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Sleep alterations in pediatric bipolar disorder versus attention deficit disorder☆

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ABSTRACT

Bipolar disorder (BD) and attention deficit/hyperactivity disorder (ADHD) share numerous clinical features, which can make the differential diagnosis challenging. Studies conducted in adults suggest that patients with BD and ADHD have different sleep patterns. However, in pediatric populations, data on these potential differences are scant. The present preliminary study was conducted to identify potential differences in sleep alterations among youths diagnosed with BD or ADHD compared to healthy controls (HC). A total of 26 patients diagnosed with BD (n = 13) or ADHD (n = 13) were compared to 26 sex- and age-matched HC ([HC_{BD}], n = 13, and [HC_{ADHD}], n = 13). All participants underwent polysomnography. The mean duration of stage N2 sleep was shorter in the BD group than in controls (HC_{BD}). The BD group also had higher (non-significant) REM density (REMd) scores than controls while mean REMd scores were lower in the ADHD group versus controls. Compared to the ADHD group, the BD group presented a shorter N2 stage, a longer first REM sleep duration (R1), and greater REMd. According to our findings, these three variables—N2 stage, REMd, and R1—appear to differentiate patients with BD from those with ADHD and from HC.

1. Introduction

Bipolar disorder (BD) is characterized by severe mood symptoms with cognitive and motor acceleration or slowing (Goldstein et al., 2005; Goldstein and Birmaher, 2012; Pavuluri et al., 2004; Wilens et al., 1999). Despite the development of new psychopharmacological treatments and advances in bipolar-specific psychotherapies in recent decades (Correll et al., 2010; Goldstein et al., 2007; Miklowitz et al., 2004; West et al., 2014), the clinical course of this disorder in pediatric populations remains closely associated with significant impairments in the child, the family, and social environs (Birmaher et al., 2006; Geller and Luby, 1997; Goldstein et al., 2009; Keenan-Miller et al., 2012).

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Diagnosis of BD is based on clinical criteria that rely on accurate reporting and interpretation of psychopathological signs. Although it is possible to obtain a reliable diagnosis using the available diagnostic criteria (Youngstrom et al., 2008), diagnosis of pediatric BD (PBD) is notoriously difficult (Rettew et al., 2009). In addition to the wide heterogeneity in the presentation and course of BD among youths, other factors that contribute to the diagnostic complexity include the fact that many youths experience a prodromal period during which sleep disturbances and anxiety symptoms are quite mild and thus difficult to detect (Egeland et al., 2000; Goldstein et al., 2017; Hauser and Correll, 2013). Secondary factors that contribute to the variable clinical expression of PBD are the modulating effect of neurodevelopment (Leibenluft et al., 2011) and high comorbidity rates (Pavuluri et al., 2005), both of which can complicate the diagnostic picture. Family characteristics are also important, both in terms of the family's impact on the child and the symptoms (Geller et al., 2002a) and in how caregivers and youths may interpret and report symptoms in different ways (Carlson et al., 2016). In addition, controversy surrounding the definition of mania in youths has resulted in the use of different definitions among research groups (Biederman et al., 2004; Geller et al., 2000; Goldstein et al., 2017; Leibenluft et al., 2003). Symptoms of mania can be confused with those of other disorders, especially attention deficit/hyperactivity disorder (ADHD), thus frequently resulting in diagnostic uncertainty. The difficulty of establishing a differential diagnosis between PBD and ADHD is due, in part, to their shared symptoms, particularly inattention and excessive motor and verbal activity (Geller et al., 2002b; Geller and Luby, 1997; Goldstein and Birmaher, 2012). Although there is evidence of sleep alterations in both disorders, sleep disturbance is a diagnostic feature of BD but not ADHD. In BD, a decreased need for sleep is a manic-related symptom (DSM-5; American Psychiatric Association, 2013) and one of the five symptoms that best discriminate patients with BD from those with ADHD and from healthy controls (HC; Geller et al., 2002b). In adults with BD, studies that have used polysomnography (PSG) consistently report decreased REM latency (REMLat) and increased REM density (REMd) in these patients when compared to HCs (Ritter et al., 2012). Sleep-wake rhythm disruption in ADHD patients is a common complaint of parents (Mindell and Owens, 2003; Staton et al., 2008) even though this disruption is not considered a DSM-5 diagnostic criteria for the disorder (American Psychiatric Association, 2013). Some of the polysomnographic studies carried out in ADHD have reported differences between patients with ADHD and controls (O'Brien et al., 2003; Kirov et al., 2004; Gruber et al., 2009; Silvestri et al., 2009; Akinci et al., 2015; Virring et al., 2016), although other studies have not found any differences (Choi et al., 2010; Prihodova et al., 2010; Wiebe et al., 2013). A meta-analysis concluded that individuals with ADHD have higher shift stages and lower sleep efficiency compared to HCs (Cortese et al., 2009).

Sleep studies in PBD are scarce and the few that have been performed have applied heterogeneous methodologies (Beauchemin and Hays, 1996; Harvey et al., 2006; Staton et al., 2008). One study reported lower REM sleep and higher N3 stage in youths with BD compared to controls (Mehl et al., 2006). By contrast, another study (Rao et al., 2002) did not find any differences between youths with unipolar or bipolar depression compared to HCs. Geller et al. (2002b) compared adolescents with BD or ADHD to controls, finding that sleep disturbances were 6.5-fold more prevalent in youths with BD than those with ADHD.

In this context, it could be valuable to explore the specific biologic characteristics of BD to better distinguish between this disorder and other disorders with shared symptoms, such as ADHD. In this regard, PSG provides an objective measure of sleep disturbances and would thus appear to be an appropriate method to explore possible sleep architecture abnormalities in both disorders.

The main aim of this preliminary study was to compare the sleep parameters measured by polysomnography in a group of pediatric patients diagnosed with PBD or ADHD and to compare these to a sample of healthy controls. Based on previous studies carried out in the adult bipolar population, we hypothesized that patients with PBD would have higher REMd and lower REMLat than youths with ADHD or HCs. A secondary aim was to examine the relationship between the polysomnographic variables and psychiatric symptoms in the bipolar group.

2. Methods

2.1. Study design

The present cross-sectional study involved a group of outpatients (age range, 6–18 years) diagnosed with one of the following subtypes of BD: BD-I, BD-II, or an operationalized definition of BD not otherwise specified (NOS) in euthymia (Birmaher et al., 2006). The second clinical group included a sample of pediatric patients diagnosed with ADHD. These two clinical groups were compared to an age- and sex-matched group of healthy youths. Sample selection was performed using a non-random convenience sampling procedure.

2.2. Participants and procedures

All participants and their parents or legal guardians signed the informed consent form prior to participation in the study. The study was approved by the Clinical Research Ethics Committee (CEIC) at the Hospital del Mar, Parc de Salut Mar. The sample consisted of 26 patients (13 in each of the clinical groups) and 26 HCs, for a total of 52 participants. The BD group was comprised of 13 individuals (BD-*I* = 7 patients, BD-II = 5, and BD-NOS = 1); of these, 46.1% were females, with a mean age of 14.0 years (*SD* = 1.1). The ADHD group (n = 13) consisted of 12 individuals diagnosed with ADHD combined subtype and one participant with ADHD hyperactive-impulsive subtype; the mean age was 11.2 years (*SD* = 0.8) and 15.4% were females. The mean age of the 26 HCs was 12.6 years (*SD* = 3.5) and 30.8% were females. The clinical sample was recruited at two outpatient clinics at the Neuropsychiatry and Drug Addiction Institute (INAD), Parc de Salut Mar in Barcelona, from September 2013 to September 2015.

The HCs were recruited from individuals treated at the Department of Neurology and Clinical Neurophysiology (Sleep Unit) at the Hospital del Mar from 2012 to 2016. A senior child and adolescent psychiatrist (XEP) reviewed the medical records of youths who underwent PSG during this period to identify potential healthy recruits who fulfilled the study inclusion/exclusion criteria. Next, the PSGs from these HCs were matched by age and sex with the PSGs obtained from the treatment groups (BD and ADHD groups) to form the two HC groups matched to the BD group (HC_{BD}) and ADHD group (HC_{ADHD}).

For all participants, eligibility criteria for study inclusion were: age $\leq$ 18 years and signed informed consent form. For the clinical patients, the inclusion criteria were: diagnosis of BD or ADHD according to DSM-5 criteria (American Psychiatric Association, 2013). Exclusion criteria for the clinical groups were: history of severe traumatic brain injury; epilepsy under anticonvulsant treatment; severe unstable medical illness; comorbid substance use disorder; intellectual disability (IQ < 70); or clinical criteria for narcolepsy, obstructive sleep apnea syndrome, or rhythmic movement disorder. For the HCs, exclusion criteria were: diagnosis of moderate-severe sleep disorder, sleep efficiency $\leq$ 75% on the PSG registry, or current pharmacological treatment.

Assessments performed in the two clinical groups included the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) interview and a neuropsychological study. A senior child and adolescent psychiatrist (XEP) administered the K-SADS-PL in both clinical groups. Clinical psychologists administered the neuropsychological studies. The following scales were administered under the supervision of the same senior psychiatrist within 6 h prior to initiation of the PSG: Children's

Depression Inventory (CDI), the Child Mania Rating Scale-Parent version (CMRS-P), and the Children's Manifest Anxiety Scale-Revised (CMAS-R). The following information was assessed and recorded: demographic data, medical and psychiatric history, family history, school performance, socio-economic status (SES), and history of drug and/or alcohol use. Urinalysis was performed in the clinical groups to determine and quantify the presence of drugs.

2.3. Measures

Children and parents were interviewed (K-SADS-PL) for the presence of current and lifetime psychiatric disorders (Kaufman et al., 1997). In the children under age 17, the neuropsychological assessment was performed using the Spanish language versions of the WISC-IV (Wechsler Intelligence Scale for Children-Fourth Edition); the WAIS-III (Wechsler Intelligence Scale for Adults) was used for the 17- and 18-year old participants (Corral et al., 2005; Seisdedos et al., 1999). The CDI (Kovacs, 1992) and the CMRS-P (Pavuluri et al., 2006) scales were used, respectively, to assess depressive and manic symptoms; the CMAS-R scale (Reynolds and Richmond, 1978) was used to assess anxiety symptoms. The Family History Screen (FHS, Weissman et al., 2000) was used to interview parents about their first- and second-degree psychiatric history.

Primary sleep disturbances were assessed using the Sleep Disturbance Scale for Children (SDSC). The parent-completed SDSC consists of 26 Likert-type items to explore the presence of the most prevalent sleep disorders in youths, with higher scores indicating a greater probability of acute sleep disorders. The scale yields an overall score (cut-off point = 39) and a specific score on seven different categories (Bruni et al., 1996).

School performance was operationalized as follows: good (no failed subjects), average (1–3 failed subjects) or poor (4 or more failed subjects). The rationale underlying the decision to allow up to 3 failed subjects in the "average" school performance was to avoid penalizing children with learning disorders related to linguistic interference (in our region children learn to speak 3 languages: Catalan, Spanish and English). The SES was evaluated through the Hollingshead index, which provides information about family socio-economic status by evaluating the occupational and educational status of the parents (Hollingshead, 1975).

For clinical and research purposes, the polysomnographic recording is divided into 30 s periods (epochs) throughout the night. Each epoch is classified into a sleep stage based on its predominant pattern. The variables evaluated during PSG assessment were: lights on and off time; total bedtime (TBT; time from lights off to lights on); total sleep time (TST; amount of sleep during the registry); sleep efficiency (SEffic: TST / TBT) x 100); sleep latency (SLat; time from lights off to first epoch); duration and percentage of sleep in stages N1, N2, N3 and REM; REM episodes (epiREM); duration of each REM episode (R); REM latency (REMLat; time from first sleep epoch to first REM epoch); REM density (REMd; ratio between rapid eye movements, present/missing, in 5-second REM sleep periods; Werth et al., 1996); and wake after sleep onset (WASO; time awake after the first epoch). The PSG was performed in a darkened, silent hospital room with regulated room temperature. The PSG recording was performed from 10 p.m. until 6 a.m. (8 h). The PSG device used in all cases was the Natus SleepWorks, v. 6.3.0 (Xltek; Natus Medical Inc.; Oakville, Canada). Manual staging was performed according to the American Academy of Sleep Medicine criteria (Iber et al., 2007), with the rater blinded to the participant's diagnostic status.

2.4. Statistical analyses

The Chi-square, Fisher's Exact test, or Mann-Whitney U test was used, as appropriate, to test for differences between diagnostic groups (BD vs. ADHD) and between the clinical groups and healthy controls (BD vs. HC_{BD} and ADHD vs. HC_{ADHD}) to compare the demographic and clinical characteristics. The Mann-Whitney U test was performed to compare the polysomnographic variables among the groups. The clinical groups were compared to their HCs (BD vs. HC_{BD} and AHDH vs. HC_{ADHD}) and to each other (BD vs. ADHD). To identify patients with the most severe mood symptoms, we used the cut-off scores provided for each scale; thus participants who scored ≥ 20 on the CDI, ≥ 21 on the CMAS-R, or ≥ 21 on the CMRS-P were considered to present, respectively, the most severe depressive, anxiety, or manic symptoms. The Mann-Whitney U test was used to compare differences in polysomnographic parameters between the patients with BD who presented the highest depressive, anxiety, and manic symptoms and their healthy controls (HC_{BD}). We also examined the possible associations between the polysomnographic variables and depressive, anxiety, and manic symptoms. Spearman's correlation coefficients were calculated to assess the association between the clinical variables (depressive, anxiety and manic symptoms) and polysomnographic variables in the BD group. Despite the use of the non-parametric test, the results are expressed as means with standard deviations. Given the preliminary nature of this study, no corrections were applied for multiple comparisons. All analyses were two-tailed and the alpha level was set at $p < .05$. All analyses were performed with the SPSS statistical software, version 21 (IBM-SPSS, Chicago, IL.; USA).

3. Results

3.1. Demographic and clinical characteristics of the sample

There were no significant differences in demographic variables (age, sex, or race) between the clinical groups and their respective control groups. Similarly, the clinical groups (BD and ADHD) did not differ in terms of age, sex, race, SES, school performance, or SDSC scores. Although most individuals in the two clinical groups (BD = 100% and ADHD = 92.3%) were receiving psychiatric medication, medication use in the BD group was significantly higher ($X^2 = 12.59$, $p = .01$), with a mean of 2.69 medications ($SD = 0.30$) in the BD group versus 1.15 ($SD = 0.02$, $U = 21.00$, $p = .001$) in the ADHD group. Of the 13 patients in the BD group, 11 were taking ≥ 2 prescription medications, with only two having a single prescription. By contrast, in the ADHD group, 3 participants were taking two prescribed medications, while 9 were taking a single medication, and one was not taking any medication.

Most (73.0%) of the patients (92.3% and 53.8%, respectively, of the BD and ADHD groups) presented psychiatric comorbidity at the time the PSG was performed. In the BD group, the most common comorbidities were: ADHD (9 cases), anxiety disorders ($n = 8$), disruptive behavioral disorders ($n = 6$, with 3 patients presenting oppositional defiant disorder [ODD] and 3 a cases each of), and diurnal enuresis ($n = 1$). In the ADHD group, the most common comorbidity was ODD ($n = 6$) followed by anxiety disorders ($n = 2$). CDI scores were higher in the BD group than in the ADHD group for the total score ($U = 32.00$, $p = .01$), the Negative Mood scale ($U = 41.00$, $p = .02$) and the Self-Esteem scale ($U = 22.00$, $p = .001$). There were no differences between the clinical groups in manic or anxiety symptoms. The demographic and clinical characteristics of the patients and healthy controls are shown in Table 1.

3.2. PSG results: comparison among the BD, ADHD and HC groups

Three pairs of comparisons were made to assess differences in the polysomnographic variables between the BD, ADHD and HC groups. These results are summarized below and shown in Table 2.

3.2.1. BD vs. HC_{BD}

Compared to HC_{BD}, the BD group presented a shorter N2 ($U = 20.50$, $p = .001$). In addition, the raw REMd values were higher in

Table 1
Demographic and clinical characteristics in clinical groups (bipolar disorder and attention deficit hyperactivity disorder) and healthy controls.

	BD (N = 13)		HC_{BD} (N = 13)		BD vs. HC_{BD}	ADHD (N = 13)		HC_{ADHD} (N = 13)		ADHD vs. HC_{ADHD}	BD vs. ADHD
	M	*(SD)*	*M*	*(SD)*	p value	*M*	*(SD)*	*M*	*(SD)*	*P value*	*P value*
Age (years)[a]	13.92	(1.07)	13.92	(1.07)	.72	11.23	(.76)	11.23	(.76)	.92	.05
Socio-economic status [a]	3.5	1.2	–	–		3.8	0.8	–	–		.08
	n	*(%)*	*n*	*(%)*	*p*	*n*	*(%)*	*n*	*(%)*	*p*	
Gender[b]					.63					.72	.20
−Male	7	(53.8)	7	(53.8)		11	(86.4)	11	(86.4)		
−Female	6	(46.2)	6	(46.2)		2	(15.4)	2	(15.4)		
Race[b]					.69					.67	.51
−European	11	(86.4)	10	(77.0)		11	(86.4)	10	(76.9)		
−American	1	(7.7)	2	(16.0)		2	(15.4)	3	(23.1)		
−Others	1	(7.7)	1	(7.0)		0	(0.0)	0	(0.0)		
School performance[b]											.63
−Good	2	(15.4)	–	–		4	(30.8)	–	–		
−Average	2	(15.4)	–	–		2	(15.4)	–	–		
−Bad	9	(69.2)	–	–		7	(53.8)	–	–		
Current pharmacological treatment (Yes/No)[b]	13	(100)	0	(100)		12	(92.3)	0	(100)		1.0
Current comorbidities (Yes/No)[b]	12	92.3	0	0		7	53.8	0	0		.03
	M	*(SD)*	*M*	*(SD)*	*p-value*	*M*	*(SD)*	*M*	*(SD)*		*pvalue*
SDSC	43.15	(2.78)	–	–		40.23	(2.66)	–	–		.35
CDI[a]											
-Total score	24.30	(3.49)	–	–		12.15	(1.82)				.007*
-Negative mood	11.38	(2.37)	–	–		4.61	(1.17)	–	–		.02*
-Self-esteem	12.92	(1.16)				7.53	(.75)	–	–		.001*
CMRS-P[a]	21.92	(2.48)	–	–		16.46	(2.23)	–	–		.09
CMAS-R[a] - Total score	16.23	(1.91)	–	–		14.46	(1.70)	–	–		.58

Note. BD: bipolar disorder; ADHD: attention deficit hyperactivity disorder; HC: healthy controls; SDSC: Sleep Disturbance Scale for Children; CDI: Children´s Depression Inventory; CMRS-P: Child Mania Rating Scale – Parent version; CMAS-R: Children's Manifest Anxiety Scale - Revised.
[a] Mann–Whitney.
[b] Chi-square/Fisher's.
* $p < .05$.

the BD group, although the difference did not reach statistical significance (U = 52.50, p = .10). There was no difference in REMLat between these two groups (U = 83.00, p = .94).

3.2.2. BD vs. ADHD

Compared to the ADHD group, the BD group presented a shorter N2 duration (U = 41.50, p = .03), longer first episode of REM duration (R1) (U = 41.50, p = .03), and higher REMd (U = 26.50, p = .003). There was no difference between the two groups in REMLat (U = 80.00, p = .81).

3.2.3. ADHD vs. HC_{ADHD}

Compared to HC_{ADHD}, the ADHD group had lower REMd values (U = 31.00, p = .01).

3.3. Comparison of the polysomnographic results between the BD patients with the most severe mood and anxiety symptoms versus their healthy controls

We performed a sub-analysis to determine if the differences in the polysomnographic variables between the BD and HC_{BD} remained stable or, conversely, were modified by affective and/or anxiety symptom severity. In this sub-analysis, we evaluated only the youths with BD who obtained the highest scores on the CMRS-P, CDI, and/or CMAS-R scales. The youths in the BD group with the highest scores on the CMRS-P scale presented a shorter N2 duration (U = 10.50, p = .002) than the HC_{BD}. The youths with BD who had the highest scores on the CDI scale showed shorter TST (U = 20.00, p = .04) and N2 durations (U = 8.50, p = .003), longer R1 duration (U = 17.00, p = .02) and higher REMd (U = 15.00, p .02) than HC_{BD}. Finally, the participants in the BD group with the highest scores on the anxiety scale obtained shorter TST (U = 9.00, p = .01) and N2 durations (U = 7.50, p = .01), a longer R1 duration (U = 12.00, p = .01), a lower SEffic percentage (U = 15.50,

Table 2
Polysomnographic variables in clinical groups (bipolar disorder and attention deficit hyperactivity disorder) and healthy controls.

	BD (n = 13)		HC_{BD} (n = 13)		BD vs. HC_{BD}	ADHD (n = 13)		HC_{ADHD} (n = 13)		ADHD vs. HC_{ADHD}	BD vs. ADHD
	M	*(SD)*	*M*	*(SD)*	*p value*	*M*	*(SD)*	*M*	*(SD)*	*p value*	*p value*
TBT	448.99	(46.02)	476.08	(34.02)	.06	472.07	(29.22)	476.65	(26.03)	.79	.21
TST	370.53	(70.05)	423.26	(59.21)	.06	413.92	(32.19)	415.96	(44.89)	.77	.09
SLat	21.45	(17.51)	13.15	(10.92)	.30	22.19	(11.21)	15.92	(10.88)	.11	.55
SEficc	81.52	(14.69)	88.90	(10.22)	.23	87.52	(4.89)	107.80	(69.32)	.36	.29
N2	164.07	(28.21)	212.65	(33.40)	.001**	186.11	(45.82)	322.50	(473.25)	.49	.03*
REMLat	188.50	(111.35)	188.72	(111.73)	.94	183.80	(71.55)	164.01	(77.12)	.47	.81
R1	23.11	(11.63)	14.69	(8.01)	.05	13.19	(7.20)	15.26	(10.50)	.66	.03*
REMd	.49	(.17)	.39	(.19)	.10	.27	(.13)	.53	(39.16)	.006*	.003**

Note. BD: bipolar disorder; ADHD: attention deficit hyperactivity disorder; HC: healthy controls; TBT: total bed time; TST: total sleep time; SLat: sleep latency; SEficc: sleep efficciency; N2: duration of Stage 2 sleep; REMLat: REM sleep latency; R1: duration of first REM episode; REMd: REM density.
* $p < .05$.
** $p < .005$.

Table 3
Spearman rank-order correlation coefficients (r_s) between psychiatric symptoms and polysomnographic variables for the bipolar group.

	TST	N1	N1%	N3%	R3	REMLat	REM	REM%	REMd
CMRS-P	−.10	−.49	−.56*	.25	−.82*	.11	.16	−.31	.16
CDI									
-Total score	−.33	.005	.11	−.29	−.71	.07	.01	−.29	.51
-Negative mood	−.30	.01	.13	−.30	−.66	.006	.06	−.28	.54
-Self-esteem	−.43	−.01	.10	−.27	−.71	.21	−.13	−.30	.33
CMAS-R									
-Total score	−.51	.16	.28	−.41	−.58	.14	−.27	−.16	.57*
-Physiological anxiety	−.18	.58*	.71**	−.62*	.15	−.29	.03	.29	.34
-Social anxiety	−.35	.25	.35	−.30	−.45	.07	−.32	−.22	.60*

Note. TST: total sleep time; N1: duration of Stage 1 sleep; N1%: duration of Stage 1 sleep as percentage of total sleep time; N3%: duration of Stage 3 sleep as percentage of total sleep time; R3: duration of third REM episode; REMLat: REM sleep latency; REM: duration of REM sleep; REM%: duration of REM sleep as percentage of total sleep time; REMd: REM density; CDI: Children´s Depression Inventory; CMRS-P: Child Mania Rating Scale – Parent version; CMAS-R: Children's Manifest Anxiety Scale - Revised.

* $p < .05$.

** $p < .01$.

$p = .03$) and a higher REMd ($U = 13.00$, $p = .02$) than the HC_{BD}.

3.4. Relationship between psychiatric symptoms and polysomnographic variables

The associations between mood symptoms, anxiety symptoms, and polysomnographic variables were evaluated only in the bipolar group. The presence of manic symptomatology was significantly and negatively correlated with R3 duration ($r = -0.82$, $p = .04$) and N1% ($r = -.56$, $p = .04$) while no association was found between depressive symptoms and the polysomnographic variables. Physiological anxiety was significantly and positively correlated with N1 duration ($r = 0.58$, $p = .03$) and N1% ($r = 0.71$, $p = .01$) but negatively with N3% ($r = -.62$, $p = .02$). The social anxiety subscale and total scores were significantly and positively correlated with REMd ($r = .60$, $p = .02$ and $r = .57$, $p = .03$ respectively; Table 3).

4. Discussion

To our knowledge, this is the first polysomnographic study performed in youths with bipolar disorder to use an ADHD control group, in addition to including healthy controls. The three main findings of this study are: (1) the presence of several significant differences in sleep structure between the BD and ADHD groups and compared to healthy controls; (2) a significant effect of mood and anxiety symptoms on sleep structure in patients with BD; and (3) significant associations between manic and anxiety symptoms and several sleep parameters.

Prior to performing this study, we hypothesised that youths with BD would present higher REMd and lower REMLat values compared to healthy controls (HC_{BD}) and youths with ADHD (Eidelman et al., 2010; Ritter et al., 2012; Sitaram et al., 1982; Talbot et al., 2009). However, our findings failed to fully corroborate this hypothesis. First, there were no significant differences in REMLat between any of the study groups. In addition, although REMd values were higher in the BD group compared to the ADHD and HC_{BD} groups, the differences between the BD group and HC_{BD} did not reach statistical significance. In addition, REMd values in the ADHD group were lower than those observed in the control group (HC_{ADHD}). Although several studies have found differences in sleep structure between ADHD and healthy youths (Akinci et al., 2015; Gruber et al., 2009; Kirov et al., 2004; O'Brien et al., 2003; Silvestri et al., 2009; Virring et al., 2016; Waldon et al., 2016), none of those differences were associated with REM sleep variables. Based on the lack of any significant association between REM sleep variables and ADHD, and given the results of an expert review that concluded that children with ADHD (compared to healthy children) present a greater change in sleep stage percentage and lower sleep efficiency (Cortese et al., 2009), we expected to find no significant differences in REM sleep variables between children with ADHD and healthy controls. Theoretically, if children diagnosed with BD presented higher REMd and lower REMLat values than healthy children, so too would children with ADHD. One potential explanation for these differences in REMd and REMLat between the ADHD and HC_{ADHD} groups is the possible influence of comorbidity and psychopharmacological treatment on sleep structure in the ADHD group (Harvey, 2008). The only polysomnographic variable that differentiated the BD group from the ADHD and HC groups was N2 stage duration. More specifically, we found that youths with BD (who underwent the PSG during the inter-episodic phase) presented a shorter N2 duration than that observed in the ADHD and HC groups. To our knowledge, this is a novel finding as no previous studies conducted in pediatric populations have reported this association. Due to the novelty of this finding in this pediatric population, we cannot compare our results to other pediatric samples. However, a similar result (i.e., shorter N2 duration in bipolar patients) was reported in a study carried out in an adult sample comparing unipolar to bipolar depression (de Maertelaer et al., 1987).

In our study, the participants in the BD group with the highest scores on the depression or anxiety scales presented a different sleep structure pattern than their controls (HC_{BD}). By contrast, no such differences were evident when the full bipolar group was compared to controls (HC_{BD}). This loss of stability in the sleep pattern in the context of severe depressive and anxiety symptoms is reflected in the gain of differentiation in R1 and TST duration and lower SEfic and higher REMd in the subgroup of BD patients with the highest anxiety symptoms. This contrasts with the lack of significant differences between the full BD group and HC_{BD} on these same variables. Similarly, bipolar patients presenting more severe depressive and anxiety symptoms also presented a similar sleep pattern.

If we take into account the intensity of mood and anxiety symptoms, this study yields three important and interesting findings. First, N2 duration was the only polysomnographic variable that differentiated bipolar patients from the ADHD and HC groups. Moreover, N2 duration was the only variable that maintained this difference even when the bipolar subgroups were used for the comparison. In other words, a shorter duration of N2 sleep is the only polysomnographic variable that differentiated the bipolar patients with highest scores on the CDI, CMRS-P, or CMAS-R scales from their matched controls (HC_{BD}). However, the N2% did not confirm this finding, thus limiting somewhat the strength of this difference. A second important finding is that REMd appears to differentiate between patients with BD and healthy participants when considering only those patients with the most severe depressive and anxiety symptoms. A third relevant finding is that children with highest scores on the depression and anxiety scales presented similarities in sleep structure when compared to the healthy controls.

Our finding regarding the decrease in N2 duration in the bipolar

group is unusual and rarely described in adult bipolar patients (de Maertelaer et al., 1987). Indeed, most studies in adults with this disorder have found no differences between patients and HCs in the duration of the N2 stage (Beauchemin and Hays, 1996; Knowles et al., 1986; Talbot et al., 2009), perhaps because this variable has received scant attention in studies of mood disorders (Eidelman et al., 2010). Regarding REMd, a study involving 28 subjects with BD in the inter-episodic phase found an increase in REMd compared to HCs when a negative mood state was induced (Talbot et al., 2009). Although we did not induce any mood states in our study, we did find that, compared to HC_{BD}, the youths with most severe depressive symptoms presented a larger difference in REMd.

Depressive symptoms are not characteristic of ADHD; however, anxiety and certain DSM manic symptoms may be present in patients diagnosed with ADHD or BD. For this reason, we expected that the bipolar group would have higher scores than the ADHD group on the CDI scale (Geller et al., 2002b; Goldstein and Birmaher, 2012). As our results show, this expectation was confirmed. In terms of the association between clinical symptoms and polysomnographic variables, anxiety presented the largest number of correlations with the polysomnographic variables. By contrast, we found that mood symptoms were poorly correlated with polysomnographic variables, a finding that is consistent with studies conducted in adults with BD (Eidelman et al., 2010). We found that REMd correlated positively with anxiety symptoms, but, in contrast to the findings from other studies (Eidelman et al., 2010), it did not correlate with depressive symptoms.

The present study has several limitations. First, this was a non-randomized cross-sectional study and no power calculation was performed, and these factors are likely to have affected our results. In addition, as in most PSG studies, the overall sample was relatively small due to recruitment difficulties (Harvey, 2008). Second, although the presence of comorbidities could affect sleep structure, we decided to include participants with co-morbid anxiety disorders because evaluating only bipolar patients without comorbidities would not be representative of the BD population (Goldstein and Birmaher, 2012). Given that most individuals from the clinical groups presented an evening chronotype, this variable was not taken into account in our analyses. However, we did not assess the chronotype in the healthy controls, which could have been biased our results. A common limitation of sleep studies, and ours is no exception, is the effect of pharmacotherapy on sleep structure (Harvey, 2008). However, the precise effect of each medication on sleep structure is unknown and difficult to quantify (Ritter et al., 2012). Although treatment withdrawal is not considered dangerous or unethical, it is important to note that studies have shown that any group of bipolar patients in which treatment could be withdrawn to facilitate the PSG would be unrepresentative of that patient population (Eidelman et al., 2010; Harvey, 2008; Harvey et al., 2006; Ritter et al., 2012). The day-to-day variability of mood/anxiety symptoms could have affected the results; to minimize the impact of this variability, we assessed mood and anxiety symptoms no more than 6 h prior to administering the PSG. Another potential limitation was the inclusion of more than one bipolar subtype (BD-I, BD-II, and BD-NOS), which was necessary due to the small sample size. The participants' sex and level of neurodevelopment could also have affected sleep structure (Harvey et al., 2006; Steiger and Kimura, 2010); to limit the potential impact of differences in these variables, both the BD and ADHD groups were compared to an age- and sex-matched group of healthy controls. We did not attempt to match the BD and ADHD groups because this would have created an unrepresentative ADHD sample (Geller et al., 2002b). Although PSG is considered the gold standard for sleep studies, we performed only one overnight PSG in the inpatient setting (Buysse et al., 2006; Harvey et al., 2006). Another potential limitation is that the K-SADS-PL, WISC-IV/WAIS-III, CDI, CMRS-P and CMAS-R assessments were not administered in the healthy controls; nonetheless, the full medical and psychiatric history of these participants were reviewed by a senior child and adolescent psychiatrist and we included only those youths who fulfilled the well-defined inclusion criteria.

The differences in sleep structure between the two clinical groups identified in this study suggest that some sleep variables could be used to differentiate between BD and ADHD, thus helping to facilitate the differential diagnosis. However, the expression of these variables during the developmental period in children and adolescents is an open question. Unlike most PSG studies carried out in adults with BD, we found that a shorter N2 duration not only differentiates adolescents with BD from patients with ADHD and healthy controls, but is also independent of mood and anxiety symptoms. Our findings suggest that REMd, N2 duration, and the first episode of REM sleep in children with BD could differentiate them from ADHD youths. Previous studies have reported an association between N2 stage and restorative function (De Gennaro and Ferrara, 2003; Hayashi et al., 2005), but the role of N2 stage in BD requires further study.

A better understanding of the association between mood/anxiety symptoms and polysomnographic variables could help to better predict the clinical course of BD. At present, differentiating between BD and other psychiatric disorders is difficult due to the large symptom overlap. For this reason, we believe it is relevant to identify and study specific biologic characteristics of pediatric patients with BD to better distinguish BD from other psychiatric disorders that also involve inattention and excessive motor and verbal activity. Our findings suggest that N2 stage, REMd, and R1 are all potential sleep variables that could help to more clearly differentiate BD from other psychiatric disorders. However, larger samples are needed to obtain a more comprehensive understanding of the difference in sleep parameters among patients with different psychiatric disorders. In this context, sleep studies, together with a greater understanding of the underlying neurophysiological substrate, could provide a theoretical framework to elucidate the etiopathogenesis of pediatric BD and to develop new strategies for the diagnosis and treatment of this condition (Harvey, 2009; Milhiet et al., 2011; Steiger and Kimura, 2010).

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Supplementary materials

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