

ORIGINAL ARTICLE

Association of a novel EEG metric of sleep depth/intensity with attention-deficit/hyperactivity, learning, and internalizing disorders and their pharmacotherapy in adolescence

Anna Ricci¹, Susan L. Calhoun¹, Fan He^{2,*}, Jidong Fang¹, Alexandros N. Vgontzas^{1,*}, Duanping Liao², Edward O. Bixler¹, Magdy Younes³ and Julio Fernandez-Mendoza^{1,*}

¹Sleep Research and Treatment Center, Department of Psychiatry and Behavioral Health, Penn State College of Medicine, Hershey, PA, USA, ²Department of Public Health Sciences, Penn State College of Medicine, Hershey, PA, USA and ³Sleep Disorders Centre, Department of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

*Corresponding author. Julio Fernandez-Mendoza, Sleep Research and Treatment Center, Department of Psychiatry and Behavioral Health, Penn State Health Milton S. Hershey Medical Center, Penn State College of Medicine, 500 University Dr. H073, Hershey, PA 17033, USA. Email: jfmendoza@psu.edu.

Abstract

Study Objectives: Psychiatric/learning disorders are associated with sleep disturbances, including those arising from abnormal cortical activity. The odds ratio product (ORP) is a standardized electroencephalogram metric of sleep depth/intensity validated in adults, while ORP data in youth are lacking. We tested ORP as a measure of sleep depth/intensity in adolescents with and without psychiatric/learning disorders.

Methods: Four hundred eighteen adolescents (median 16 years) underwent a 9-hour, in-lab polysomnography. Of them, 263 were typically developing (TD), 89 were unmedicated, and 66 were medicated for disorders including attention-deficit/hyperactivity (ADHD), learning (LD), and internalizing (ID). Central ORP during non-rapid eye movement (NREM) sleep was the primary outcome. Secondary/exploratory outcomes included central and frontal ORP during NREM stages, in the 9-seconds following arousals (ORP-9), in the first and second halves of the night, during REM sleep and wakefulness.

Results: Unmedicated youth with ADHD/LD had greater central ORP than TD during stage 3 and in central and frontal regions during stage 2 and the second half of the sleep period, while ORP in youth with ADHD/LD on stimulants did not significantly differ from TD. Unmedicated youth with ID did not significantly differ from TD in ORP, while youth with ID on antidepressants had greater central and frontal ORP than TD during NREM and REM sleep, and higher ORP-9.

Conclusions: The greater ORP in unmedicated youth with ADHD/LD, and normalized levels in those on stimulants, suggests ORP is a useful metric of decreased NREM sleep depth/intensity in ADHD/LD. Antidepressants are associated with greater ORP/ORP-9, suggesting these medications induce cortical arousability.

Statement of Significance

Conventional polysomnography measures of sleep depth have been challenged on methodological and pathophysiological grounds, as they have not allowed for developing standardized biomarkers transdiagnostic across disorders associated with poor sleep, including psychiatric and neurodevelopmental disorders. The odds ratio product (ORP) is a validated, standardized measure of sleep depth/intensity derived from quantitative electroencephalogram analyses that range from 0 (deep sleep) to 2.5 (full wakefulness), discriminates between sleep-wake states, and is sensitive to sleep disruption. This is the first report to show that higher ORP is a useful metric of decreased sleep depth/intensity in unmedicated attention/learning disorders and that stimulants may normalize ORP in these youth. In contrast, antidepressants in youth with mood/anxiety disorders are associated with increased cortical arousability during sleep.

Key words: adolescence; arousability; odds ratio product; psychopathology; sleep depth

Submitted: 22 July, 2021; Revised: 17 November, 2021

© The Author(s) 2021. Published by Oxford University Press on behalf of Sleep Research Society. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com

Introduction

Poor sleep is a common complaint among youth with psychiatric and learning disorders [1] and specific features of the sleep electroencephalogram (EEG) are associated with cognitive and emotional processes in typically developing (TD) youth [2]. The brain undergoes morphological changes associated with cortical maturation [2–5] and pubertal development [6–8] in the transition to adolescence, which is a critical period for the persistence and onset of sleep disturbances and psychopathology [9–18]. Increases or decreases in the synchronized EEG oscillations of non-rapid eye movement (NREM) sleep have been associated with psychiatric/learning disorders in adolescence [19, 20]; however, with the exception of sleep spindles and early-onset schizophrenia [21–24], the literature on prevalent disorders in youth, including attention-deficit/hyperactivity (ADHD) [14, 18, 25, 26], learning (LD) [27–30], and internalizing (ID) disorders [31, 32], has produced inconsistent results. Traditional polysomnography (PSG) metrics of sleep depth/intensity do not appropriately account for individual differences and are affected by technical and methodological factors that differ across settings, labs, and hardware [33, 34]. Moreover, inter-rater variability in sleep stage scoring adds uncertainty when using the proportion of time spent in sleep stages as a measure of sleep intensity [33, 35]. Therefore, standardized EEG biomarkers of sleep depth/intensity may be a useful tool that can better translate to research and clinical settings alike.

The odds ratio product (ORP) is a continuous, standardized measure of sleep depth/intensity that ranges from 0 (never occurs during wakefulness or arousals) to 2.5 (never occurs during sleep) [33–39]. In adults, ORP is a validated measure of NREM and REM sleep depth, with studies showing greater ORP is associated with more awakenings, higher arousability, and shorter sleep duration [33, 34, 40]. Furthermore, ORP provides a more sensitive and reliable measure of sleep intensity than traditional sleep EEG parameters, including stage 3 of NREM sleep (N3) also known as slow wave sleep (SWS) [34]. ORP-derived metrics allow for measuring the impact of cortical arousals on sleep depth as they occur even during SWS [38, 41, 42]. ORP-9 measures sleep depth during the 9 s following EEG arousals, with lower ORP-9 indicating faster progression back to deep sleep following an arousal and higher values slower progression back to deep sleep [34, 38, 41]. Although ORP has been well-described in adults, including large cohorts [43, 44], and appears to be a promising clinical and developmental tool [45, 46], no studies have examined ORP in youth with psychiatric/learning disorders, which is of particular interest as sleep depth rapidly declines during adolescence [3, 7, 46–49].

Thus, we examined ORP in TD adolescents, those with psychiatric/learning disorders, and on pharmacological treatment to better understand the relationship between disrupted sleep and psychopathology in adolescents. We hypothesized that adolescents with psychiatric/learning disorders will have greater central ORP during NREM sleep than TD adolescents, a degree of decreased sleep depth/intensity not captured by traditional PSG architecture (i.e. N3/SWS).

Methods

Sample

The Penn State Child Cohort (PSCC) adolescent study consists of 421 subjects aged 12–23 years [12, 50–53]. The PSCC was

established to study sleep disorders in youth and has been described previously in detail [50, 52–55]. Briefly, subjects were identified across 18 schools via a validated survey [56] and 700 of them were randomly selected to participate in an in-lab study, of whom 421 were assessed 6–13 years later as adolescents (60.1% response rate), who were the focus of the present study. As previously reported, the baseline demographic characteristics of these 421 subjects (mean age 8.7 years, 46.1% female, 21.9% racial/ethnic minority) that returned for the follow-up study were commensurate with the original cohort ($N = 700$, mean age 8.7 years, 47.3% female, 23.7% racial/ethnic minority) and with those who did not return for the follow-up ($n = 279$, mean age 8.6 years, 47.8% female, 29.3% racial/ethnic minority) [50, 51]. All subjects or parents/legal guardians provided informed written consent for the study protocol, which was approved by Penn State's Institutional Review Board.

Demographic and clinical measures

All subjects underwent a clinical history and physical examination performed by trained human research technologists, including medical students or residents, supervised by an experienced scientist-clinician (physician or psychologist) as well as a 3-hour standardized neurobehavioral assessment performed by a trained psychometrist [57, 58]. Sex, race, ethnicity, and date of birth were reported during the clinical history. Height and weight were measured during the physical exam and the body mass index (BMI) percentile was calculated [59]. Please see the [Supplementary Methods](#) for a detailed description of other demographic and clinical measures of the sample including Tanner stage, circadian preference, insomnia symptoms, and substance use as well as details on the specific tests the participants performed during the neurobehavioral assessment.

The structured clinical history schedule is used in routine studies to gather past and current history of medical and psychiatric conditions, with modifications performed for this child cohort (e.g. focus on ADHD, LD, and other behavioral disorders). During the clinical history, subjects or their parent were asked whether there was a presence of a psychiatric or behavioral disorder with the question “Has your child/have you ever been treated for a psychiatric/behavioral disorder?” [58]. This question was followed-up with the option to specify whether the disorder was ADHD, LD, or other disorder; for the latter, the diagnosis was specified with an open-ended question by which the presence of ID (e.g. depressive, generalized anxiety, post-traumatic stress, obsessive-compulsive disorders), externalizing disorders (e.g. oppositional defiant disorder), or autism spectrum disorder was determined [12, 58]. In addition, subjects or their parents had the option to specify their self-reported severity of these disorders as mild, moderate, or severe, with about half (47%) of this sample rating their disorders as mild. They also had the option to specify whether these disorders were being currently treated or had been treated in the past; there were no significant differences between those with a past or current history of treatment in key neurocognitive and behavioral measures and, thus, they were combined together in the analyses [57, 58]. See [Supplementary Table S1](#) for comorbidity across these disorders.

Current medication use was ascertained during the clinical history and on an evening pre-PSG questionnaire [12, 58]. Medications were classified by an experienced registered pediatric nurse [12] as psychotropic medications for psychiatric conditions (e.g. stimulants, antidepressants/anxiolytics, hypnotics)

and non-psychotropic medications for medical conditions (e.g., steroids, asthma/allergy, cardiac, insulin) [58]. Data on non-pharmacological (e.g. behavioral, school-based) treatments were not available. See [Supplementary Table S2](#) for co-existence across psychotropic medications and [Supplementary Table S3](#) for a list of the psychotropic drug in each category.

The above data informed the definition of our diagnostic groups. The TD group included youth who were never treated for or diagnosed with any psychiatric/learning disorder. The unmedicated group included youth who had a diagnosis of a psychiatric/learning disorder and were not being treated with psychotropic medications. The medicated group included youth who had a psychiatric/learning disorder and were being treated with psychotropic medications. Specific groups of youth with ADHD and/or LD, given their high comorbidity (see [Supplementary Table S1](#) and [Supplementary Methods](#)), treated or untreated with stimulants and absent of any other comorbid disorder as well as youth with ID treated or untreated with antidepressants/anxiolytics, were also identified.

Polysomnography

The sleep study consisted of a one-night PSG conducted in sound-, light-, and temperature-controlled rooms. Registered PSG technicians (RPSGT) applied electrodes to the subject's scalp, face, and legs at 19:00–20:00. Sleep data were recorded for 9-hours of time-in-bed from “lights out” (21:00–23:00) until “lights on” (06:00–08:00) to adjust to the subject's habitual sleep schedule. All 421 recordings were performed using TWin Recording and Analysis (Grass Telefactor, West Warwick, RI) with a sampling rate of 200 Hz and filter settings at 0.1–70.0 Hz. PSGs were visually scored by RPSGTs in 30-second epochs following standard criteria, blind from subjects' characteristics [50, 54, 60, 61]. Please see the [Supplementary Methods](#) for additional details regarding PSG measures.

Odds ratio product

All 421 PSGs were converted into European data format (EDF) files and analyzed in a blind manner using a commercialized sleep scoring system (Michele Sleep Scoring, Cerebra Health, Sleep Disorders Centre, University of Manitoba, Winnipeg, CA). Details on ORP development and calculation can be found in the [Supplementary Methods](#) and in multiple publications in adults [33–39, 62, 63]. Briefly, ORP was measured in consecutive 3-second epochs by applying the fast Fourier transform to central and frontal derivations and calculating the sum of powers in four frequency ranges (0.33–2.33 Hz, 2.67–6.33 Hz, 7.0–14.0 Hz, and 14.0–35.0 Hz) to produce a scale from 0 (never occurs during wakefulness/arousals) to 2.5 (never occurs during sleep), with values from 0 to 1.0 predicting sleep and 2.0 to 2.5 predicting full wakefulness [36, 62]. Three-second ORP values in C3-M2/C4-M1 and in F3-M2/F4-M1 were averaged for central and frontal ORP, respectively. Averages of the measurement for all 30-second epochs in wake and sleep stages were obtained. Central ORP during NREM sleep (ORP_{NREM}) was the primary outcome. Because NREM sleep is a dynamic process, it was further examined by decomposing into stage 1 (ORP_{N1}), stage 2 (ORP_{N2}), stage 3 (ORP_{N3}), and following cortical arousals (ORP_9), as secondary outcomes [34, 38]. To calculate ORP_9 the average ORP in the first 9-seconds (three 3-second epochs) following the end of each NREM

arousal was determined, and the values obtained for all NREM arousals were averaged [38, 43]. A slower return to deep sleep following arousals (higher ORP_9) leaves the individual in a high arousability state, thereby, increasing the likelihood of repeat arousals [38, 43, 63]. Other secondary outcomes included: ORP in the first half (ORP_{1st}) and the second half (ORP_{2nd}) of the sleep period and change between ORP_{1st} and ORP_{2nd} (ORP_{Δ}), with higher ORP_{2nd} indicating deeper sleep earlier in the night [34], as well as ORP during REM sleep (ORP_{REM}) and wakefulness (ORP_{wake}) at central and frontal derivations [34, 40].

Statistical analyses

Only three subjects had missing ORP data ($N = 418$). Demographic/clinical characteristics of the sample are presented as means and proportions for continuous and categorical variables, respectively. Analysis of variance and Pearson's chi-square tests were used to compare these variables across TD, unmedicated and medicated youth. First, multivariable-adjusted general linear models (MGLM) examined differences between TD, unmedicated, and medicated youth on the primary outcome (central ORP_{NREM}), while adjusting for sex, race/ethnicity, age, BMI percentile, apnea hypopnea index (AHI), oxygen saturation (min SpO_2), periodic limb movement index (PLMI), insomnia symptoms, alcohol, tobacco or drug use, and non-psychotropic medication use. These covariates, described in detail in the [Supplementary Methods](#), were chosen based on conceptual/theoretical grounds (e.g. sex and age as biological variables) as well as statistical grounds (i.e. significant differences between study groups). Thereafter, differences across specific diagnostic groups and their indicated pharmacotherapy (unmedicated ADHD/LD [$n = 60$], unmedicated ID [$n = 27$], ADHD/LD on stimulants [$n = 26$], and ID on antidepressants/anxiolytics [$n = 26$]) were tested. Data are expressed as multivariable-adjusted means (SD) and p -values at ≤ 0.05 were considered statistically significant. Similar MGLM were used to test differences between groups on all secondary outcomes, which are considered exploratory and hypothesis-generating with post hoc comparisons of individual group pairs by means of the Fisher's test. Effect sizes (Cohen's d) were calculated for the primary and secondary outcomes to inform strength of association and future studies. Statistical analyses were conducted using SPSS Statistics version 26 (IBM Corp. 2019, Armonk, NY).

Results

Sample characteristics

As shown in [Table 1](#), the 418 subjects with ORP data were 12–23 years (median 16 years), 90.2% were adolescents aged 12–19 years [64], while only 41 subjects were ≥ 20 years. Medicated and unmedicated youth with psychiatric/learning disorders reported higher attention, thought, internalizing, and externalizing scores (all $p < 0.001$) and showed worse objective neurocognitive functioning (all $p \leq 0.04$) than TD youth, except Stroop interference in unmedicated youth ($p = 0.08$). Additionally, unmedicated and medicated youth were more likely to report insomnia symptoms (both $p \leq 0.003$) and tobacco or drug use than TD youth (all $p \leq 0.02$), except medicated youth in drug use ($p = 0.24$). Medicated youth spent a greater proportion of the night in N1 ($p = 0.03$) and had a greater PLMI ($p = 0.009$) than TD

Table 1. Demographic, clinical, and sleep characteristics of the sample

	Overall (N = 418)	TD (n = 263)	Unmedicated (n = 89)	Medicated (n = 66)	P
Female	192 (45.9%)	126 (47.9%)	36 (40.4%)	30 (45.5%)	0.473
Racial/ethnic minority	92 (22.0%)	58 (22.1%)	23 (25.8%)	11 (16.7%)	0.395
Age, years	16.4 (2.3)	16.4 (2.3)	16.6 (2.3)	16.2 (2.1)	0.544
BMI, percentile	65.3 (28.5)	63.2 (28.9)	69.1 (27.7)	68.2 (27.3)	0.161
Tanner stage	4.2 (0.8)	4.2 (0.8)	4.2 (0.6)	4.2 (0.8)	0.865
1–3	64 (15.8%)	45 (17.6%)	11 (12.6%)	8 (12.9%)	0.429
4–5	340 (84.2%)	210 (82.4%)	76 (87.4%)	54 (87.1%)	
Disorders					
ADHD	99 (23.7%)		54 (60.7%)	45 (68.2%)	n/a
LD	39 (9.3%)		28 (31.5%)	11 (16.7%)	
Other	66 (15.8%)		30 (33.7%)	36 (54.5%)	
ID	59 (14.1%)		27 (30.3%)	32 (48.5%)	
ED	5 (1.2%)		5 (5.6%)	0 (0.0%)	
ASD	3 (0.7%)		1 (1.1%)	2 (3.0%)	
Medications					
Any non-psychotropic	170 (40.7%)	104 (39.5%)	30 (33.7%)	36 (54.5%)	0.027
Any psychotropic	66 (15.8%)				n/a
Stimulants	40 (9.6%)			40 (60.6%)	
Other psychoactive	36 (8.6%)			36 (54.5%)	
Sleep	8 (1.9%)			8 (12.1%)	
Substance use					
Caffeine	352 (84.6%)	222 (85.1%)	78 (87.6%)	52 (78.8%)	0.303
Tobacco	45 (10.8%)	17 (6.5%)	15 (16.9%)*	13 (19.7%)*	<0.001
Alcohol	105 (25.7%)	62 (24.0%)	25 (29.1%)	18 (27.7%)	0.599
Drugs	31 (7.7%)	14 (5.4%)	11 (13.4%)*	6 (9.8%)	0.047
Behavioral outcomes					
Attention problems	55.5 (7.1)	53.5 (5.3)	58.4 (8.2)*	59.6 (8.4)*	<0.001
Thought problems	55.0 (6.3)	53.4 (4.8)	57.1 (6.9)*	58.5 (8.4)*	<0.001
Internalizing symptoms	50.8 (10.5)	48.9 (9.4)	53.9 (10.5)*	54.3 (12.7)*	<0.001
Externalizing behaviors	49.0 (10.1)	46.6 (9.3)	53.0 (9.9)*	52.9 (10.6)*	<0.001
Neurocognitive outcomes					
Verbal IQ	101.8 (10.6)	103.4 (9.9)	98.8 (11.4)*	99.6 (10.8)*	<0.001
Nonverbal IQ	105.8 (11.7)	107.6 (10.8)	103.5 (12.8)*	102.0 (12.3)*	<0.001
Reading achievement	105.3 (10.0)	107.6 (8.6)	100.7 (11.9)*	102.7 (9.5)*	<0.001
Math achievement	101.3 (13.9)	105.0 (12.9)	93.8 (12.9)*	96.7 (13.8)*	<0.001
Coding	9.6 (2.6)	10.2 (2.5)	8.9 (2.2)*	8.5 (2.7)*	<0.001
Symbol search	10.0 (2.4)	10.4 (2.4)	9.5 (2.2)*	9.4 (2.5)*	0.002
Vigilance	102.6 (12.0)	104.0 (11.6)	100.7 (11.9)*	99.7 (13.7)*	0.022
Distractibility	107.5 (8.9)	108.6 (7.4)	106.0 (11.0)*	104.9 (10.6)*	0.006
Digit span backward	6.9 (2.4)	7.3 (2.4)	6.2 (2.4)*	6.3 (2.5)*	<0.001
Stroop interference	53.6 (6.7)	54.2 (6.8)	52.8 (6.1)	52.1 (7.1)*	0.032
Visual-motor integration	85.3 (12.3)	87.1 (12.0)	82.2 (12.7)*	82.6 (12.0)*	<0.001
Circadian preference	25.8 (5.1)	26.1 (5.0)	25.7 (4.9)	25.0 (5.7)	0.244
M-type	134 (32.1%)	91 (34.7%)	24 (27.0%)	19 (28.8%)	0.687
I-type	153 (36.7%)	93 (35.5%)	35 (39.3%)	25 (37.9%)	
E-type	130 (31.2%)	78 (29.8%)	30 (33.7%)	22 (33.3%)	
Weekdays schedule					
Bedtime, hh:mm	22:56 (1:33)	22:49 (1:28)	23:11 (1:41)*	23:07 (1:39)	0.090
Rising time, hh:mm	7:24 (2:02)	7:11 (1:46)	7:44 (2:22)*	7:50 (2:22)*	0.014
Weekends schedule					
Bedtime, hh:mm	24:14 (1:42)	24:03 (1:38)	24:39 (1:45)*	24:24 (1:46)	0.014
Rising time, hh:mm	9:50 (1:56)	9:42 (1:46)	10:05 (2:10)	10:02 (2:13)	0.185
Insomnia symptoms	157 (37.6%)	77 (29.3%)	48 (53.9%)*	32 (48.5%)*	<0.001
Polysomnography					
SOL, min	26.3 (24.4)	25.5 (20.8)	24.7 (18.4)	31.4 (39.8)	0.164
Awakenings, #	36.3 (12.0)	35.8 (11.0)	36.0 (10.3)	38.8 (17.1)	0.197
WASO, min	69.4 (43.3)	68.1 (41.0)	70.5 (41.3)	73.2 (53.9)	0.667
TST, min	446.7 (55.2)	448.6 (50.0)	447.0 (48.2)	438.7 (78.9)	0.423
SE, %	82.6 (10.1)	83.0 (9.2)	82.7 (8.7)	81.1 (14.6)	0.388
N1, %	1.0 (1.5)	0.9 (1.1)	0.8 (0.8)	1.4(2.8)*#	0.054
N2, %	53.5 (9.8)	53.5 (9.6)	53.6 (8.1)	53.3 (12.6)	0.981
N3, %	26.9 (9.2)	27.0 (9.1)	26.4 (7.9)	27.5 (11.1)	0.780

Table 1. Continued

	Overall (N = 418)	TD (n = 263)	Unmedicated (n = 89)	Medicated (n = 66)	P
NREM, %	80.4 (4.9)	80.5 (4.6)	80.0 (4.7)	80.8 (6.0)	0.614
REM, %	18.5 (5.0)	18.5 (4.6)	19.1 (4.8)	17.8 (6.4)	0.282
AHI, events/hour	2.4 (3.5)	2.1 (2.5)	3.2 (5.1)*	2.8 (4.2)	0.036
Min SpO ₂	91.5 (5.2)	92.0 (3.4)	89.6 (8.4)*	91.8 (4.9)*	<0.001
PLMI, events/hour	3.9 (6.1)	3.4 (5.8)	4.0 (6.7)	5.6 (6.2)*	0.031

Data are means (SD) and number of cases (percentage) for continuous and categorical/ordinal variables, respectively. *p*-values from Pearson chi-square test for categorical variables and from between-subjects analysis of variance for continuous variables. ADHD, attention-deficit/hyperactivity disorder; AHI, apnea/hypopnea index; ASD, autism spectrum disorder; BMI, body mass index; ED, externalizing disorder; E-type, evening circadian preference; ID, internalizing disorder; IQ, intelligence quotient; I-type, intermediate circadian preference; LD, learning disorder; Min SpO₂, minimum oxygen saturation; M-type, morning circadian preference; NREM, non-rapid eye movement sleep; PLMI, periodic limb movement index; N1, epochs scored as NREM sleep stage 1; N2, epochs scored as NREM sleep stage 2; N3, epochs scored as NREM sleep stage 3 or 4; REM, rapid eye movement sleep; SE, sleep efficiency; SOL, sleep onset latency; TD, typically developing; TST, total sleep time; WASO, wake after sleep onset.

**p* ≤ 0.05 versus TD; **p* ≤ 0.05 versus unmedicated.

Table 2. Association of psychiatric/learning disorders with the primary outcome

	TD	Unmedicated	Medicated	P
Central ORP _{NREM}				
Overall	(n = 263) 0.53 (0.16)	(n = 89) 0.57 (0.16)	(n = 66) 0.60 (0.16)*	0.006
ADHD/LD		(n = 60) 0.59 (0.22)*	(n = 26) 0.53 (0.12)	
ID		(n = 27) 0.56 (0.14)	(n = 26) 0.67 (0.20)*#	

Data are means (SD). ADHD/LD, attention-deficit/hyperactivity disorder and/or learning disorder (unmedicated or medicated with stimulants); ID, internalizing disorder (unmedicated or medicated with antidepressants/anxiolytics); NREM, non-rapid eye movement sleep; ORP, odds ratio product; TD, typically developing.

**p* ≤ 0.05 versus TD; **p* ≤ 0.05 versus unmedicated.

youth. Unmedicated youth had a higher AHI (*p* = 0.02) and lower SpO₂ (*p* < 0.001) than TD. No significant differences in N3 (i.e. SWS) were found between groups.

Association of psychiatric/learning disorders with ORP

Table 2 shows that there were significant between-groups differences in our primary outcome (central ORP_{NREM}). Medicated youth had greater central ORP_{NREM} (*p* = 0.003, *d* = 0.437) than TD youth, while in unmedicated youth the difference in central ORP_{NREM} was not statistically significant compared to TD (*p* = 0.06, *d* = 0.250).

Secondary outcomes showed medicated youth also had greater frontal ORP_{NREM} (*p* = 0.003, *d* = 0.421) than TD youth (Table 3). When stratifying by NREM stage, medicated youth had greater central and frontal ORP_{N1} (*p* = 0.05 [*d* = 0.281] and *p* = 0.02 [*d* = 0.334], respectively), ORP_{N2} (*p* = 0.003 [*d* = 0.444] and *p* = 0.002 [*d* = 0.485], respectively), and ORP_{N3} (*p* = 0.004 [*d* = 0.364] and *p* = 0.02 [*d* = 0.322], respectively) than TD youth, while unmedicated youth had greater central ORP_{N3} (*p* = 0.03, *d* = 0.261) than TD youth (Supplementary Table S4). When examining NREM arousals, medicated youth had greater central and frontal ORP-9 (both *p* < 0.001, *d* = 0.439 and *d* = 0.558, respectively) than TD youth (Table 3). When stratifying by sleep period, medicated youth had greater central (*p* = 0.01, *d* = 0.349) and frontal (*p* = 0.001, *d* = 0.512) ORP_{2ndh} and frontal ORP_{1st} (*p* = 0.02, *d* = 0.294) and ORP_Δ (*p* = 0.04,

d = 0.312) than TD youth, while unmedicated youth had greater central ORP_{2ndh} (*p* = 0.05, *d* = 0.250) than TD youth (Supplementary Table S4). Medicated youth also had greater central (*p* = 0.03, *d* = 0.304) and frontal (*p* = 0.004, *d* = 0.385) ORP_{REM} and frontal ORP_{wake} (*p* = 0.01, *d* = 0.363) than TD youth (Table 3). All effect sizes for these comparisons are reported in Supplementary Table S5.

Association of ADHD/LD with ORP

As shown in Table 2, unmedicated youth with ADHD/LD had greater central ORP_{NREM} (*p* = 0.02, *d* = 0.312) than TD youth, while those with ADHD/LD on stimulants did not significantly differ from TD or unmedicated youth with ADHD/LD (both *p* ≥ 0.18). Self-reported severity of ADHD/LD was significantly associated with increasing central ORP_{NREM} (*p*-linear = 0.02), as unmedicated youth with moderate-to-severe ADHD/LD showed a stronger degree of association with the primary outcome (*n* = 14, 0.65 [0.33], *p* = 0.01, *d* = 0.468) than those with mild ADHD/LD (*n* = 46, 0.57 [0.18], *p* = 0.130, *d* = 0.235) when compared to TD.

On secondary outcomes, unmedicated youth with ADHD/LD had greater frontal ORP_{NREM} (*p* = 0.04, *d* = 0.225) than TD youth, while those with ADHD/LD on stimulants did not differ in frontal ORP_{NREM} from TD or unmedicated youth with ADHD/LD (both *p* ≥ 0.47; Table 3). Unmedicated youth with ADHD/LD had greater central and frontal (both *p* = 0.05, *d* = 0.281 and *d* = 0.234, respectively) ORP_{N2} and central ORP_{N3} (*p* = 0.02, *d* = 0.318) than TD youth, while youth with ADHD/LD on stimulants did not significantly differ from TD or unmedicated youth with ADHD/LD in ORP_{N1}, ORP_{N2}, or ORP_{N3} at either derivation (all *p* ≥ 0.21; Figure 1 and Supplementary Table S4).

Secondary outcomes also showed that unmedicated youth with ADHD/LD had greater central (*p* = 0.04, *d* = 0.222) and frontal (*p* = 0.01, *d* = 0.303) ORP-9 than TD youth (Table 3). Unmedicated youth with ADHD/LD had greater central (*p* = 0.02, *d* = 0.286) and frontal (*p* = 0.008, *d* = 0.315) ORP_{2ndh} than TD youth, while those with ADHD/LD on stimulants did not significantly differ from TD or unmedicated youth with ADHD/LD in ORP_{1st}, ORP_{2ndh}, or ORP_Δ at either derivation (all *p* ≥ 0.14; Figure 1 and Supplementary Table S4). Youth with ADHD/LD unmedicated or on stimulants did not significantly differ from TD or each other in ORP_{wake} or ORP_{REM} at either derivation (all *p* ≥ 0.10), except in frontal ORP_{wake}, which was greater in unmedicated youth with ADHD/LD than TD (*p* = 0.05, *d* = 0.178; Table 3). All effect sizes for these comparisons are reported in Supplementary Table S6.

Table 3. Association of psychiatric/learning disorders with secondary outcomes

	TD	Unmedicated	Medicated	P
Frontal ORP _{NREM}				
Overall	0.67 (0.19)	0.71 (0.20)	0.75 (0.19)*	0.007
ADHD/LD		0.72 (0.25)*	0.69 (0.16)	
ID		0.70 (0.17)	0.83 (0.28)*,#	
Central ORP-9				
Overall	0.82 (0.21)	0.86 (0.21)	0.91 (0.20)*	0.003
ADHD/LD		0.87 (0.24)*	0.87 (0.19)	
ID		0.83 (0.18)	0.96 (0.25)*,#	
Frontal ORP-9				
Overall	0.93 (0.21)	0.98 (0.22)	1.05 (0.22)*	<0.001
ADHD/LD		1.00 (0.25)*	1.01 (0.19)	
ID		0.95 (0.22)	1.13 (0.27)*,#	
Central ORP _{REM}				
Overall	0.69 (0.23)	0.71 (0.23)	0.76 (0.23)*	0.082
ADHD/LD		0.74 (0.31)	0.72 (0.27)	
ID		0.72 (0.22)	0.81 (0.30)*	
Frontal ORP _{REM}				
Overall	0.78 (0.26)	0.81 (0.26)	0.88 (0.26)*	0.014
ADHD/LD		0.84 (0.33)	0.84 (0.29)	
ID		0.84 (0.25)	0.96 (0.33)*	
Central ORP _{wake}				
Overall	1.55 (0.31)	1.60 (0.30)	1.61 (0.30)	0.254
ADHD/LD		1.61 (0.31)	1.60 (0.28)	
ID		1.57 (0.25)	1.61 (0.29)	
Frontal ORP _{wake}				
Overall	1.58 (0.27)	1.62 (0.28)	1.68 (0.28)*	0.031
ADHD/LD		1.63 (0.29)	1.67 (0.25)	
ID		1.63 (0.23)	1.70 (0.25)*	

Data are means (SD). ADHD/LD, attention-deficit/hyperactivity disorder and/or learning disorder (unmedicated or medicated with stimulants); ID, internalizing disorder (unmedicated or medicated with antidepressants/anxiolytics); NREM, non-rapid eye movement sleep; ORP, odds ratio product; REM, rapid eye movement sleep; TD, typically developing.

* $p \leq 0.05$ versus TD; # $p \leq 0.05$ versus unmedicated.

Association of ID with ORP

Table 2 shows unmedicated youth with ID did not differ from TD in central ORP_{NREM} ($p = 0.43$, $d = 0.199$), while those with ID on antidepressants/anxiolytics had greater central ORP_{NREM} than TD ($p < 0.001$, $d = 0.773$) and unmedicated youth with ID ($p = 0.02$, $d = 0.637$). Medicated youth with mild ($p < 0.001$, $d = 0.791$) and moderate-to-severe ID ($p < 0.001$, $d = 1.199$) both showed a strong degree of association with the primary outcome when compared to TD.

On secondary outcomes, unmedicated youth with ID did not significantly differ from TD in frontal ORP_{NREM} ($p = 0.32$, $d = 0.166$), while those with ID on antidepressants/anxiolytics had greater frontal ORP_{NREM} than TD ($p < 0.001$, $d = 0.669$) and unmedicated youth with ID ($p = 0.01$, $d = 0.561$; Table 3). Unmedicated youth with ID did not significantly differ from TD in ORP_{N1}, ORP_{N2}, or ORP_{N3} at either derivation (all $p \geq 0.24$), while those with ID on antidepressants/anxiolytics had greater central and frontal ORP_{N1} ($p = 0.05$ [$d = 0.388$] and $p = 0.003$ [$d = 0.597$], respectively) and ORP_{N2} (both $p < 0.001$, $d = 0.721$ and $d = 0.738$, respectively), and central ORP_{N3} ($p = 0.01$, $d = 0.498$) than TD youth (Figure 2 and Supplementary Table S4). Youth with ID on antidepressants/anxiolytics also had greater frontal ORP_{N1} ($p = 0.04$, $d = 0.578$) and central ($p = 0.02$, $d = 0.600$) and frontal ($p = 0.01$, $d = 0.566$) ORP_{N2} than unmedicated youth with ID (Figure 2 and Supplementary Table S4). Unmedicated youth with ID did not significantly differ from TD in ORP-9 at either derivation (both $p \geq 0.59$). Youth with ID on antidepressants/anxiolytics had greater ORP-9 at central

and frontal derivations than TD youth (both $p < 0.001$, $d = 0.606$ and $d = 0.827$, respectively) and unmedicated youth with ID ($p = 0.02$, $d = 0.597$ and $p = 0.003$, $d = 0.731$, respectively; Table 3).

Secondary outcomes also showed that unmedicated youth with ID did not significantly differ from TD in ORP_{1st}, ORP_{2nd}, or ORP_A at either derivation (all $p \geq 0.15$), while those with ID on antidepressants/anxiolytics had greater central and frontal ORP_{1st} (both $p = 0.02$, $d = 0.486$ and $d = 0.515$, respectively) and ORP_{2nd} ($p = 0.002$ [$d = 0.664$] and $p < 0.001$ [$d = 0.715$], respectively) and frontal ORP_A ($p = 0.002$, $d = 0.485$) than TD youth (Figure 2 and Supplementary Table S4). Youth with ID on antidepressants/anxiolytics had greater frontal ORP_{2nd} ($p = 0.01$, $d = 0.619$) and ORP_A ($p = 0.007$, $d = 0.592$) than unmedicated youth with ID (Figure 2 and Supplementary Table S4). Unmedicated youth with ID did not significantly differ from TD in ORP_{wake} or ORP_{REM} at either derivation (all $p \geq 0.17$). Youth with ID on antidepressants/anxiolytics had greater ORP_{wake} and ORP_{REM} than TD youth at both derivations (all $p \leq 0.03$) except central ORP_{wake} ($p = 0.33$, $d = 0.200$). All effect sizes for these comparisons are reported in Supplementary Table S6.

Discussion

This study provides an initial report of ORP in adolescents from the general population with psychopathology and on pharmacotherapy as compared to TD youth. The greater central ORP during NREM sleep found in unmedicated youth with

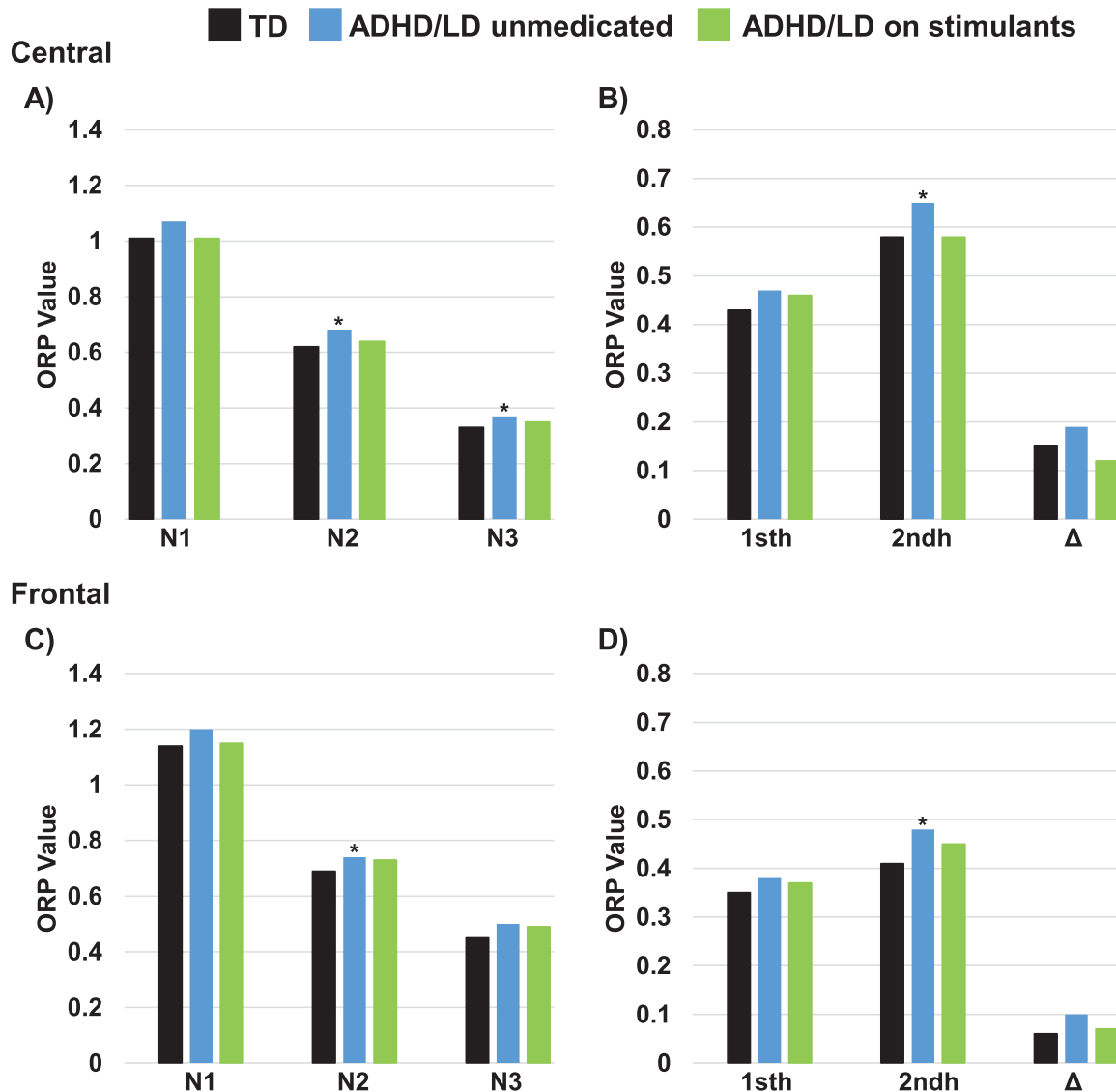


Figure 1. ORP metrics during NREM sleep in medicated and unmedicated youth with attention-deficit/hyperactivity and/or learning disorders (ADHD/LD). (A) and (C) show ORP values during NREM sleep stages N1, N2, and N3 in typically developing (TD) youth, those with ADHD/LD and unmedicated, and those with ADHD/LD on stimulants. (B) and (D) show ORP values during the first (1st) and second (2ndh) halves of the sleep period as well as the change between the two (Δ). * $p \leq 0.05$ versus TD.

moderate-to-severe attention/learning disorders suggests that it may be a useful biomarker of decreased NREM sleep depth/intensity in these youth, while stimulant medications appear to normalize central ORP_{NREM}, and thus, NREM sleep depth in these youth. In contrast, unmedicated youth with mood/anxiety disorders did not significantly differ from TD youth in ORP metrics, while antidepressants/anxiolytics in these adolescents were associated with greater ORP than TD and unmedicated youth with mood/anxiety disorders, suggesting that these pharmacotherapies, particularly antidepressants, may induce cortical arousability during sleep.

First, we provide data on ORP in TD adolescents across sleep and wake states as it ranges from 0 (deep sleep) to 2.5 (full wakefulness). ORP during quiescent wakefulness (ORP_{wake}) showed the greatest values, followed by ORP_{REM}, then ORP_{NREM}.

ORP gradually decreased from N1 through N3, indicating progressively deeper sleep. Additionally, ORP in TD youth was lower in the first half than the second half of the sleep period, consistent with sleep depth/intensity decreasing across the night as homeostatic sleep drive dissipates [65]. Moreover, the observed ORP values in TD youth are lower than those previously reported in middle-aged and older adults [43, 66], which is developmentally expected [46–48] and provides further support to the reliability and validity of the reference values reported herein for ORP in youth.

We also report data on ORP in unmedicated youth with ADHD/LD and found that these youth showed significantly decreased sleep depth/intensity (greater ORP) than TD youth during NREM sleep in central regions, while those with unmedicated ID did not. Specifically, unmedicated youth with ADHD/LD had lower

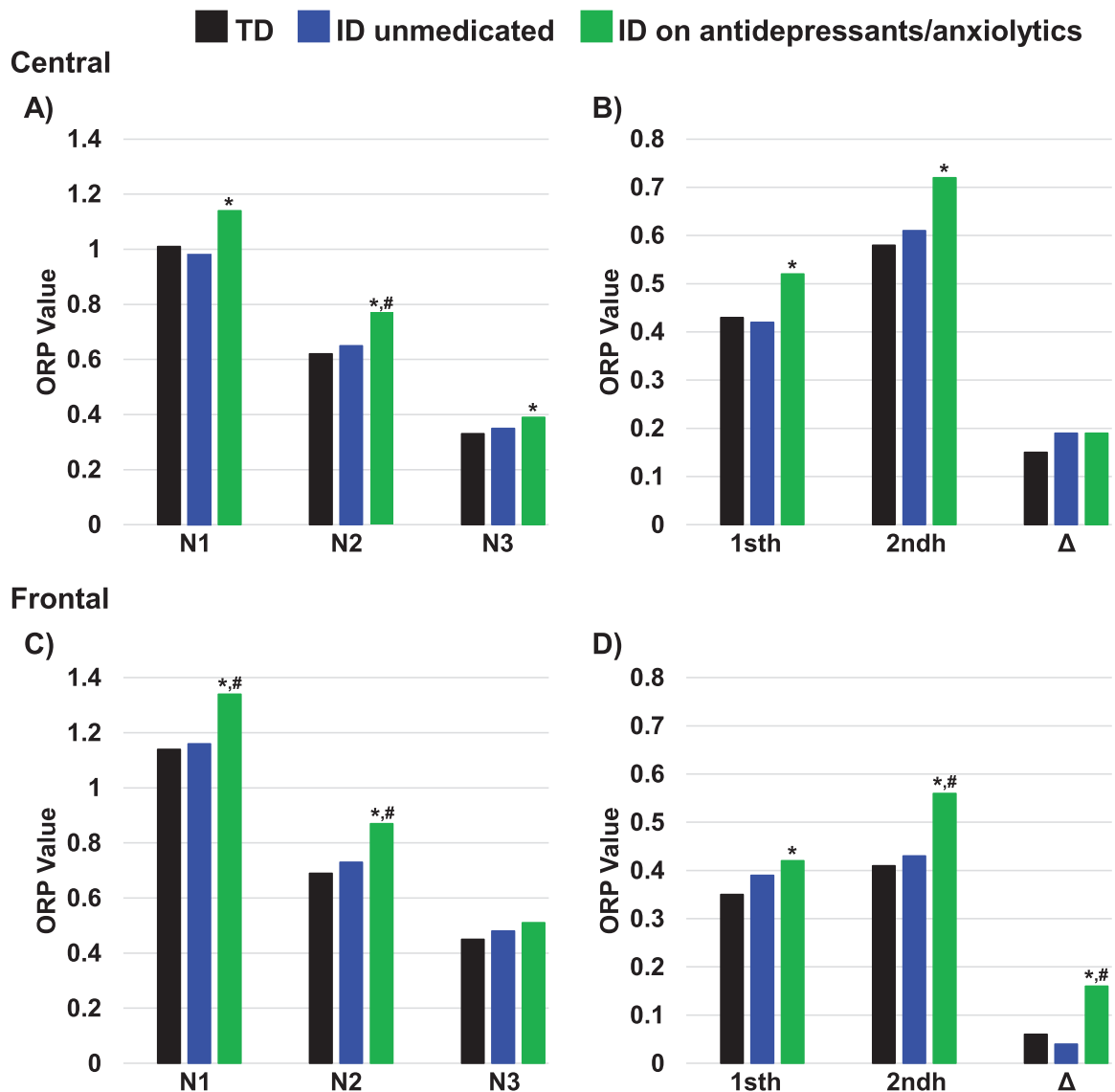


Figure 2. ORP metrics during NREM sleep in medicated and unmedicated youth with internalizing disorders (ID). (A) and (C) show ORP values during NREM sleep stages N1, N2, and N3 in TD youth, those with ID and unmedicated, and those with ID on antidepressants/anxiolytics. (B) and (D) show ORP values during the first (1sth) and second (2ndh) halves of the sleep period as well as the change between the two (Δ). * $p \leq 0.05$ versus TD. # $p \leq 0.05$ versus unmedicated.

sleep depth/intensity during N2 and N3, and the second half of the sleep period in central and frontal regions as well as a slower progression back to deep sleep following arousals (greater ORP-9), with small-to-medium effect sizes. It is important to note that our population-based sample was predominantly comprised of youth who reported mild cases of ADHD/LD, which is developmentally expected as essential symptoms and impact on functioning of these disorders decreases in the transition to adolescence [17], and that those with moderate-to-severe unmedicated ADHD/LD showed a stronger association with central ORP during NREM sleep, with a medium effect size. Our data are consistent with previous findings of decreased slow wave activity (SWA), a spectral marker of sleep depth, in unmedicated youth with clinically significant ADHD [14]. Neuroimaging studies have also shown reduced neural connectivity and myelination in clinical samples of youth with ADHD [67, 68] which

may be the neurobiological basis for the decreased NREM sleep depth/intensity and increased arousability observed in these youth. Reduced cortical connectivity in youth with ADHD or LD may lead to decreased ability to produce the synchronized oscillations of NREM sleep, resulting in less deep sleep (greater ORP), and may increase these adolescents' susceptibility to cortical arousals (greater ORP-9), as NREM oscillations protect the sleeping brain from external sensory stimuli and, thus, help prevent sleep fragmentation [69, 70]. As previously shown in adults [34], our study suggests that ORP may be a more reliable and sensitive measure of sleep depth/intensity than traditional PSG metrics, specifically SWS [34], which did not differ between unmedicated and TD youth.

We also report ORP in adolescents on pharmacotherapy, who experienced decreased NREM and REM sleep depth/intensity and showed a greater vulnerability to the impact of arousals than

TD and unmedicated youth with psychiatric/learning disorders. However, the decreased sleep depth (higher ORP) in medicated adolescents was driven by those with ID on antidepressants/anxiolytics, while adolescents with ADHD/LD on stimulants did not significantly differ from TD youth. Thus, stimulants may help normalize the decreased sleep depth/intensity in adolescents with ADHD/LD, commensurate with a previous SWA study [14]. ORP may serve to identify who among those with ADHD/LD may benefit the most from stimulant therapy, such as those with lower sleep depth/intensity (higher ORP) may benefit from timed or combined therapeutic options, which requires testing in clinical trials. Together with our unmedicated ADHD/LD data discussed above, these findings on the association of stimulants with ORP can serve future clinical trials by indicating the need to study moderate-to-severe attention/learning disorders and consider a medium effect size ($d \sim 0.47$) to adequately power the study if using ORP as a primary outcome.

In contrast to stimulants, antidepressants/anxiolytics in adolescents with ID were associated with decreased sleep depth (greater ORP), with medium-to-large effect sizes, a finding that was independent of their higher PLMI. This is relevant because antidepressants, particularly selective serotonin reuptake inhibitors (SSRI), are well-known to not only generate sleep-related movements, including PLMs, but also increase chin muscle tone, suggesting that these medications may exert their disruptive motor effect via a downstream circuitry under the control of brainstem nuclei [71, 72]. Our ORP data suggest that antidepressants, which were in the vast majority (77%) SSRIs (Supplementary Table S3), may also exert a disruptive upstream cortical effect during REM and NREM sleep. The higher ORP/ORP-9 across both cortical regions and sleep and wake states in medicated adolescents with ID indicates that these medications, particularly antidepressants, may lead to increased cortical arousability and possibly worsen sleep stability in adolescents with mood/anxiety disorders [71–73], which may be a source of lack of efficacy or adverse outcomes in at least a subset of these adolescents [74], a hypothesis to be tested in clinical trials with adjunct behavioral and/or pharmacological sleep therapies.

The present study findings must be discussed in light of several potential limitations. The sleep study consisted of one-night PSG, which may be affected by the first-night-effect and may not be representative of the subjects' habitual sleep at home; however, spectral EEG measures show greater night-to-night stability than traditional sleep continuity/architecture parameters [75, 76] and current sleep studies in routine care are conducted with one-night PSG, which assures translation to and replicability in clinical samples and cohorts. Although the effective sample consisted of 418 subjects, when stratifying by diagnoses and pharmacotherapies the sample sizes ranged from 26 to 60 subjects, reducing power to find statistically significant differences. In addition, we did not have specific subtype diagnoses for the ADHD (e.g. combined type, inattentive type, or hyperactive type) or LD (impaired reading, mathematics, or written expression) groups and, thus, we were unable to provide a detailed breakdown based on their subtype heterogeneity. Additionally, ratings of disorder severity were based on self-reports of perceived severity without structured interviewing of current essential symptoms and impact on functioning. As mentioned in the Methods section, data for other therapies (e.g. behavioral) for psychiatric/learning disorders were unavailable. Due to the cross-sectional design and observational nature of our study, causal attributions should not be made and randomized clinical

trials are necessary to test ORP as a primary sleep outcome. Overall, this population-based study provides an important initial report of ORP in youth and identifies where future work is needed in clinical trials as well as experimental studies that have more stringent inclusion and exclusion criteria for both TD youth and those with psychopathology.

In summary, we provide data on ORP in a population-based sample of TD adolescents and those with psychopathology and pharmacotherapy. The greater ORP during NREM sleep in unmedicated youth with ADHD/LD suggests that it may be a useful EEG biomarker of decreased sleep depth/intensity in these disorders, while NREM sleep intensity in adolescents with unmedicated ID appears to be yet unaffected. Stimulants appear to normalize central NREM ORP in youth with ADHD/LD, while antidepressants are associated with greater ORP/ORP-9 in frontal and central regions in youth with ID, suggesting the latter medications may disrupt sleep by inducing cortical arousability.

Supplementary Material

Supplementary material is available at *SLEEP* online.

Acknowledgments

This study was performed at the Sleep Research and Treatment Center and Clinical Research Center of Penn State College of Medicine and all their staff are highly commended by their efforts.

Funding

Research reported in this publication was supported by the National Institute of Mental Health (NIMH), National Heart, Lung, and Blood Institute (NHLBI), and the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH) under Awards Number R01MH118308 (J.F.-M.), R01HL136587 (J.F.-M.), R01HL97165 (E.O.B./D.L.), R01HL63772 (E.O.B.), and UL1TR000127 (Sinoway).

Disclosure Statement

Financial disclosure: M.Y. developed, and has a patent on, the ORP analysis technology used in this study, which has been licensed to Cerebra Health (Winnipeg, Manitoba, Canada), and he is a shareholder and receives royalties and consultation fees from Cerebra Health. A.R., S.L.C., F.H., J.F., A.N.V., D.L., E.O.B., and J.F.-M. declare that they have no financial conflicts of interest.

Nonfinancial disclosure: None declared.

References

1. Alfano CA, et al. The role of sleep in childhood psychiatric disorders. *Child Youth Care Forum*. 2009;**38**(6):327–340.
2. Gorgoni M, et al. Sleep EEG oscillations in neurodevelopmental disorders without intellectual disabilities. *Sleep Med Rev*. 2020;**49**:101224.
3. Feinberg I, et al. Longitudinal sleep EEG trajectories indicate complex patterns of adolescent brain maturation. *Am J Physiol Regul Integr Comp Physiol*. 2013;**304**(4):R296–R303.

4. Giorgio A, et al. Longitudinal changes in grey and white matter during adolescence. *Neuroimage*. 2010;**49**(1):94–103.
5. Huttenlocher PR. Synaptic density in human frontal cortex—developmental changes and effects of aging. *Brain Res*. 1979;**163**(2):195–205.
6. Campbell IG, et al. Sex, puberty, and the timing of sleep EEG measured adolescent brain maturation. *Proc Natl Acad Sci USA*. 2012;**109**(15):5740–5743.
7. Colrain IM, et al. Changes in sleep as a function of adolescent development. *Neuropsychol Rev*. 2011;**21**(1):5–21.
8. Giedd JN, et al. Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci*. 1999;**2**(10):861–863.
9. Patten CA, et al. Depressive symptoms and cigarette smoking predict development and persistence of sleep problems in US adolescents. *Pediatrics*. 2000;**106**(2):E23.
10. Roberts RE, et al. Chronic insomnia and its negative consequences for health and functioning of adolescents: a 12-month prospective study. *J Adolesc Health*. 2008;**42**(3):294–302.
11. Roberts RE, et al. Persistence and change in symptoms of insomnia among adolescents. *Sleep*. 2008;**31**(2):177–184. doi:[10.1093/sleep/31.2.177](https://doi.org/10.1093/sleep/31.2.177)
12. Fernandez-Mendoza J, et al. Natural history of insomnia symptoms in the transition from childhood to adolescence: population rates, health disparities and risk factors. *Sleep*. 2021;**44**(3). doi:[10.1093/sleep/zsaa187](https://doi.org/10.1093/sleep/zsaa187)
13. Hysing M, et al. Trajectories of sleep problems from adolescence to adulthood. Linking two population-based studies from Norway. *Sleep Med*. 2020;**75**:411–417.
14. Furrer M, et al. Sleep EEG slow-wave activity in medicated and unmedicated children and adolescents with attention-deficit/hyperactivity disorder. *Transl Psychiatry*. 2019;**9**(1):324.
15. Pfeifer JH, et al. Puberty initiates cascading relationships between neurodevelopmental, social, and internalizing processes across adolescence. *Biol Psychiatry*. 2021;**89**(2):99–108.
16. Shaw P, et al. Adolescent attention-deficit/hyperactivity disorder: understanding teenage symptom trajectories. *Biol Psychiatry*. 2021;**89**(2):152–161.
17. Sivertsen B, et al. Trajectories of sleep problems from childhood to adolescence: a population-based longitudinal study from Norway. *J Sleep Res*. 2017;**26**(1):55–63.
18. Ringli M, et al. Topography of sleep slow wave activity in children with attention-deficit/hyperactivity disorder. *Cortex*. 2013;**49**(1):340–347.
19. Hamann C, et al. Association between depressive symptoms and sleep neurophysiology in early adolescents. *J Child Psychol Psychiatry*. 2019;**60**(12):1334–1342.
20. Reda F, et al. Sleep-related declarative memory consolidation in children and adolescents with developmental dyslexia. *Brain Sci*. 2021;**11**(1):73.
21. Gerstenberg M, et al. Reduced sleep spindle density in adolescent patients with early-onset schizophrenia compared to major depressive disorder and healthy controls. *Schizophr Res*. 2020;**221**:20–28.
22. Kuula L, et al. Schizotypal traits are associated with sleep spindles and rapid eye movement in adolescence. *J Sleep Res*. 2019;**28**(1):e12692.
23. Saletin JM, et al. Stage 2 sleep EEG sigma activity and motor learning in childhood ADHD: a pilot study. *J Clin Child Adolesc Psychol*. 2017;**46**(2):188–197.
24. Tesler N, et al. Reduced sleep spindle density in early onset schizophrenia: a preliminary finding. *Schizophr Res*. 2015;**166**(1–3):355–357.
25. Prehn-Kristensen A, et al. Sleep promotes consolidation of emotional memory in healthy children but not in children with attention-deficit hyperactivity disorder. *PLoS One*. 2013;**8**(5):e65098.
26. Prehn-Kristensen A, et al. Reduced sleep-associated consolidation of declarative memory in attention-deficit/hyperactivity disorder. *Sleep Med*. 2011;**12**(7):672–679.
27. Bruni O, et al. Sleep spindle activity is correlated with reading abilities in developmental dyslexia. *Sleep*. 2009;**32**(10):1333–1340. doi:[10.1093/sleep/32.10.1333](https://doi.org/10.1093/sleep/32.10.1333)
28. Limoges E, et al. Atypical sleep architecture and the autism phenotype. *Brain*. 2005;**128**(Pt 5):1049–1061.
29. Maski K, et al. Sleep dependent memory consolidation in children with autism spectrum disorder. *Sleep*. 2015;**38**(12):1955–1963. doi:[10.5665/sleep.5248](https://doi.org/10.5665/sleep.5248)
30. Tessier S, et al. Intelligence measure and stage 2 sleep in typically-developing and autistic children. *Int J Psychophysiol*. 2015;**97**:58–65.
31. Wilhelm I, et al. Widespread reduction in sleep spindle activity in socially anxious children and adolescents. *J Psychiatr Res*. 2017;**88**:47–55.
32. Tesler N, et al. Increased frontal sleep slow wave activity in adolescents with major depression. *Neuroimage Clin*. 2016;**10**:250–256.
33. Younes M. The case for using digital EEG analysis in clinical sleep medicine. *Sleep Sci Pract*. 2017;**1**:2.
34. Younes M, et al. Comparing two measures of sleep depth/intensity. *Sleep*. 2020;**43**(12). doi:[10.1093/sleep/zsaa127](https://doi.org/10.1093/sleep/zsaa127)
35. Younes M, et al. Staging sleep in polysomnograms: analysis of inter-scorer variability. *J Clin Sleep Med*. 2016;**12**(6):885–894.
36. Younes M, et al. Odds ratio product of sleep EEG as a continuous measure of sleep state. *Sleep*. 2015;**38**(4):641–654. doi:[10.5665/sleep.4588](https://doi.org/10.5665/sleep.4588)
37. Younes M, et al. Utility of technologist editing of polysomnography scoring performed by a validated automatic system. *Ann Am Thorac Soc*. 2015;**12**(8):1206–1218.
38. Younes M, et al. Immediate postarousal sleep dynamics: an important determinant of sleep stability in obstructive sleep apnea. *J Appl Physiol* (1985). 2016;**120**(7):801–808.
39. Younes M, et al. Minimizing interrater variability in staging sleep by use of computer-derived features. *J Clin Sleep Med*. 2016;**12**(10):1347–1356.
40. Mazzotti DR, et al. Odds ratio product as a measure of sleep depth during REM sleep: effects on REM duration and REM sleep fragmentation. *Sleep*. 2020;**43**(Suppl 1):A20. doi:[10.1093/sleep/zsaa056.048](https://doi.org/10.1093/sleep/zsaa056.048)
41. Yu JL, et al. Relation between arousability and outcome of upper airway stimulation in the Stimulation for Apnea Reduction (STAR) Trial. *J Clin Sleep Med*. 2021;**17**(4):797–801.
42. Bonnet MH, et al. The scoring of arousal in sleep: reliability, validity, and alternatives. *J Clin Sleep Med*. 2007;**3**(2):133–145.
43. Younes M, et al. Mechanism of excessive wake time when associated with obstructive sleep apnea or periodic limb movements. *J Clin Sleep Med*. 2020;**16**(3):389–399.
44. Azarbarzin A, et al. Interhemispheric sleep depth coherence predicts driving safety in sleep apnea. *J Sleep Res*. 2021;**30**(2):e13092.
45. Malhotra A, et al. Metrics of sleep apnea severity: beyond the AHI. *Sleep*. 2021;**44**(7). doi:[10.1093/sleep/zsab030](https://doi.org/10.1093/sleep/zsab030)
46. Ricci A, et al. Maturation trajectories of non-rapid eye movement slow wave activity and odds ratio product in a population-based sample of youth. *Sleep Med*. 2021;**83**:271–279.
47. Gaudreau H, et al. Age-related modifications of NREM sleep EEG: from childhood to middle age. *J Sleep Res*. 2001;**10**(3):165–172.

48. Kurth S, et al. Mapping of cortical activity in the first two decades of life: a high density sleep electroencephalogram study. *J Neurosci*. 2010;**30**(40):13211–13219.
49. Ringli M, et al. Developmental aspects of sleep slow waves: linking sleep, brain maturation and behavior. *Prog Brain Res*. 2011;**193**:63–82.
50. Bixler EO, et al. Natural history of sleep disordered breathing in prepubertal children transitioning to adolescence. *Eur Respir J*. 2016;**47**(5):1402–1409.
51. Fernandez-Mendoza J, et al. Insomnia is associated with cortical hyperarousal as early as adolescence. *Sleep*. 2016;**39**(5):1029–1036. doi:[10.5665/sleep.5746](https://doi.org/10.5665/sleep.5746)
52. Fernandez-Mendoza J, et al. Insomnia symptoms with objective short sleep duration are associated with systemic inflammation in adolescents. *Brain Behav Immun*. 2017;**61**:110–116.
53. Fernandez-Mendoza J, et al. Association of pediatric obstructive sleep apnea with elevated blood pressure and orthostatic hypertension in adolescence. *JAMA Cardiol*. 2021;**6**(10):1144–1151.
54. Bixler EO, et al. Sleep disordered breathing in children in a general population sample: prevalence and risk factors. *Sleep*. 2009;**32**(6):731–736. doi:[10.1093/sleep/32.6.731](https://doi.org/10.1093/sleep/32.6.731)
55. Calhoun SL, et al. Prevalence of insomnia symptoms in a general population sample of young children and preadolescents: gender effects. *Sleep Med*. 2014;**15**(1):91–95.
56. Ali NJ, et al. Snoring, sleep disturbance, and behaviour in 4-5 year olds. *Arch Dis Child*. 1993;**68**(3):360–366.
57. Puzino K, et al. Behavioral, neurocognitive, polysomnographic and cardiometabolic profiles associated with obstructive sleep apnea in adolescents with ADHD. *J Child Psychol Psychiatry*. 2021 (online ahead of print). doi:[10.1111/jcpp.13491](https://doi.org/10.1111/jcpp.13491)
58. Frye SS, et al. Neurocognitive and behavioral significance of periodic limb movements during sleep in adolescents with attention-deficit/hyperactivity disorder. *Sleep*. 2018;**41**(10). doi:[10.1093/sleep/zsy129](https://doi.org/10.1093/sleep/zsy129)
59. Kuczmarski RJ, et al. 2000 CDC growth charts for the United States: methods and development. *Vital Health Stat* 11. 2002;**246**:1–190.
60. Rechtschaffen A, et al. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. *Clin Neurophysiol*. 1969;**26**:644.
61. Iber C, et al. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*. Westchester, IL: The American Academy of Sleep Medicine; 2007.
62. Malhotra A, et al. Performance of an automated polysomnography scoring system versus computer-assisted manual scoring. *Sleep*. 2013;**36**(4):573–582. doi:[10.5665/sleep.2548](https://doi.org/10.5665/sleep.2548)
63. Younes M, et al. Characteristics and reproducibility of novel sleep EEG biomarkers and their variation with sleep apnea and insomnia in a large community-based cohort. *Sleep*. 2021;**44**(10). doi:[10.1093/sleep/zsab145](https://doi.org/10.1093/sleep/zsab145)
64. World Health Organization. Adolescent Health. https://www.who.int/health-topics/adolescent-health#tab=tab_1. Accessed June 7, 2021.
65. Tononi G, et al. Sleep function and synaptic homeostasis. *Sleep Med Rev*. 2006;**10**(1):49–62.
66. Penner CG, et al. The odds ratio product (an objective sleep depth measure): normal values, repeatability, and change with CPAP in patients with OSA. *J Clin Sleep Med*. 2019;**15**(8):1155–1163.
67. Curatolo P, et al. The neurobiological basis of ADHD. *Ital J Pediatr*. 2010;**36**(1):79.
68. Suskauer SJ, et al. Functional magnetic resonance imaging evidence for abnormalities in response selection in attention deficit hyperactivity disorder: differences in activation associated with response inhibition but not habitual motor response. *J Cogn Neurosci*. 2008;**20**(3):478–493.
69. Dang-Vu TT, et al. Spontaneous brain rhythms predict sleep stability in the face of noise. *Curr Biol*. 2010;**20**(15):R626–R627.
70. Dang-Vu TT, et al. Sleep spindles predict stress-related increases in sleep disturbances. *Front Hum Neurosci*. 2015;**9**(68):00068.
71. Ferri R, et al. Increased chin muscle tone during all sleep stages in children taking SSRI antidepressants and in children with narcolepsy type 1. *Sleep*. 2021;**44**(11). doi:[10.1093/sleep/zsab147](https://doi.org/10.1093/sleep/zsab147)
72. Ferri R, et al. Leg movements during sleep in children treated with serotonergic antidepressants. *Sleep*. 2021 (online ahead of print). doi:[10.1093/sleep/zsab236](https://doi.org/10.1093/sleep/zsab236)
73. McKillop LE, et al. Diazepam effects on local cortical neural activity during sleep in mice. *Biochem Pharmacol*. 2021;**191**:114515.
74. Chekroud AM, et al. Reevaluating the efficacy and predictability of antidepressant treatments: a symptom clustering approach. *JAMA Psychiatry*. 2017;**74**(4):370–378.
75. Israel B, et al. Short-term stability of sleep and heart rate variability in good sleepers and patients with insomnia: for some measures, one night is enough. *Sleep*. 2012;**35**(9):1285–1291. doi:[10.5665/sleep.2088](https://doi.org/10.5665/sleep.2088)
76. Tan X, et al. High inter-night reliability of computer-measured NREM delta, sigma, and beta: biological implications. *Biol Psychiatry*. 2000;**48**(10):1010–1019.