Sleep study in Disruptive Mood Dysregulation Disorder and Bipolar children

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Introduction. Decreased need for sleep has been proposed as a core symptom of mania and it has been associated with the pathogenesis of Bipolar Disorder. The emergence of Disruptive Mood Dysregulation Disorder (DMDD) as a new diagnostic has been controversial and much has been speculated about its relationship with the bipolar spectrum. REM sleep fragmentation could be a biomarker of affective disorders and it would help us to differentiate them from other disorders.

Method. Polysomnographic cross-sectional study of children with DMDD, bipolar disorder and Attention Deficit Hyperactivity Disorder (ADHD). All participants underwent a psychiatric semi-structured interview to obtain the diagnosis, comorbidities and primary sleep disorders. DMDD's sample was performed following DSM5 criteria.

Goals. Perform polysomnography in a sample of bipolar, DMDD and ADHD children and compare their profiles to provide more evidence about the differences or similarities between bipolar disorder and DMDD.

Results. Bipolar group had the highest REM density values while ADHD had the lowest. REM density was not statiscally different between bipolar phenotypes. REM density was associated with antidepressant treatment, episodes of REM and their interaction. REM latency was associated with antipsychotic treatment and school performance. Bipolar patients had higher scores on the depression scale than DMDD and ADHD groups.

Conclusions. No significant differences between the two compared affective disorders were found. However there were differences in REM density between bipolar and ADHD groups. REM sleep study could provide a new theoretical framework to better understand the pathogenesis of pediatric bipolar disorder.

Keywords: Sleep patterns, Polysomnography, Bipolar Disorder, Severe Mood Dysregulation, Disruptive Mood Dysregulation Disorder, Attention Deficit Hyperactivity Disorder

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Estudio del sueño en niños con Trastorno de Disregulación Disruptivo del Estado de Ánimo y Bipolares

Introducción. La disminución de la necesidad de sueño ha sido propuesta como síntoma nuclear de manía y ha sido relacionada con la etiopatogenia del Trastorno Bipolar. La irrupción del Trastorno de Disregulación Disruptivo del Estado de Ánimo (TDDEA) como nueva categoría diagnóstica en el DSM5 ha sido controvertida y mucho se ha especulado acerca de su relación con el espectro bipolar. La fragmentación del sueño REM podría ser un biomarcador de los trastornos afectivos y ayudarnos a diferenciarlos de otros trastornos.

Metodología. Estudio transversal polisomnográfico en niños con TDDEA, bipolaridad y con Trastorno por Déficit de Atención e Hiperactividad (TDAH). A todos los participantes se les realizó una entrevista psiquiátrica semi-estructurada para la obtención del diagnóstico, la detección de posibles comorbilidades y de los trastornos primarios del sueño. La obtención de la muestra TDDEA se realizó siguiendo los criterios recomendados por el DSM5.

Objetivos. Realizar un estudio polisomnográfico en una muestra de niños TDDEA, Trastorno Bipolar Pediátrico (TBP) y TDAH y comparar sus perfiles, para aportar mayor evidencia acerca de las diferencias o semejanzas entre el TBP y el TDDEA.

Resultados. El grupo bipolar presentó los valores más altos de densidad REM mientras que el grupo TDAH presentó los más bajos. La densidad REM no presentó diferencias estadísticamente significativas entre los distintos fenotipos bipolares. La densidad REM se asoció con el tratamiento antidepresivo, los episodios de REM y su interacción. La

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latencia REM se asoció con el tratamiento antipsicótico y el rendimiento escolar. Los pacientes bipolares presentaron mayores puntuaciones en la escala de depresión que los grupos TDDEA y TDAH.

Conclusiones. No se encontraron diferencias significativas entre los dos trastornos afectivos comparados aunque sí se hallaron diferencias en la densidad REM entre los grupos bipolar y TDAH. El estudio del sueño REM podría proporcionar un nuevo marco teórico para comprender mejor la etiopatogenia del trastorno bipolar pediátrico.

Palabras Clave: Patrones del sueño, Polisomnografía, Trastorno Bipolar, Severe Mood Dysregulation, Trastorno Disruptivo y Disregulado del Estado de Ánimo, Déficit de Atención e Hiperactividad

INTRODUCTION

Sleep disturbances, including insomnia and a decreased need for sleep (DNS), are highly prevalent in Pediatric Bipolar Disorder (PBD)[1]. Though considered an underrated symptom[2], DNS is one of the most frequent and specific symptoms of a maniac episode[2-6]. Its specificity and prevalence facilitate a mania diagnosis and thus, it has been proposed as a nuclear symptom[1,6] (condition marker). It is also considered a prodrome frequent in mania[7], which facilitates its early detection, and present in inter-episode periods (trait marker)[1,4,8-10]. DNS is not so age dependant[5], so its study in children could be generalized to other stages in life. Likewise, it could become a worse functioning marker in respect to Type I bipolars that do not suffer from it[1]. Therefore, its presence could justify more specific interventions. DNS could be related to Type I BD[10] etiopathogenesis and become an endophenotype of affective disorders, since it fulfills several of its characteristics[11].

Leibenluft's *Severe Mood Dysregulation* (SMD) helped operate irritability and tried to attenuate a growing over diagnosis of pediatric bipolar disorder (PBD)[12-14]. It seems that the evolution of SMD preceded a one polar depression episode or a later anxiety disorder[15] and not a PBD[12,14]. It was thought that perhaps SMD and PBD could share the same physiopathology *continuum*[12,15]. In such context, the *Disruptive Mood Dysregulation Disorder* (DMDD)[12] arose in the DSM5 as a new diagnosis category. The DMDD is characterized by the presence of outbursts of temper of an intensity disproportioned to the stressors generating them, with chronic irritability, angry or sad mood between said outbursts. DMDD and SMD differ in the over excitement symptoms (not present in DMDD) and onset age (earlier in DMDD)[12]. DNS is not a symptom of any of these entities while insomnia, as an overexcitement symptom can be present in SMD. The latter is the reason why some authors believe that the results of previous SMD studies cannot be generalized to DMDD[12,13]. To date, research on DMDD is limited[16]. It's currently believed that both DMDD and SMD precede one polar depression more than PBD[16].

Studies on PBD are few and with heterogeneous results[1,3,8-10,17-19]. Polisomnography is an objective way to measure sleep and is considered its gold standard[20,21]. The fragmentation of REM (Rapid Eye Movement) sleep, that is, a decrease of REM latency (RemLat) and an increase of REM density (REMd), is the most frequent result on sleep studies of bipolar patients[8], which could make it a specific marker for affective disorders[18]. Brain structures associated to REM sleep such as the tonsil[20] have been proposed as mood regulators and their malfunction as a possible etiopathogeny BD cause[4,17].

The study proposes the **hypothesis** that bipolar children, DMDD and Attention-Deficit Hyperactivity Disorder without any other associated psychiatric comorbidity ($ADHD_{wc}$) show different polisomnographic patterns since they are different clinical entities. On one side, the $ADHD_{wc}$ group is used as a pathological control group due to the high comorbidity that both affective disorders have with ADHD[5,12]. On the other side, the group is used as a "healthy" control group due to the lack of significant polisomnographic differences shown in other studies between ADHD and healthy subjects[22]. The purpose of the study is to conduct a polisomnographic study on a sample of DMDD, PBD and $ADHD_{wc}$ children and compare profiles, in order to support evidence on the differences or similarities between PBD and DMDD.

METHOD

Design

A transversal study with Night Polisomnography Video (PSG) performed on 6 to 18 year old subjects diagnosed with DMDD, PBD (type I, II or non specified) and $ADHD_{wc}$ according to DSM5 criteria. The sample was selected following a non random process of convenience, selecting subjects linked to the centers during two years (from September 2013 to September 2015).

Sample

A total of 35 participants 65.7% males and mean age of 12.3 years old, including 14 subjects with DMDD (40% of the sample, 64.3% males and mean age 11.7 years), 13 with PBD (37.1%, PBD I= 7, PBD II= 5 and PBD NOS= 1; 53.9% males and mean age 13.9) and 8 with ADHD wc (22.9%, 87.5% males, and mean age 11.4 years). 85.71% of the sample (78.6% DMDD group, 100% PBD group and 75% ADHD wc group) were under psychotropic drugs. 7 subjects in DMDD group were taking two or more psychotropic drugs while only 3 had no treatment. Psychotropic drugs in DMDD group were: methilphenidate (7 subjects), atomoxetine (1 subject), antidepressants (1 fluoxetine and 1 citalopram) and antipsychotics (4 risperidone, 2

aripiprazole and 2 paliperidone). In the PBD group there were 11 subjects with two or more psychotropic drugs (methilphenidate (1), atomoxetine2), antidepressants (1 fluoxetine, 1 citalopram, 2 sertraline and 1 venlafaxine), antipsychotics (4 risperidone, 6 aripiprazole, 2 paliperidone and 3 quetiapine), lithium (5) and valproate (5) while just two subjects were taking a single psychotropic drug. In the ADHDwc group there were 3 subjects without psychopharmacological treatment while the remaining 5 were taking methylphenidate. 74.28% of the sample (100% DMDD group, 92.3% PBD group and 0.0% ADHDwc group) had psychiatric comorbidity at the time of the PSG. The comorbidities of the DMDD group were with anxiety disorders (10 subjects), ADHD and other behavioral disorders (13 subjects with ADHD and 10 with other behavioral disorders) and nocturnal enuresis (1). Subjects from the PBD group presented comorbidity with anxiety disorders (8 subjects), ADHD and other behavioral disorders (9 subjects with ADHD and 6 with other behavioral disorders), daytime enuresis (1) and major depressive disorder (4). Inclusion criteria were to belong to any gender, age of up to 18 years, show DMDD, PBD or $ADHD_{wc}$ diagnosis according to DSM5 criteria and sign an informed consent. Exclusion criteria were: to be older than 18 years, an antecedent of a severe traumatic brain injury, epilepsy under anti seizure treatment, unstable and severe medical disease, disorder due to substance use, intellectual development disorder (IDD, IQ<70), comply with clinical criteria for Narcolepsy, sleep Apnoea/Hypopnoea, restless legs syndrome, or periodic legs movement syndrome, comorbidity with other psychiatric disorders only on the $ADHD_{wc}$ group (comorbidity with other learning disorders was accepted) and an important idiomatic barrier. The sample was obtained through Child and Juvenile Mental Health Centers (CJMHC) in Sant Marti (91.43% of the sample) and Ciutat Vella (8.57%).

Evaluation

All participants and their parents/tutors signed the informed consent to participate in the study. The project was assessed and approved by the Ethical Investigation Committee of the Clinic – EICC Parc de Salut Mar. All participants were administered the K-SADS-PL (Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version) psychiatric diagnosis interview in order to obtain the diagnosis and detect existent comorbidity[23] and a neuropsychological study was done on them to discard IDD (Wechsler Intelligence Scale for Children Fourth Edition (WISC-IV)[24] for under 16 year olds and Wechsler Intelligence Scale for Adults (WAIS III)[25] for over 16 year olds). Psychopathological variables were obtained through the Children's Depression Inventory (CDI) for depression symptoms[26], the Child Mania Rating Scale – Parent version (CMRS-P) for mania symptoms[27] and the Children's Manifest Anxiety Scale Revised (CMAS-R) for anxiety symptoms[28]. School performance was made operative considering good (no fails), medium (1 to 3 failures) or bad (4 or more failures). Primary sleep disorders were assessed through Bruni's sleep disturbance scale for children (Sleep disturbance Scale for Children, SDSC)[29] and through the PSG[6]. The SDSC is a hetero-applied scale of 27 likert type items that detects youngster's sleep disruption (from the beginning and maintenance, restless legs syndrome, respiratory sleep disorders, arousal disorders, disorders of the vigil to sleep transit, excessive sleepiness, and perspiration) with a cut out point of 39 points. If the subject reaches the cut out point, punctuations for each of the disorder groups must be analyzed, stating, again for each group, a new cut out point and an interval that if met must be considered as existent. The assessed polisomnographic variables were the total recording period, the total period of sleep, the percentage of sleep efficiency, the sleep latency, time and percentage of N1, N2, and N3 stages, REM time and percentage, REM numbers (RemNum), each REM duration, REM latency (REMLat), and REM density (REMd)[18,20,21]. The PSG was done in a hospital room, under regulated dark, silence and temperature conditions. The recording began at 22:00 hours and ended at 06:00 hours the next day. The PSG device used was a Natus Sleep Works 6.3.0 (C1998-2008 Xltek by Natus. Oakville, Canada). Manual staging was done according to criteria by the American Academy of Sleep Medicine (AASM, 2007)[30]. The REMd was defined as the ratio between rapid eye movements, present/absent, considering mini-stages of 5 seconds in REM phase. Likewise, personal and family psychiatric, medical and physiological antecedents were registered (family history screen[31] FHS), as well as socio-biographical antecedents and pharmacological-toxicology history. The participant's socio-economic data was registered too (Hollinsghead Index[32], HI).

Identification of the DMDD group

The same diagnosis criteria used by Axelson and his team were used[13]. To diagnose DMDD and adjust it to criteria required by the DSM5 the following items from KSADS-PL were used: 1.- Severe and recurrent anger outbursts were obtained from: punctuation item 3 "Severe outbursts 2-5 times a week" from "Loss of Control" criteria of the Opposition/Negativity Defiant Disorder (ODD); 2.- Chronic irritability from: punctuation item 3 "gets easily angry daily or almost each day" and "gets angry or resentful daily or almost each day" from "gets angry or upset easily" and "Anger or resentment" respectively of ODD Supplement (ODDs); 3.- Length from: ODDs was administered independently from ODD's diagnosis compliance or not in order to assess if symptoms persisted for at least 6 months. Nevertheless, this criteria differs from DMDD in that at least 12 months are required without a period of 3 or more consecutive months without symptoms; 4.- Disability on more than 1 area from ODDs including if the disability

occurs in 3 areas (social, family and school); 5.- Specific mania symptoms lasting over 1 day cannot exist; 6.- Symptoms do not only occur in the context of a psychotic or affective disorder or cannot be better explained by any other disorder.

Statistical Analysis

A univariate descriptive analysis of each of the study's variables was done. A bivariate analysis to evaluate differences between groups followed, using the Fisher's exact test for qualitative variables and Kruskal-Wallis test for quantitative ones. Wilcoxon rank-sum test was used to detect differences between two groups. When the problem of Multiple Comparisons arose (when doing 3 pairs of comparisons) the False Discovery Rate procedure was used to adjust the statistical significance of each comparison.

For each sleep depending variable a manual modellin process was done to adjust a Multiple Lineal Regression Model (MLRM) using every independent variable from the study, following Hosmer and Lemshow directives[33]. The goodness of fit was assessed and the basic hypothesis checked for each model. In case any of the dependent variables was not normal, a logarithmical transformation was applied in order to normalize it and the regression model adjusted. Results were made exponential so they could be expressed in terms of the original variable. Due the logarithm's properties, coefficients of less than 1 will show negative effects while those over 1 will show positive effects. Coefficients may be expressed in percentage. All statistical analyses were done with STATA 12.0 software (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

RESULTS

There were no statistically significant differences between the 3 groups (PBD, DMDD and $ADHD_{wc}$) for gender, ethnicity, comorbidity, school performance, and psycho-pharmacological treatment qualitative variables. Likewise, there were no statistically significant differences between the groups for the distribution of quantitative variables age, total marks on SDSC. CMRS-P and CMAS-R scales (Table 1). The distribution of variables CDI and REMd was different between the 3 diagnosed groups. The differences for pair were compared between PBD and $ADHD_{wc}$, between $ADHD_{wc}$ and DMDD and between DMDD and PBD. CDI and REMd values were significantly higher in the PBD group than in $ADHD_{wc}$ and DMDD groups, while there were no significant differences between $ADHD_{wc}$ and DMDD (Table 1).

Regarding polisomnographic variable REMd, values for bipolar phenotypes (PBD I, II and NS) were compared. The average REMd for PBD I group was 0.517 (range: 0.21; 0.77) with a standard deviation of 0.176, while the average REMd of PBD II group was 0.462 (range: 0.12; 0.62) with a standard deviation of 0.21. The difference in the distribution of REMd between both groups was not statistically significant (p=0.6847) using Wilcoxon rank-sum test.

When studying the polisomnographic dependant variables, REMd and REMLat were the only ones for which the independent variables showed an association and the ones for which results of the regression models are showed. (Table 2). Regression models were adjusted for age, gender and group. Variables treatment with antidepressants, REMNum, and their interaction, were statistically significant in the MRLM of the REMd (Table 2; Figure 1). The PBD group showed a significantly higher REMd than group $ADHD_{wc}$ (0.179 (0.046; 0.312)) while not showing differences with the DMDD group (0.091 (-0.028; 0.210)) (Figure 2). The model's adjusted coefficient of determination was 46.30%.

The REMLat had to be logarithmically transformed to adjust the MRLM. REMLat was significantly lower in subjects treated with antipsychotics compared to non treated subjects (0.603 (0.382; 0.952), that is, children treated showed a reduction in REMLat of 39.7% (4.8%; 61.8%). REMLat was significantly higher in children with bad school performance compared to children with good performance (1.1716 (1.138; 2.587)), that is, children with a bad performance showed an increase in REMLat of 71.6% (13-8%; 158.7%). Diagnosis groups PBD, DMDD and $ADHD_{wc}$ did not show a significantly different REMLat. The model's adjusted coefficient of determination was 16.08% (Table 2).

CONCLUSIONS

As far as we know, this could be the first study done with a PSG to children and adolescents with DMDD.

The only psychopathological variable that differentiates the bipolar group from the other two are depression symptoms, being higher in the PBD group and with no statistically significant differences between groups DMDD and $ADHD_{wc}$.

The only polisomnographic variable that differentiates the bipolar group from the other two is REMd, being higher in the PBD group and with no statistically significant differences between groups DMDD and $ADHD_{wc}$. On the other hand, the REMd shows no difference between bipolar phenotypes. The REMLat does not differentiate the study groups but does show an association with antipsychotic treatment and school performance.

Getting higher marks for depression symptoms in the PBD group[17] was expected from the study, due to the fact that, except sadness in the DMDD group, depression symptoms are not characteristics of the other two groups.

Table 1 Descriptive Characteristics of the sample

	$ADHD_{wc}$ (n = 8)	PBD (n = 13)	DMDD (n = 14)	p-value
Qualitative Variables				Fisher's
Gender				
Boy	7 (87.5%)	7 (53.9%)	9 (64.3%)	0.317
Girl	1 (12.5%)	6 (46.1%)	5 (35.7%)	
Ethnicity				
European	7 (87.5%)	11 (84.6%)	12 (85.7%)	1.000
American	1 (12.5%)	1 (7.7%)	2 (14.3%)	
Other	0	1 (7.7%)	0	
Comorbidity	6 (75.0%)	12 (92.3%)	14 (100.0%)	0.163
School Performance				
Good	2 (25.0%)	2 (15.4%)	5 (35.7%)	0.762
Medium (1 to 3 failures)	2 (25.0%)	2 (15.4%)	2 (14.3%)	
Bad (≥ 4 failures)	4 (50.0%)	9 (69.2%)	7 (50.0%)	
Psychopharmacology Treatment	6 (75.0%)	13 (100.0%)	11 (78.6%)	0.206
Quantitative Variables				Kruskal-Wallis
Age				
Average (SD)	11.4 (2.4)	13.9 (3.9)	11.7 (2.8)	0.1580
Min/ Max	8 / 15	7 / 18	6 / 17	
REMd				
Average (SD)	0.26 (0.12)	0.49 (0.17)	0.37 (0.13)	0.0063[1]
Min / Max	0.14 / 0.45	0.12 / 0.77	0.17 / 0.63	
REMLat				
Average (SD)	201.7 (69.4)	188.5 (111.4)	158.1 (45.3)	0.1957
Min / Max	92 / 325.5	63 / 418.5	59 / 247	
SDSC_TS				
Average (SD)	37.9 (6.9)	43.15 (10.0)	39.2 (9.7)	0.3894
Min / Max	31 / 53	32 / 60	27 / 66	
CDI_TOTAL_S				
Average (SD)	11.6 (7.1)	24.3 (12.6)	13 (6.4)	0.0113[2]
Min / Max	5 / 23	9 / 47	5 / 23	
CMRS_TS				
Average (SD)	14.6 (10.0)	21.9 (9.0)	16.1 (7.6)	0.1032
Min / Max	3 / 33	1 / 33	5 / 27	
CMAS_ANS_TOTAL				
Average (SD)	13.9 (8.8)	16.2 (6.9)	14.7 (4.4)	0.7313
Min / Max	2 / 25	5 / 25	5 / 21	

SD: Standard Deviation of data; REMd: REM density; REMLat: REM latency; SDSC_TS: total scores on the primary sleep disorder scale SDSC; CDI_TOTAL_S: total score on the depression symptoms scale CDI; CMRS_TS: total score on the mania symptom scale CMRS; CMAS_ANS_TOTAL: total score on the anxiety scale CMAS.

[1] Difference by pair, significant after adjustment using FDR: PBD, ADHD= 0.005*; ADHD, DMDD= 0.133; DMDD, PBD = 0.023*

[2] Differences by pair, significant after adjustment using FDR: PBD, ADHD= 0.012*; ADHD, DMDD= 0.630; DMDD, PBD = 0.011*

* = statistically significant

Table 2 **Lineal Regression Models Adjusted for REMd and REMLat. Model Coefficients and Confidence Intervals at 95%**

	REMd		REMLat	
	Coef.	CI(95%)	Coef.	CI(95%)
Gender (Boy)				
Girl	-0.009	(-0.116; 0.098)	0.888	(0.609; 1.296)
Age	0.010	(-0.006; 0.027)	0.971	(0.915; 1.030)
Group ($ADHD_{wc}$)				
PBD	0.179*	(0.046; 0.312)	1.349	(0.703; 2.589)
DMDD	0.091	(-0.028; 0.210)	1.082	(0.683; 1.714)
Treatment with Antidepressants (No)				
Yes	0.390*	(0.115; 0.666)	0.902	(0.588; 1.385)
REMNum	0.072*	(0.018; 0.127)		
Interaction with Antidepressants treatment* REM treatment	-0.077°	(-0.164; 0.011)		
School performance (Good)				
Medium (1 to 3 failures)			1.202	(0.689; 2.097)
Bad (≥ 4 failures)			1.716*	(1.138; 2.587)
Treatment with Antipsychotic (No)				
Yes			0.603*	(0.382; 0.952)
Adjusted coefficient of determination (R^2) of the model	46.30%		16.08%	

REMd: density REM; REMLat: REM latency; Coef: coefficient; CI: coefficient interval. Reference categories for qualitative variables between parenthesis. Variables in gray were not included in the corresponding multiple lineal regression model.

* p-value ≤ 0.05

° p-value ≤ 0.10

As in the majority of studies we found a REMd increase in the bipolar group[17,18,34]. In some studies REMd was also associated with psychopathological variables[34], while in others, such as ours, such association could not been verified[18]. In a study done by Talbot and his team on adult bipolar patients in inter-episode phase, REMd was also the only polisomnographic variable differentiating bipolar patients from the control group, and no association between the REMd and psychopathological variables[34] was found. As in a study done by Baroni[1] on bipolar children, our study did not find any specific sleep results between different bipolar phenotypes.

The hypothesis of this study cannot be verified, since, even though it is true that REMd is significantly higher in the PBD group than in the $ADHD_{wc}$ group, the REMd of the DMDD group shows intermediate results between both groups but not significantly different to any of them. Consequently, we cannot conclude that bipolar children and children with DMDD show different polisomnographic patterns. It is also true, that the crude REMd values of the DMDD group are different that the results of the PBD group, showing a tendency towards the values of the $ADHD_{wc}$ group. Nevertheless, the difference between the REMd values of the bipolar group and the DMDD group is lost when the other variables are introduced in the study's regression model, possibly due to such a small size sample. The higher similarity of the REMd between groups DMDD and $ADHD_{wc}$ could be explained by the high comorbidity of the ADHD in the DMDD group.

In this study, REMd shows an association with antidepressant treatment, and both an interaction with REMNum. That is, children treated with antidepressants show a higher REMd than non treated children and as the subject shows more REMNum, said association decreases

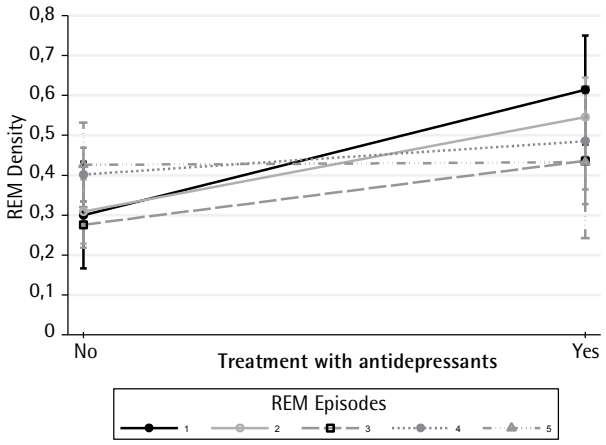

Figure 1a — *Predicted REM density mean values and its 95%CI obtained by the adjusted Multiple Linear Regression Model, by treatment with antidepressants and number of REM episodes*

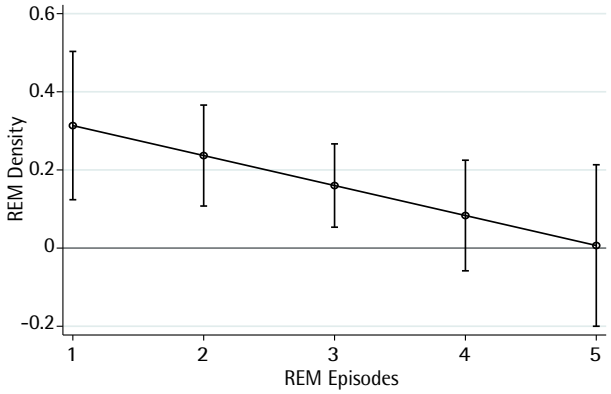

Figure 1b — *Difference between the predicted mean values of the REM density for those taking and not taking antidepressants and its 95%CI, by number of episodes REM. Results of the adjusted Multiple Linear Regression Model*

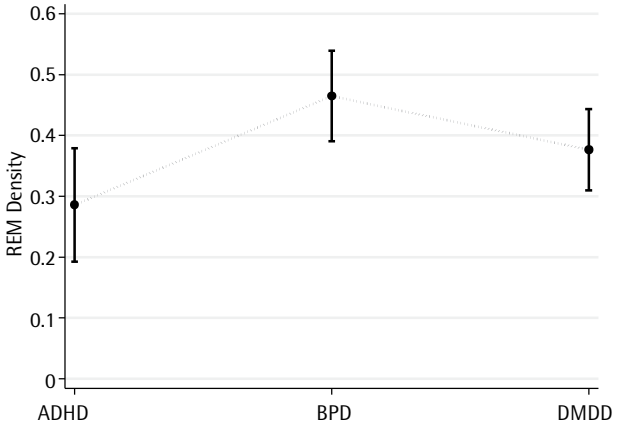

Figure 2 — *Predicted REM density mean values and its 95%CI obtained by the adjusted Multiple Linear Regression Model, by group of patients*

until completely disappearing (in children with 4 or 5 REMNum, the REMd does not show significant differences to children that are not under antidepressant treatment). It is generally believed that Selective Inhibitors of Serotonin Recapture (SSRI), especially fluoxetine, could suppress REM sleep[35-37]. In this study, as in the one by Eidelman[17], subjects under treatment with REM suppression drugs show a higher REMd. Considering that the pharmacological effect was controlled in the three study groups and that no antidepressant treatment was modified a month prior to the PSG we believe that the REMd increase in the bipolar group cannot be attributed to the use of SSRI.

A second association between psychotropic drugs and the polisomnographic variables occurred between anti-psychotics and the REMLat in the sense that patients treated with anti-psychotics show a decreased REMLat compared to children not treated with said drugs. This was an unexpected association and again, it could hardly be explained just by the pharmacological effect since anti-psychotics tend to suppress REM sleep[35-37] and, as such, we expected to find an increase in the REMLat instead of a reduction.

The REMLat is also associated to school performance in the sense that a bad performance is significantly associated to a REMLat increase. Few studies exist on sleep disorders and school performance and none that relate the latter with polisomnographic variables. A meta-analysis[38] that studied variables "sleep quality", "sleep length" and "drowsiness" only showed a slight relation between these and school performance while other studies did not find any association[39].

Study Limitations

The study is transversal and the sample was selected non-randomly. Comorbidity between the ADHD and PBD and

DMDD groups[12-14] could influence the polisomnographic registry. For such reason, the pathological control group $ADHD_{wc}$ was included. On the other hand, getting free of comorbidity samples in both groups would not be representative[40]. A frequent limitation of sleep studies is the effect of psychotropic drugs on polisomnographic variables[4,20]. The exact effect of each drug on the polisomnographic registry is unknown and hard to quantify and the effect of combining different drugs almost impossible to know[8,34]. Nevertheless, any possible effect on the registry was controlled. We believe withdrawing treatment from the bipolar and DMDD groups dangerous and unethical[4,8,34] and that if we were to withdraw treatment from a sample in order to perform a v-PSGN would be little representative[17,20,40]. Even though no association between psychopathological and polisomnographic variables was observed in this study, or between these and bipolar phenotypes, there is a chance that the day to day variability of affective symptoms or that bipolar phenotype had an effect on the polisomnographic registry[19]. Likewise, the different neurodevelopmental moments and the subject's gender could also affect polisomnographic variables[11,20]. There are inherent limitations to hospital PSG. Even though the study was developed in a proper environment, it is a hospital different to the subject's environment. Thus on the one hand, the so called "first night at a hospital" effect occurred, and on the other hand, the subject's routines were eliminated[20,21]. A healthy control group could not be obtained in this study. The $ADHD_{wc}$ group was used to control the possible ADHD effect on the polisomnographic study as well as on the healthy control group. We consider that children with $ADHD_{wc}$ show a REMd similar to healthy children since the polisomnographic pattern of children with ADHD could not be significantly different to that of healthy children[22]. If it were different, the REMd polisomnographic variable is not implied in such difference[41]. Finally, the study's sample is small[4], as in most sleep studies of bipolar children, since it is difficult for subjects to participate.

Summing up, no significant differences were found between the affective disorders studied. Significant differences in the REMd between the bipolar group and the $ADHD_{wc}$ group were found. This lack of difference in the REMd between both affective disorders could be the result of a very small sample or to its common affective nature and to the widespread believe that though PBD and DMDD are different clinical entities, they could share the same pathophysiological *continuum*. We believe two of the study's findings are important: the REMd difference found in the bipolar group and in the $ADHD_{wc}$ group and the lack of differences in the polisomnographic variables in Type I and Type II PBD. In the current context in which PBD's boundaries seem to evaporate, we consider more important than ever to find biomarkers to help us differentiate PBD from other psychiatric disorders. In the field of children and juvenile psychiatry, it is usually ADHD the disorder harder to differentiate from PBD, especially when accompanied with an emotional deregulatory component. The REMd could help us in achieving said differentiation, especially when it seems its values remain stable in the different bipolar phenotypes. Without a doubt, studying REMd in the PBD, and consequently, its neurophysiologic subtract, requires special attention since REMd could become a PBD biomarker.

In such a way, studying sleep could provide a new theoretical framework to better comprehend PBD's etiopathogeny and to help us develop new strategies to diagnose and treat it[9].

CONFLICT OF INTERESTS

The main author declares that there is no commercial, financial or personal relationship that could affect this study's results or conclusions, the same that did not receive any financing.

REFERENCES

1. Baroni A, Hernandez M, Grant MC, Faedda GL. Sleep disturbances in pediatric bipolar disorder: a comparison between bipolar I and bipolar NOS. Front Psychiatry. 2012;3:22.
2. Soutullo CA, Chang KD, Díez A, Figueroa A, Escamilla I, Rapado M, et al. Bipolar disorder in children and adolescents: international perspective on epidemiology and phenomenology. Bipolar Disord. 2005;7(6):497-506.
3. Beauchemin KM, Hays P. Dreaming away depression: the role of REM sleep and dreaming in affective disorders. J Affect Disorders. 1996;41(2):125-33.
4. Harvey AG. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. Am J Psychiatry. 2008;16(7):820-9.
5. Demeter CA, Youngstrom EA, Carlson GA, Frazier TW, Rowles BM, Lingler J, et al. Age differences in the phenomenology of pediatric bipolar disorder. J Affect Disorders. 2013;147(1-3):295-303.
6. Lofthouse N, Fristad M, Splaingard M, Kelleher K. Parent and child reports of sleep problems associated with early-onset bipolar spectrum disorders. J Fam Psychol. 2007;21(1):114-23.
7. Correll CU, Hauser M, Penzner JB, Auther AM, Kafantaris V, Saito E, et al. Type and duration of subsyndromal symptoms in youth with bipolar I disorder prior to their first manic episode. Bipolar Disord. 2014;16(5):478-92.
8. Ritter PS, Marx C, Lewtschenko N, Pfeiffer S, Leopold K, Bauer M, et al. The characteristics of sleep in patients with manifest bipolar disorder, subjects at high risk of developing the disease and healthy controls. J Neural Transm. 2012;119(10):1173-84.
9. Milhiet V, Etain B, Boudebesse C, Bellivier F. Circadian biomarkers, circadian genes and bipolar disorders. J Physiol Paris. 2011;105(4-6):183-9.
10. Harvey AG. The adverse consequences of sleep disturbance in pediatric bipolar disorder: implications for intervention. Child Adolesc Psychiatric Clin N Am. 2009;18(2):321-38.
11. Steiger A, Kimura M. Wake and sleep EEG provide biomarkers in depression. J Psychiatr Res. 2010;44 (4):242-52.
12. Towbin K, Axelson D, Leibenluft E, Birmaher B. Differentiating bipolar disorder-not otherwise specified and severe mood dysregulation. J Am Acad Child Adolesc Psychiatry. 2013;52(5):466-81.

13. Axelson D, Findling RL, Fristad MA, Kowatch RA, Youngstrom EA, Horwitz SM, et al. Examining the proposed disruptive mood dysregulation disorder diagnosis in children in the longitudinal assessment of manic symptoms study. J Clin Psychiatry. 2012; 73(10):1342-50.
14. Brotman MA, Schmajuk M, Rich BA, Dickstein DP, Guyer AE, Costello EJ, et al. Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. Biol Psychiatry. 2006;60(9):991-7.
15. Stringaris A, Rowe R, Maughan B. Mood dysregulation across developmental psychopathology-general concepts and disorder specific expressions. J Child Psychol Psychiatry. 2012; 53(11):1095-7.
16. Copeland WE, Angold A, Costello EJ, Egger H. Prevalence, comorbidity, and correlates of DSM-5 proposed disruptive mood dysregulation disorder. Am J Psychiatry. 2013;170(2):173-9.
17. Eidelman P, Talbot LS, Gruber J, Hairston I, Harvey AG. Sleep architecture as correlate and predictor of symptoms and impairment in inter-episode bipolar disorder: taking on the challenge of medication effects. J Sleep Res. 2010;19(4):516-24.
18. Hudson JI, Lipinski JF, Frankenburg FR, Grochocinski VJ, Kupfer DJ. Electroencephalographic sleep in mania. Arch Gen Psychiatry. 1988;45(3):267-73.
19. Staton D. The impairment of pediatric bipolar sleep: hypotheses regarding a core defect and phenotype-specific sleep disturbances. J Affect Disord. 2008;108(3):199-206.
20. Harvey AG, Mullin BC, Hinshaw SP. Sleep and circadian rhythms in children and adolescents with bipolar disorder. Dev Psychopathol. 2006;18(4):1147-68.
21. Buysse DJ, Ancoli-Israel S, Edinger JD, Lichstein KL, Morin CM. Recommendations for a standard research assessment of insomnia. Sleep. 2006;29(9):1155-73.
22. Choi J, Yoon IY, Kim HW, Chung S, Yoo HJ. Differences between objective and subjective sleep measures in children with attention deficit hyperactivity disorder. J Clin Sleep Med. 2010;6(6):589-95.
23. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry. 1997;36(7):980-8.
24. Corral S, Arribas D, Santamaría P, Sueiro MJ, Pereña J. Escala de Inteligencia de Wechsler para niños-IV. Madrid: TEA Ediciones; 2005.
25. Seisdedos N, Corral S, Cordero A, De la Cruz MV, Hernández MV, Pereña J. WAIS III. Manual Técnico. Madrid: TEA Ediciones; 1999.
26. Kovacs M. Children's depression inventory. North Tonawanda, NY: Multi-Health Systems, Inc; 1992.
27. Pavuluri MN, Henry DB, Devineni B, Carbray JA, Birmaher B. Child Mania Rating Scale: development, reliability, and validity. J Am Acad Child Adolesc Psychiatry. 2006;45(5):550-60.
28. Reynolds C, Richmond B. What I think and feel: A revised measure of children's manifest anxiety. J Abnorm Psychol. 1978;6:271-80.
29. Bruni O, Ottaviano S, Guidetti V, Romoli M, Innocenzi M, Cortesi F, et al. The Sleep Disturbance Scale for Children (SDSC). Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. J Sleep Res. 1996;5:251-61.
30. Iber C, Ancoli-Israel S, Chesson A, Quan SF; for the American Academy of Sleep Medicine. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, 1st ed.: Westchester, Illinois: American Academy of Sleep Medicine; 2007.
31. Weissman MM, Wickramaratne P, Adams P, Wolk S, Verdeli H, Olfson M. Brief screening for family psychiatric history: The Family History Screen. Arch Gen Psychiatry. 2000;57(7):675-82.
32. Hollingshead AA. Four-factor index of social status. Unpublished manuscript, Yale University, New Haven, CT; 1975.
33. Hosmer DW, Lemeshow, S. Model-Building Strategies and Methods for Logistic Regression. In: Shewhart, WA, Wilks SS. Applied Logistic Regression. Second Edition. John Wiley & Sons, Inc., Hoboken, NJ, USA; 2000. p. 91-142.
34. Talbot LS, Hairston IS, Eidelman P, Gruber J, Harvey AG. The effect of mood on sleep onset latency and REM sleep in interepisode bipolar disorder. J Abnorm Psychol. 2009;118(3):448-58.
35. Armitage R, Emslie G, Rintelmann J. The effect of fluoxetine on sleep EEG in childhood depression: a preliminary report. Neuropsychopharmacology. 1997;17(4):241-5.
36. Obermeyer WH, Benca RM. Effects of drugs on sleep. Otolaryngol Clin North Am. 1999;32(2):289-302.
37. Ferrarelli F, Benca RM. Neurophysiology and neuroimaging of human sleep. In: Winkelman JW, Plante DT. Foundations of psychiatric sleep medicine. First Edition. Cambridge: University Press; 2010. p. 36-58.
38. Dewald JF, Meijer AM, Oort FJ, Kerkhof GA, Bögels SM. The influence of sleep quality, sleep duration and sleepiness on school performance in children and adolescents: a meta-analytic review. Sleep Med Rev. 2010;14(3):179-89.
39. Eliasson A, Eliasson A, King J, Gould B, Eliasson A. Association of sleep and academic performance. Sleep Breath. 2002;6(1):45-8.
40. Harvey AG, Schmidt DA, Scarnà A, Semler CN, Goodwin GM. Sleep-related functioning in euthymic patients with bipolar disorder, patients with insomnia, and subjects without sleep problems. Am J Psychiatry. 2005;162(1):50-7.
41. Gruber R, Xi T, Frenette S, Robert M, Vannasinh P, Carrier J. Sleep disturbances in prepubertal children with attention déficit hyperactivity disorder: a home polysomnography study. Sleep. 2009;32(3):343-50.