracious, Youngstrom, Findling, & Calabrese, 2002). Information was completed using the Beck Depression Inventory-II (BDI-II) (Beck, Steer, Ball, & Ranieri, 1996) (cut off < 10), the Child Mania Rating Scale (CMRS) (Pavuluri, Henry, Devineni, Carbray, & Birmaher, 2006) (cut off < 20) and the Mood Disorder Questionnaire (MDQ) (Wagner et al., 2006) (cut off < 17). Psychosis was evaluated using the Positive and Negative Symptom Scale (PANSS) (Kay, Fiszbein, & Opler, 1987) (< 70 mild psychosis, 95 moderate, > 115 severe), and the Symptom Assessment in Schizophrenic Prodromal Scale (SOPS) (Miller et al., 2003) (Likert scale from 0-6, 0-1 absent or questionably symptoms; 2-5 prodromic or subthreshold; 6=severe psychotic symptoms; cut off <95 for the global scale, and 20-30 for each subscale). The Spanish version of the Screening for Child Anxiety Related Disorders (SCARED) (Birmaher et al., 1999) (cut off < 25) was used to measure anxiety symptoms. Attentional deficits were assessed using the Conner's Rating Scale (Conners-48) (Goyette & Conners, n.d.) (cut off < 69$^{th}$ percentile). The presence of life-time suicidal ideation or behaviors was measured based on the K-SADS-PLE and the Suicidal Ideation Questionnaire (SIQ) (Reynolds, 1991) (cut off < 30). For the BD group, the severity of the last episode and the level of clinical remission at the time of inclusion was rated on a Likert scale from 0-7 from the Clinical Global Impression scale (CGI) (W., 1976), which includes two components: a) CGI-Severity Illness (CGI-SI) (scored as 0=unable to evaluate; 1=healthy or not ill; 2=doubtfully ill; 3=mildly ill; 4=moderately ill; 5=significantly ill; 6=severely ill; 7=one of the most severe cases); b) CGI-Clinical Improvement (CGI-GI), based on the evaluator's impression at the time of inclusion in the study (scored as 0= unable to evaluate; 1=significant improvement; 2=moderate improvement; 3=mild improvement; 4=not improvement; 5=slightly worse; 6=moderately worse; 7=significantly worse).

Previous exposure to stressful life events was self-reported by the participants and their parents using the Schedule for

Stressful Life Events (SLES) (Williamson et al., 2003). Two measures were obtained for each participant: first, total number of stressful life events from a list of 80 items; and second, subjective level of impact of each life event (scored from 1=no impact; 2=slight impact; 3=moderate impact; 4=significant impact).

Functionality in daily-life was measured using two different scales: 1) Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983), considering scores lower than 70 as impairment; and 2) Premorbid Adjustment Scale (PAS) (Cannon-Spoor, Potkin, & Wyatt, 1982), which includes a general classification (based on a Likert scale from 0= no impairment; to 6=severe impairment), and age-specific questionnaires (≤11 years old; 12-15; 16-18; ≥19) in order to collect data about social skills, peer and romantic relationships, school performance and grades. Information about performance at school was completed using the K-SADS-PLE, and included information such as grade point average, special education needs, and repeated school years. No problems at all or not repeated grades were scored as good performance.

### Statistical analyses

Continuous variables are expressed as means and standard deviations (SD), and categorical variables as numbers and percentages. Correlations between scales were assessed using Pearson and Spearman coefficients. Conditional logistic regression models were used to determine variables associated with BD compared to HC. Variables that showed group differences at $p<0.05$ in univariate analyses were included as potential covariates in subsequent multivariate models. The number of variables to be included was limited using the m/10 rule (where m is the number of cases) to prevent over-fitting the model; in our sample 4 variables were the maximum. In addition to functionality, different combinations of covariates were tested based on: 1) clinical meaning, including socio-demographic information, phenomenology, stressful life events and others; and 2) a p-value <0.2 for each variable. The final selection was based in both the lowest p-values and lowest Akaike information criterion (AIC) score (where lower scores indicate a better fit). In the end, we ran an automatic procedure of selection based on forward stepwise logistic regression. The odds ratio and 95% confidence interval were estimated in all models. All analyses were performed using the program R version 3.3.1 for Windows 7 with library survival v.2.40-1.

## Results

### Sociodemographic and premorbid characteristics

We have a total of 88 participants, 44 BD and 44 HC, matched 1:1 by gender and age. More girls were included in the study than boys, with a total of 48 girls, 24 in each group, and 40 boys, 20 in each group. The average age was 16.07±1.82 years/old, with a difference of maximum two years within each pair (Table 1). Almost all participants were Caucasian (96.6%), and the majority lived with both biological parents (68.2%). A lower SES was significantly associated with BD [46.07 ± 13.77 vs. 53.26 ± 11.08; OR 0.94 (0.89, 0.98); $p<0.01$)], and was adjusted for in the final models.

A family history of mental disorders in first-degree relatives was significantly associated with the BD group [75% vs. 22.7%; OR 9 (2.63, 29.67); $p<0.001$], specifically with affective disorders [59.1% vs. 9.1%; OR 12.5 (2.96, 52.77); $p<0.001$]. Only one BD subject and no HC had a family history of psychosis. No relation was found with other disorders or suicidality.

BD and HC were similar in terms of previous medical history. A total of 23.9% reported moderate to severe complications during pregnancy or delivery. Almost 75% recalled some type of previous illness, allergies being the most common. One-third reported a previous medical hospitalization, mainly respiratory complications, which was more closely associated with the BD group [40.9% vs. 18.2%; OR 2.67 (1.04, 6.81); $p=0.04$]. Most participants were pubertal at the time of inclusion (93.2%).

### Phenomenology

Focusing on the BD group (N=44), type I was more prevalent than type II (84.1%) (Table 2). 77.2 % of BD patients (34/44) reported lifetime psychotic symptoms, two thirds (21/34) of which were at a threshold level based on the DSM-5 classification. A total of 88.6% of BD patients presented lifetime comorbidity, mainly with anxiety disorders (59.1%), followed by attention deficit/hyperactivity disorder (ADHD) and conduct disorder (CD) (12/44, 27.3% for both). All BD patients were taking medication with a mean of 2.11 ± 0.92 psychotropics (see Table 2 for more information). Two thirds of BD (77.2%) had at least one previous psychiatric hospitalization (mean: 1.88 ± 2.01), which lasted one month on average (37.71 ± 61.08). The majority (N=41, 93.2%) recalled symptoms for a long period previously, with their first contact with a specialist at an average age of 10.86 ± 3.99. Three years later, the majority received a diagnosis of depression (70.5%). Finally, the formal diagnosis of BD occurred at a mean age of 15.18 ± 1.83.

Nearly 40% of HC adolescents reported previous contact with mental health services as a child (mean age of 7.76 ± 3.21) (Table 3a), although it was significantly more associated with the BD group [93.2% vs. 38.6%; OR 13 (3.09, 54.77); $p<0.001$). As expected, a formal previous DSM-5 diagnosis was mainly associated with the BD group [90.9% vs. 6.8%; OR 13 (3.09, 54.77); $p<0.001$]. The three HC with previous DSM-5 diagnoses suffered from minor disorders such as enuresis, dyslexia and grief. Two HC were still classified as dyslexic at the time of inclusion. None of the HC were under medication.

**Table 1. Differences between controls and persons with bipolar disorder in socio-demographics, family and past medical history ▪**

| | Whole sample N (88) | Bipolar I/II group N (44) | Control group N (44) | Univariate Analysis OR (95% CI) | p-value |
|---|---|---|---|---|---|
| Socio-demographics | | | | | |
| Age at intake (mean, SD; min, max) | 16.07 ± 1.82 (12, 19) | 16 ± 1.9 | 16.14 ± 1.75 | MV | MV |
| Sex: Female (n, %) | 48 (54.5) | 24 (54.5) | 24 (54.5) | MV | MV |
| Race: White (n, %) | 85 (96.6) | 41 (93.2) | 44 (100) | NA | NA |
| Adopted: No (n, %) | 86 (97.7) | 42 (95.5) | 44 (100) | NA | NA |
| Living with biological parents at intake (n, %) | 60 (68.2) | 29 (65.9) | 31 (70.5) | 0.83 (0.36, 1.93) | 0.67 |
| SES at intake (mean, SD; min, max) | 49.66 ± 12.94 (13, 66) | 46.07 ± 13.77 | 53.26 ± 11.08 | 0.94 (0.89, 0.98) | **0.01** |
| Psychiatric Family Hx | | | | | |
| 1st degree Psychiatric Family Hx (n, %) | 43 (48.9) | 33 (75) | 10 (22.7) | 9 (2.63, 29.67) | **<0.001** |
| Family Hx of Psychotic DO (n, %) | | 1 (2.3) | 0 | NA | NA |
| Family Hx of Affective DO (n, %) | 30 (34.1) | 26 (59.1) | 4 (9.1) | 12.5 (2.96, 52.77) | **<0.001** |
| Family Hx of Anxiety DO (n, %) | 6 (6.8) | 2 (4.5) | 4 (9.1) | 0.5 (0.09, 2.73) | 0.42 |
| Family Hx of Drug Abuse DO (n, %) | 2 (2.3) | 1 (2.3) | 1 (2.3) | 1 (0.06, 15.99) | 0.99 |
| Family Hx of Other DO (n, %) | 4 (4.5) | 3 (6.8) | 1 (2.3) | 3 (0.31, 28.84) | 0.34 |
| 1st degree Suicidal Family Hx (n, %) | | 6 (13.6) | 0 | NA | NA |
| Medical Hx | | | | | |
| Perinatal complications: Yes (n, %) | 21 (23.9) | 12 (27.3) | 9 (20.5) | 1.6 (0.52, 4.89) | 0.41 |
| Weight at birth kg (mean, SD; min, max) | 3.24 ± 0.53 (1.9, 4.5) | 3.23 ± 0.55 | 3.24 ± 0.52 | 0.91 (0.34, 2.47) | 0.86 |
| Past medical Hx: Yes (n, %) | 65 (73.9) | 35 (79.5) | 30 (68.2) | 2.0 (0.68, 5.85) | 0.21 |
| Past hospitalizations: Yes (n, %) | 26 (29.5) | 18 (40.9) | 8 (18.2) | 2.67 (1.04, 6.81) | 0.04 |
| Allergies: Yes (n, %) | 18 (20.5) | 10 (22.7) | 8 (18.2) | 1.33 (0.46, 3.84) | 0.59 |
| Autoimmune DO: Yes (n, %) | | 4 (9.1) | 0 | NA | NA |
| Pubertal: Yes, Tanner 4-5 (n, %) | 82 (93.2) | 41 (93.2) | 41 (93.2) | 1 (0.21, 4.95) | 1 |

OR: odds ratio; CI: confidence interval; SD: standard deviation; SES: socioeconomic status; Hx: history; DO: disorder; MV: Matching variable; NA: Not applicable;

▪ All cases and controls matched by gender and age.

Sporadic or recreational drug use was quite prevalent in both groups (65.9% for BD vs. 79.5% for HC), with alcohol as the most popular drug in both groups (50% BD vs. 56.8% HC), whereas tobacco was more common in adolescents with BD [43.2% BD vs. 11.4% HC; OR 7.5 (1.72, 32.8); p<0.01], and caffeine in HC [18.2% BD vs. 65.9% HC; OR 0.05 (0.01, 0.34), p<0.01]. Additionally, one third of adolescents in both groups reported cannabis use. Five BD patients had tried cocaine, and four amphetamines for recreational purposes. Diagnostic criteria for substance abuse or dependence were significantly associated with the BD group [45.5% BD vs. 15.9% HC; OR 5 (1.45, 17.27), p=0.01].

As expected, being in the BD group was significantly associated with higher scores in almost all categories (mania, depression, psychosis, anxiety, attention deficit) and in all reports (evaluators, adolescents and parents) (Table 3b/3c). Based on the evaluators' clinical scales, 21/44 BD (47.7%) have achieved clinical remission, with average scores of 6.95 ± 6.4 on HDRS-17, 6.77 ± 6.17 on YMRS; 53.79 ± 20.12 on PANSS; and 25.14 ± 18.31 on SOPS. However, adolescents reported mild depression (BDI: 16.63 ± 13.83) and anxiety (SCARED: 28.5 ± 19.24), and their parents noted attentional problems, with Conner-48 close to the cut-off point (67.71 ± 17.25). HC scored below the clinical threshold on all scales.

Half of BD patients (50%) reported lifetime suicidal thoughts during the face-to-face interview, with 14 (31.8%) recalling a previous suicide attempt (1.66 ± 0.83 suicidal attempts on average) (Table 3b). Lifetime non-suicidal self-injury behaviors (NSSIB) were present in 11 BD patients (11/44, 25%), all of whom had reported lifetime suicidal ideation. One HC (2.3%) recalled an episode of NSSIB in

| Table 2. Phenomenology of Persons With Bipolar Disorder (N=44) | |
|---|---|
| **Mood Disorder (DO) characteristics** | |
| Bipolar subtype: Bipolar I (n, %) | 37 (84.1) |
| Lifetime Psychotic symptoms: Yes (n, %) | 34 (77.2) |
| Psychosis threshold (n, %) | 21 (47.7) |
| Psychosis subthreshold (n, %) | 13 (29.5) |
| Age first diagnosis any Mood DO (mean, SD; min, max) | 14.02 ± 1.84 (10, 17) |
| Age first diagnosis Bipolar DO (mean, SD; min, max) | 15.18 ± 1.83 (12, 17) |
| Polarity first Bipolar Episode: | |
| Mania (n, %) | 13 (29.5) |
| Depression (n, %) | 31 (70.5) |
| Hospitalizations: Yes (n, %) | 34 (77.2) |
| Number hospitalizations (mean, SD; min, max) | 1.88 ± 2.01 (1, 12) |
| Duration hospitalizations in days (mean, SD; min, max) | 37.71 ± 61.08 (3,368)* |
| Age first hospitalization (mean, SD; min, max) | 14.44 ± 1.79 (11, 17) |
| **Psychiatric History** | |
| Previous contact with Mental Health: Yes (n, %) | 41 (93.2) |
| Age first contact Mental Health (mean, SD; min, max) | 10.86 ± 3.99 (3, 17) |
| Reasons for referral (40/41): | |
| Emotional problems (n, %) | 21 (47.7) |
| Behavioral problems (n, %) | 10 (22.7) |
| Anxiety problems (n, %) | 6 (13.6) |
| Neurodevelopmental problems (n, %) | 3 (6.8) |
| Other (n, %) | 3 (6.8) |
| Previous psychiatric diagnosis: Yes (n, %) | 40 (90.9) |
| Affective DO (n, %) | 15 (34.1) |
| ADHD (n, %) | 6 (13.6) |
| ODD/CD (n, %) | 4 (9.1) |
| Anxiety DO (n, %) | 5 (11.4) |
| OCD (n, %) | 2 (4.5) |
| AN/BN (n, %) | 4 (9.1) |
| Psychotic DO (n, %) | 2 (4.5) |
| Substance Abuse (n, %) | 1 (2.3) |
| **Lifetime Psychiatric DO (past and current)** | |
| Number of current Diagnoses (mean, SD) | 2.3 ± 1.47 |
| Lifetime comorbidity hx: Yes (n, %) | 39 (88.6) |
| Lifetime Psychotic DO (n, %) | 0 |
| Lifetime Affective DO (n, %) | 44 (100) |
| Lifetime Anxiety DO w/o (n, %) | 26 (59.1) |
| Lifetime OCD DO (n, %) | 3 (6.8) |
| Lifetime AN/BN DO (n, %) | 11 (25) |
| Lifetime ADHD DO (n, %) | 12 (27.3) |
| Lifetime CD/ODD DO (n, %) | 12 (27.3) |
| Lifetime PTSD DO (n, %) | 3 (6.8) |
| Lifetime Elimination DO (n, %) | 3 (6.8) |
| Lifetime Other DO (n, %) | 11 (25) |

*continued*

| Table 2. continued | |
|---|---|
| **Lifetime Psychiatric DO (past and current)** | |
| Number of current Diagnoses (mean, SD) | 2.3 ± 1.47 |
| Lifetime comorbidity hx: Yes (n, %) | 39 (88.6) |
| Lifetime Psychotic DO (n, %) | 0 |
| Lifetime Affective DO (n, %) | 44 (100) |
| Lifetime Anxiety DO w/o (n, %) | 26 (59.1) |
| Lifetime OCD DO (n, %) | 3 (6.8) |
| Lifetime AN/BN DO (n, %) | 11 (25) |
| Lifetime ADHD DO (n, %) | 12 (27.3) |
| Lifetime CD/ODD DO (n, %) | 12 (27.3) |
| Lifetime PTSD DO (n, %) | 3 (6.8) |
| Lifetime Elimination DO (n, %) | 3 (6.8) |
| Lifetime Other DO (n, %) | 11 (25) |
| **Past treatment** | |
| Previous treatments: Yes (n, %) | 34 (77.3) |
| Number of previous treatments (mean, SD; min, max) | 2.09 ± 0.86 (1, 3) |
| Previous exposure to antipsychotics: Yes (n, %) | 24 (54.5) |
| Mean exposed to Chlorpromazine equivalents in the past (mean, SD) | 238.76 ± 225.16 |
| Time exposed to Chlorpromazine equivalents in days (mean, SD) | 345.92 ± 368.03 |
| **Current treatment** | |
| Current treatment: Yes (n, %) | 44 (100) |
| Number of current treatment (mean, SD; min, max) | 2.11 ± 0.92 (0,4) |
| Antipsychotics: Yes (n, %) | 35 (79.5) |
| Chlorpromazine equivalents dose mg/day | 273.76 ± 192.33 |
| Time exposure Chlorpromazine equivalents, days (mean, SD) | 207.97 ± 396.71 |
| Lithium dose mg/day: Yes (n, %) | 29 (61.9) |
| Doses Lithium (mean, SD) | 636.36 ± 484.69 |
| Time exposed to lithium, days (mean, SD) | 114.48 ± 234.14 |
| Antidepressants: Yes (n, %) | 7 (15.9) |
| Antiseizures: Yes (n, %) | 11 (25) |

SD: standard deviation; DO: disorder; OCD: obsessive-compulsive disorder; AN/BN: anorexia or bulimia nervosa; ADHD: attention deficit/ hyperactivity DO; CD/ODD: conduct or oppositional Defiant DO; PTSD: post-traumatic stress DO.

*1 BD had a diagnosis of Anorexia Nervosa with 368 days on inpatient unit

the past, in the context of grief without any other relation to suicidality or psychiatric symptoms.

Moreover, based on the CGI-SI/GI (Table 3c), many BD patients had been moderately to extremely ill at some point since BD onset (65.9%), although the majority (88.6%) had experienced at least mild improvement at the time of assessment (88.6%), 72.7% moderate to significant improvement.

### *Stressful life events, psychosocial functioning and school performance*

In our study, HC reported a relatively high number of lifetime stressful events (7.9 ± 7.18) (Table 4). However, the average in the BD group was almost twice that number (14.03 ± 10.72), which was statistically significant [OR 1.1 (1.01, 1.2); p=0.02]. In the BD the impact was also reported to be slightly greater [41.81 ± 38.09 vs. 19.62 ± 20.85; OR 1.04 (1, 1.07); p=0.03]. The data from the parents was similar to that of the adolescents' reports (see Table 4). It is important to note that adolescents and their parents identified different life events as stressors, although correlation between measures was estimated as strong (Spearman Rho=0.54, p<0.001).

Regarding functionality, lower scores on the CGAS were significantly associated with the BD group [59.89 ± 12.1 BD vs. 85.44 ± 4.03 HC; OR 0.64 (0.48, 0.86); p<0.01]. On the PAS general scale, higher scores were significantly

**Table 3. Differences between controls and persons with bipolar disorder in self and hetero-reported symptoms scales ▪**

| | All sample N (88) | Bipolar I/II group N (44) | Control group N (44) | Univariate Analysis OR (95% CI) | p-value |
|---|---|---|---|---|---|
| **a) DSM-5 diagnosis:** | | | | | |
| Past Psychiatric History | | | | | |
| Previous mental health contact: Yes (n, %) | 58 (65.9) | 41 (93.2) | 17 (38.6) | 13 (3.09, 54.77) | **<0.001** |
| Age of first contact (mean, SD; min,max) | 10 ± 4.02 (3, 17) | 10.86 ± 3.99 | 7.76 ± 3.21 | 1.75 (0.99, 3.09) | 0.06 |
| Previous psychiatric diagnosis: Yes (n, %) | 43 (48.9) | 40 (90.9) | 3 (6.8) | 12 (2.84, 50.77) | **<0.001** |
| Lifetime Psychiatric DO (past and current) | | | | | |
| Number of current diagnoses (mean, SD) | | 2.3 ± 1.47 | 0.16 ± 0.37 | NA | NA |
| Lifetime Comorbidity History: Yes (n, %) | | 39 (88.6) | 0 | NA | NA |
| Lifetime Psychotic DO (n, %) | | 0 | 0 | NA | NA |
| Lifetime Affective DO (n, %) | | 44 (100) | 0 | NA | NA |
| Lifetime Anxiety DO w/o (n, %) | | 26 (59.1) | 0 | NA | NA |
| Lifetime OCD DO (n, %) | | 3 (6.8) | 0 | NA | NA |
| Lifetime AN/BN DO (n, %) | | 11 (25) | 0 | NA | NA |
| Lifetime ADHD DO (n, %) | | 12 (27.3) | 0 | NA | NA |
| Lifetime CD/ODD DO (n, %) | | 12 (27.3) | 0 | NA | NA |
| Lifetime PTSD DO (n, %) | | 3 (6.8) | 0 | NA | NA |
| Lifetime Elimination DO (n, %) | | 3 (6.8) | 0 | NA | NA |
| Lifetime Other DO* (n, %) | | 11 (25) | 2 (4.5) | 10 (1.28, 78.12) | **0.03** |
| Lifetime Drug Abuse/Dependence DO (n, %) (past and current) | | | | | |
| History drugs abuse: abuse/dependence vs. sporadic/absent | 27 (30.7) | 20 (45.5) | 7 (15.9) | 5 (1.45, 17.27) | 0.01 |
| History drugs any: sporadic/abuse/dependence vs. absent | 64 (72.7) | 29 (65.9) | 35 (79.5) | 0.3 (00.8, 1.09) | 0.07 |
| History OH | 47 (53.4) | 22 (50) | 25 (56.8) | 0.69 (0.3, 1.62) | 0.4 |
| History caffeine | 37 (42) | 8 (18.2) | 29 (65.9) | 0.05 (0.01, 0.34) | **<0.01** |
| History cannabis | 29 (32.9) | 17 (38.6) | 12 (27.3) | 1.62 (0.67, 3.92) | 0.28 |
| History hallucinogens | | 0 | 0 | NA | NA |
| History inhalants | | 0 | 0 | NA | NA |
| History opiods | | 0 | 0 | NA | NA |
| History sedatives, hipnotics, and anxiolytics | | 0 | 0 | NA | NA |
| History stimulants (anfetamines, cocaine and other) | | 9 (20.4) | 0 | NA | NA |
| History tobacco | 24 (27.3) | 19 (43.2) | 5 (11.4) | 7.5 (1.72, 32.8) | **<0.01** |
| History other | | 0 | 0 | NA | NA |
| **b) Dimensional scales:** | | | | | |
| Evaluator's reported: | | | | | |
| YMRS (mean, SD; max and minimum) | 3.56 ± 5.44 (0, 22) | 6.77 ± 6.17 | 0.34 ± 0.78 | 2.13 (1.1, 4.1) | **0.02** |
| HDRS_17 (mean, SD; max and minimum) | 4.08 ± 5.48 (0, 29) | 6.95 ± 6.4 | 1.20 ± 1.66 | 1.54 (1.18, 2) | **<0.01** |

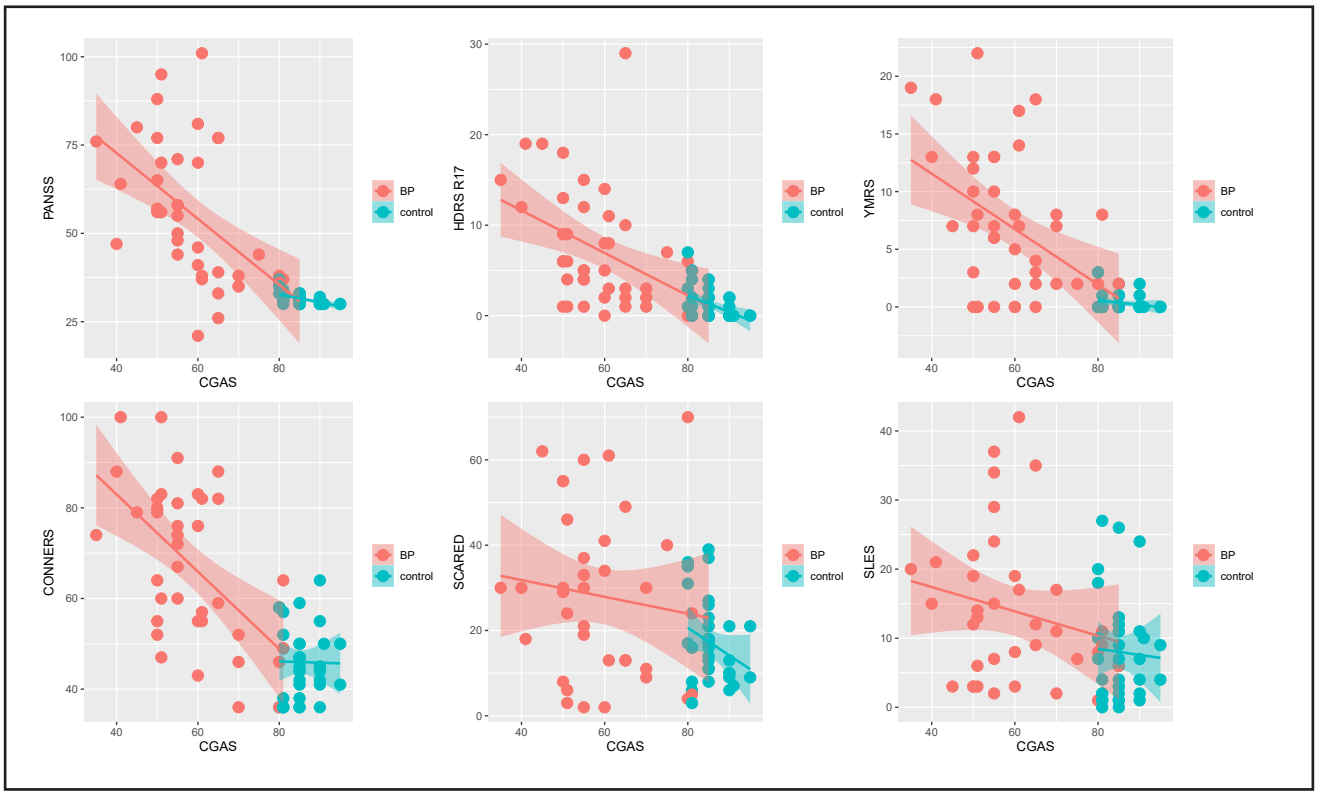
*continued*

**Table 3 continued**

| | All sample N (88) | Bipolar I/II group N (44) | Control group N (44) | Univariate Analysis OR (95% CI) | p-value |
|---|---|---|---|---|---|
| **b) Dimensional scales:** | | | | | |
| Evaluator's reported: | | | | | |
| PANSS total (mean, SD; min, max) | 42.36 ± 17.96 (21, 101) | 53.79 ± 20.12 | 31.45 ± 1.61 | 1.25 (1.06, 1.49) | 0.01 |
| PANSS positive (mean, SD; min, max) | 10 ± 5.5 (4, 28) | 13.14 ± 6.64 | 7 ± 0.1 | 2.1 (0.99, 4.46) | 0.05 |
| PANSS negative (mean, SD; min, max) | 8.64 ± 3.82 (4, 26) | 10.36 ± 4.93 | 7 ± 0.1 | 2.29 (1.02, 5.11) | **0.04** |
| PANSS general (mean, SD; min, max) | 24.15 ± 10.84 (15, 57) | 31.29 ± 11.78 | 17.34 ± 1.63 | 1.94 (1.03, 3.65) | **0.04** |
| SOPS total (mean, SD; min, max) | 13.34 ± 17.56 (0, 66) | 25.14 ± 18.31 | 1.55 ± 1.98 | 1.89 (0.82, 4.34) | 0.14 |
| SOPS positive (mean, SD; min, max) | 3.06 ± 5.56 (0, 26) | 5.98 ± 6.69 | 0.14 ± 0.63 | 2.13 (1.15, 3.96) | **0.02** |
| SOPS negative (mean, SD; min, max) | 3.52 ± 5.48 (0, 21) | 6.77 ± 6.2 | 0.27 ± 0.9 | 2.19 (1.17, 4.1) | **0.01** |
| SOPS disorganization (mean, SD; min, max) | 2.64 ± 3.98 (0, 15) | 5.14 ± 4.37 | 0.14 ± 035 | 6.38 (1.25, 32.54) | **0.03** |
| SOPS general (mean, SD; min, max) | 4.1 ± 4.8 (0, 16) | 7.25 ± 5 | 0.95 ± 1.2 | 2.17 (1.27, 3.71) | **<0.01** |
| Adolescent's self-reported: | | | | | |
| BDI (mean, SD; min, max) | 10.61 ± 12 (0, 57) | 16.63 ± 13.83 | 4.11 ± 3.63 | 1.18 (1.04, 1.33) | **<0.01** |
| SIQ (mean, SD; min, max) | 10.44 ± 15.41 (0, 68) | 17.31 ± 18.97 | 3.39 ± 4.16 | 1.16 (1.03, 1.31) | **0.01** |
| MDQ (mean, SD; min, max) | 5.76 ± 4.38 (0, 13) | 9.11 ± 3.06 | 2.5 ± 2.67 | 1.76 (1.41, 2.2) | **<0.001** |
| Scale of morningness (mean, SD; min, max) | 31.61 ± 5.99 (16, 44) | 31.43 ± 6.23 | 31.79 ± 5.84 | 1.01 (0.92, 1.1) | 0.91 |
| SCARED (mean, SD; min, max) | 22.54 ± 16.01 (2, 70) | 28.05 ± 19.24 | 17.03 ± 9.33 | 1.05 (1.01, 1.09) | **0.01** |
| Suicidal ideation (n, %) | | 22 (50) | 0 | NA | NA |
| Suicidal attempt (n, %) | | 14 (31.8) | 0 | NA | NA |
| Number of suicidal attempt (mean, SD; min, max) | | 1.6 ± 0.83 (0, 3) | 0 | NA | NA |
| Self-injurious behavior (n, %) | 12 (13.6) | 11 (25) | 1 (2.3) | 11 (1.42, 85.2) | **0.02** |
| Parents' self-reported: | | | | | |
| Conners p >70: Yes (n, %) | | 19 (43.2) | 0 | NA | NA |
| Conners_total (mean, SD; min, max) | 56.71 ± 17.32 (36, 100) | 67.71 ± 17.25 | 45.71 ± 7.86 | 1.11 (1.03, 1.2) | **<0.01** |
| CMRS (mean, SD; min, max) | 7.61 ± 11.28 (0, 42) | 13.82 ± 13.17 | 1.39 ± 2.28 | 1.3 (1.03, 1.63) | **0.03** |
| P-YMRS (mean, SD; min, max) | 6.69 ± 8.13 (0, 36) | 10 ± 10.06 | 3.38 ± 3.19 | 1.13 (1.02, 1.26) | **0.02** |
| **c) Clinical Global Impression (CGI)** | | | | | |
| CGI_SI: moderatly ill to one of the most severe (n, %) | | 29 (65.9) | 0 | NA | NA |
| CGI_GI: moderatly to much improvement (n, %) | | 32 (72.7) | 0 | NA | NA |
| CGI_GI: mildly to much improvement (n, %) | | 39 (88.6) | 0 | NA | NA |
| Clinical remission* | | 21 (47.7) | 0 | NA | NA |

OR: odds ratio; CI: confidence interval; SD: standard deviation; NA: Not applicable; DO: disorder; OCD: obsessive-compulsive disorder; AN/BN: anorexia or bulimia nervosa; ADHD: attention deficit/ hyperactivity DO; CD/ODD: conduct or oppositional Defiant DO; PTSD:post-traumatic stress DO. * Other DO: elimination DO; tics; learning DO; borderline personality traits; autistic traits. YMRS: Young mania rating scale; HDRS_17:Hamilton depression rating scale; PANSS: Positive and negative symptom scale; SOPS: prodromal symptoms scale; BDI: Beck Depression Inventory; SIQ: Suicidal ideation questionnaire; MDQ: Mood disorders questionnaire; SCARED: screen for child anxiety related disorders; CMRS: child mania rating scale; P-YMRS: parent's Young mania rating scale; CGI: clinical global impression scale; CGI-SI: severity of the illness at last acute episode; CGI-GI: general improvement after treatment. Clinical remission defined as HDRS-17<8, YMRS equal or <12.
▪ All cases and controls mached by gender and age. In bold p-values =<0.05.

**Figure 1. Correlations between CGAS and Psychiatric Symptoms**




more associated with BD than HC [4.23 ± 2.86 BD vs. 1.88 ± 0.5 HC; OR 4.98 (1.39, 17.83); p=0.02]. Both measures were strongly correlated (rho=-0.51, p<0.001) therefore, to avoid colinearity, only CGAS data were included in the multivariate analyses.

Lower academic performance based on the K-SADS-PLE was significantly associated with the BD group [47.7% BD vs. 95.5% HC; CI 0.05 (0.01, 0.34); p<0.01]. At the time of the study, only 35.4% of the sample was enrolled in post-secondary education, which was slightly less associated with the BD group, although not sufficiently significant due to the small sample size [20% BD vs. 52.2% HC; OR 0.22 (0.05, 1.03); p=0.05].

Finally, in both the BD group and HC group, a negative correlation was found between the intensity of clinical symptoms and functionality based on CGAS (Fig. 1). The strongest correlation with the CGAS score was for attenuated psychotic symptoms, either measured by the PANSS scale [(BD: rho=-0.65; p<0.001); (HC: rho=-0.57; p<0.001)], or by the prodromic scale SOPS, but the latter was only associated with lower functionality in the BD group [rho=-0.67; p<0.001]. In both the BD group and the HC group, the association between functionality and the presence of subthreshold depressive symptoms based on the HDRS-17 was scored as medium [(BD: rho=-0.5; p<0.01); (HC: rho=-0.46; p<0.01)]. Finally, for the BD group but not the HC group, subthreshold mania on the YMRS and subthreshold attentional symptoms on the Conner-48 also presented a medium score (rho=-0.39, and rho=-0.46 respectively; p<0.01 for both). No significant correlations were found between functionality and the presence of anxiety, or previous exposure to stressful life events.

### *Multivariate analyses*

We ran several multivariate analyses with functionality based on CGAS, SES, and other clinically relevant variables such as socio-demographics, comorbid categorical disorders, persistence of clinical symptoms, lifetime suicidality and NSSIB, stressful life events, and school performance. Once we controlled for SES and family history differences, CGAS and school performance were found to be the most statistically significant associations with the BD group compared to HC [respectively: OR 0.65 (0.46, 0.93), p=0.02; OR 0.03 (0.01, 0.67), p=0.03] (Table 5a). Furthermore, when we included substance abuse/dependence DO, CGAS was still the most significant variable [OR 5.93 (0.47, 75.18), p=0.17**;** OR 0.67 (0.49, 0.92), p=0.01] (Table 5b). Even when clinical symptoms were included [HDRS-17: OR 1.69 (0.85, 3.38), p=0.26; PANSS: OR 1.69 (0.85, 3.38), p=0.13] and adjusted for SES, CGAS remained the most significant result associated with the BD group [OR 0.7 (0.53, 0.94), p=0.02] (Table 5c). Finally, CGAS and school performance were confirmed as the most discriminative

**Table 4. Differences between controls and persons with bipolar disorder in life events exposure and levels of functionality▪**

| Previous exposure to life events | All sample N (88) | Bipolar I/II group N (44) | Control group N (44) | Univariate Analysis OR (95% CI) | p-value |
|---|---|---|---|---|---|
| Adolescent report: | | | | | |
| SLES_number of events (mean, SD; min, max) | 10.88 ± 9.53 (0, 42) | 14.03 ± 10.72 | 7.9 ± 7.18 | 1.1 (1.01, 1.2) | 0.02 |
| SLES_impact (mean, SD; min, max) | 30.42 ± 32.27 (0, 139) | 41.81 ± 38.09 | 19.62 ± 20.85 | 1.04 (1, 1.07) | 0.03 |
| Parents report: | | | | | |
| SLES_number of events (mean, SD; min, max) | 7.05 ± 7.2 (0, 35) | 10.54 ± 8.05 | 3.74 ± 4.23 | 1.23 (1.04, 1.45) | 0.02 |
| SLES_impact (mean, SD; min, max) | 22.41 ± 26.36 (0, 137) | 35.19 ± 30.7 | 10.29 ± 13.03 | 1.07 (1.01, 1.13) | 0.02 |
| Functionality | | | | | |
| CGAS (mean, SD; min, max) | 72.52 ± 15.59 (35, 95) | 59.89 ± 12.1 | 85.44 ± 4.03 | 0.65 (0.48, 0.87) | <0.01 |
| PAS general (mean, SD; min, max) (N=83) | 3.01 ± 2.32 (1, 16) | 4.23 ± 2.86 | 1.88 ± 0.5 | 4.98 (1.39, 17.83) | 0.02 |
| Academically performance | | | | | |
| Overall performance: good (n, %) | 63 (71.6) | 21 (47.7) | 42 (95.5) | 0.05 (0.01, 0.34) | <0.01 |
| Some problems or repeated one grade | 21 (23.9) | 19 (43.2) | 2 (4.5) | | |
| Repeated more than one grade or dropped of school | | 4 (9.1) | 0 | | |
| Post-secondary education: yes (n, %) (N=48) | 17 (35.4) | 5 (20) | 12 (52.2) | 0.22 (0.05, 1.03) | 0.05 |

OR: odds ratio; CI: confidence interval; SD: standard deviation; NA: Not applicable; SLES: stressful live events schedule; CGAS: children's global assessment scale; PAS: premorbid adjustment scale. ▪ All cases and controls matched by gender and age.

variables in the stepwise regression model [OR 0.68 (0.49, 0.94), p=0.02; OR 0.04 (0.01, 0.47), p=0.01], adjusted for YMRS [OR 1.99 (0.89, 4.48), p=0.09] (Table 5d).

## Discussion

In summary, BD patients were found to be associated with lower SES and a stronger family history of psychiatric disorders, more specifically affective disorders. No associations were found regarding medical or perinatal history. Both BD and HC patients reported unexpectedly high rates of alcohol and cannabis abuse, but drug dependence was more strongly associated with BD. Most BD subjects were of subtype I, and had an onset during late adolescence, preceded by a prolonged prodromic stage of mainly unspecific affective symptoms. Although most of them showed clinical improvement after intensive treatment, the BD group remained significantly more associated with subthreshold and threshold symptoms when compared with HC. The BD group was also associated with a higher number and higher intensity of stressful life events, lower levels of functionality, and lower academic performance at school. A clear correlation was found between persistent symptomatology and lower levels of functionality in both groups, with psychosis being the strongest correlation. Finally, in a series of multivariate analyses, lower levels of functionality in daily life and lower academic performance remained the most significant findings associated with BD.

A relation between lower SES and BD has been consistently reported in the literature, as well as high levels of heritability (up to 60% depending on the study) (Birmaher et al., 2009; Strober, 1992; Wozniak et al., 2012). Nowadays, we are beginning to think that both variables may be associated, but we do not understand exactly how. The economic burden associated with mental disease is well documented in studies with adult samples (Whiteford, Ferrari, Degenhardt, Feigin, & Vos, 2015). More recently, a large longitudinal study has also confirmed the impact of continuous exposure to poverty during childhood and the risk for psychiatric disorders in adolescence and, interestingly, even after controlling for the presence of mental disorders in first-degree relatives (Björkenstam et al., 2017). In our study, the initial exploratory analyses found an association between poverty and a family history of mental disorders, as well as an association between poverty and lower functionality. However, when all variables were analyzed together, only lower functionality showed a statistically significant association with BD.

**Table 5. Multivariate analyses: CGAS, SES and other clinical relevant variables***

| | Multivariate Analysis OR 95% CI | p-value | | Multivariate Analysis OR 95% CI | p-value |
|---|---|---|---|---|---|
| **5a: CGAS, socio-demographics and functionality** | | | **5b: CGAS, socio-demographics and categorical DO** | | |
| SES at intake | 0.92 (0.84 - 1.02) | 0.1 | SES at intake | 0.93 (0.86 - 1.01) | 0.09 |
| 1st degree Psychiatric Family Hx | 8.88 (0.61 - 121) | 0.1 | 1st degree Psychiatric Family Hx | 5.24 (0.6 - 45.54) | 0.17 |
| CGAS | 0.65 (0.46 - 0.93) | 0.02 | CGAS | 0.67 (0.49 - 0.92) | 0.01 |
| Overall performance: good | 0.03 (0.01 - 0.67) | 0.03 | Hx Substance Abuse/ Dependence DO | 5.93 (0.47 - 75.18) | 0.17 |
| **Akaike information criteria** | **30.76** | | **Akaike information criteria** | **35.66** | |
| **5c: CGAS, socio-demographics and symptoms** | | | **5d*: CGAS, socio-demographics and functionality** | | |
| SES at intake | 0.92 (0.84 - 1.02) | 0.1 | CGAS | 0.68 (0.49, 0.94) | 0.02 |
| CGAS | 0.7 (0.53 - 0.94) | 0.02 | Overall performance: good | 0.04 (0.01, 0.47) | 0.01 |
| HDRS-17 | 1.69 (0.85 - 3.38) | 0.13 | YMRS | 1.99 (0.89, 4.48) | 0.09 |
| PANSS | 0.64 (0.29 - 1.4) | 0.26 | **Akaike information criteria** | **29.66** | |
| **Akaike information criteria** | **37.89** | | | | |

OR: odds ratio; CI: confidence interval; SES: Socioeconomic status; CGAS: children's global assessment scale; DO: disorder; Hx: history; HDRS_17: Hamilton depression rating scale; PANSS: positive and negative symptom scale.
▪ All cases and controls matched by gender and age. *Stepwise logistic regression

The fact that most BD subjects came from an inpatient unit may explain the predominance of BD subtype I in our sample (Carlson et al., 2012; Hirneth, Hazzell, Hanstock, & Lewin, 2015; Shapiro et al., 2014; Tillman et al., 2008). Since most of our patients were adolescents and not children, the majority showed an episodic nature (Birmaher, Axelson, Goldstein, et al., 2009; Geller et al., 2008; Strober et al., 1995), where clear and distinctive episodes of depressive or elated mood could be identified (Axelson et al., 2006; Birmaher, Axelson, Strober, et al., 2009; Demeter et al., 2013; Lazaro et al., 2007). Psychosis was very common in our sample, as expected, since we recruited from an inpatient ward (Chan, Stringaris, & Ford, 2011; Goes et al., 2007; Hirneth et al., 2015; Soutullo et al., 2009; Tillman et al., 2008). Lifetime suicidal thoughts and suicidal attempts were also unexpectedly prevalent, in fact, it was higher than in most previous studies (Chan et al., 2011; Geller et al., 2008; Goldstein et al., 2009; Lázaro et al., 2007), although in line with recent studies with adolescents (Shapiro et al., 2014). A quarter of BD patients and one HC reported NSSIB, which today is seen as a very widespread phenomenon, especially in Europe (Brunner et al., 2014).

Consistent with previous genetic and high-risk studies (Axelson et al., 2015; Correll et al., 2014; Duffy, Alda, Hajek, Sherry, & Grof, 2010), most BD patients recalled a long prodromic phase rather than an acute onset. It was characterized by unspecific affective and behavioral problems, followed by a depressive episode, and the eventual diagnosis of BD during late-adolescence.

The duration and number of psychiatric hospitalizations, and the type and dosage of medication were in line with the most updated and evidence-based international guidelines (Alvaro & Romero, 2011; Goldstein et al., 2017; Goodwin et al., 2016; Yatham et al., 2018). Despite that, half of the BD sample continued to report subthreshold or even mild to moderate symptoms after a long recovery process as documented in the literature (Birmaher et al., 2006; Geller et al., 2008).

Sporadic drug use was very frequent in both BD and HC samples, where half of the adolescents reported alcohol consumption and a third, either cannabis or tobacco. High rates of sporadic drug use are a major concern in the European Union, with prevalence rates of between 15–45% for ages 15–24 years, and as high as 80% for alcohol consumption ("Statistical Bulletin 2017— Prevalence of drug use/ www.emcdda.europa.eu"). However, drug abuse/dependence was significantly less prevalent, and was specifically associated with the BD group, as expected (Birmaher, Axelson, Monk, et al., 2009; Geller et al., 2008; Hirneth et al., 2015; Shapiro et al., 2014). Nonetheless, when drug abuse/dependence DO was combined in the multivariate models with CGAS, SES differences and family history, only CGAS remained significantly related with BD.

The number of stressful life events was high in both groups, and both the total number of events and the intensity were significantly more associated with the BD group. Several studies in adults (Johnson, 2005; Koenders et al., 2014; Lex, Bäzner, & Meyer, 2017) and adolescents (Romero et al., 2009, 2010; Rucklidge, 2006; Tillman et al., 2003) have observed a higher number of stressful life events in BD and depressive patients compared with healthy controls, or patients with other less severe psychiatric disorders. Interestingly, stressful life events have also been associated with a lower socioeconomic status (Koenders et al., 2014; Romero et al., 2010), although the direction of causality is unclear. It should be noted that, in our sample, stressful life events and lower socioeconomic status were more closely associated with one another than either was with the BD or HC group.

In line with available evidence, and confirming our a priori hypothesis, low levels of functioning were clearly associated with the BD group in all the multivariate analyses. Over the last decade, several studies reported high levels of functional impairment in children and adolescents with BD (Birmaher, Axelson, Goldstein, et al., 2009; Carlson et al., 2012; Geller et al., 2008; Jansen et al., 2012; Judd et al., 2002; Tohen et al., 2003), with the highest impact in the areas of family and peer relationships and academic performance (Best, Bowie, Naiberg, Newton, & Goldstein, 2017; Geller, Bolhofner, et al., 2000; Goldstein et al., 2009; Lewinsohn et al., 2000). In fact, compared with other chronic medical conditions like heart surgery, arthritis and other autoimmune diseases, adolescents with BD rank lowest in terms of quality of life (Freeman et al., 2009). Moreover, functional impairment was reported to be greater among adolescents with BD than children with BD, regardless of whether onset was in childhood or adolescence (Biederman et al., 2005; Goldstein et al., 2009). Interestingly, whereas studies in adults with BD consistently report lower levels of functioning than HC (Grande et al., 2016; Judd et al., 2008), the majority of studies found no differences regarding the level of academic attainment (Martinez-Aran et al., 2007; Torres et al., 2017). In our adolescent sample, even after extensive treatment was provided, and from a very early age, BD was significantly associated with both overall functional impairment and a lower academic level compared to HC. Furthermore, the difficulties observed may be linked to a partial response to treatment, with almost two thirds of BD patients reporting persistent sub-syndromic symptoms over time. In addition, we were able to confirm a correlation between the presence of even slight clinical symptoms and low CGAS scores, in both BD and HC groups. This was consistent with previous findings, with psychotic symptoms showing the strongest correlation (Goldstein et al., 2009; Hua et al., 2011; Mendez et al., 2019). However, low CGAS scores remained as the strongest association with the BP group even after including mania, depression and psychosis in the multivariate models.

Certain limitations of the study must be highlighted. We cannot rule out the possibility of a selection bias, taking into account the heterogeneity in socio-economic status. Information about mental health history and the appearance of the first symptoms was recalled retrospectively as were medical history and obstetric complications. History of drug use was based on direct reporting without relying on a urine sample. Although recruitment involved a variety of hospital departments, most BD patients arrived from the inpatient unit and may have suffered from a more severe form of the disease. Some healthy controls had previous contact with mental health services, although they did not have any major mental disorder at the time of the study. Although extensive treatment was provided, half of BD patients did not achieve full clinical remission. Finally, the sample was relatively small, which limits the power to detect differences between HC and the two BD subtypes.

In summary, even when early detection and evidence-based treatment is provided, the onset of bipolar disorder during youth limits the capacity for normal performance in daily activities compared to controls without any mental disease. From a clinical perspective, it is important to pay attention to the persistence of sub-threshold symptoms, and reinforce the social and occupational aspects of treatment.

## Acknowledgements / Conflicts of Interest

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