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Original Article

ORIGINAL ARTICLE

Sleep electroencephalogram evidence of delayed brain maturation in attention deficit hyperactivity disorder: a longitudinal study

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Abstract

Study Objectives: This study investigates whether longitudinally measured changes in adolescent brain electrophysiology corroborate the maturational lag associated with attention deficit hyperactivity disorder (ADHD) reported in magnetic resonance imaging (MRI) studies and cross-sectional sleep electroencephalogram (EEG) data.

Methods: Semiannually nine adolescents diagnosed with ADHD (combined presentation, DSM-V criteria, mean age 12.39 ± 0.61 years at first time-point, two females) and nine typically developing controls (12.08 ± 0.35 years, four females) underwent all-night laboratory polysomnography, yielding four recordings.

Results: Sleep macrostructure was similar between groups. A quadratic model of the age change in non-rapid eye movement (NREM) delta (1.07–4 Hz) power, with sex effects accounted for, found that delta power peaked 0.92 ± 0.37 years later in the ADHD group. A Gompertz function fit to the same data showed that the age of most rapid delta power decline occurred 0.93 ± 0.41 years later in the ADHD group ($p = 0.037$), but this group difference was not significant ($p = 0.38$) with sex effects accounted for. For very low frequency (0.29–1.07 Hz) EEG, the ADHD lag (1.07 ± 0.42 years later, $p = 0.019$) was significant for a Gompertz model with sex effects accounted for ($p = 0.044$). Theta (4–7.91 Hz) showed a trend ($p = 0.064$) toward higher power in the ADHD group. Analysis of the EEG decline across the night found that standardized delta and theta power in NREMP1 were significantly ($p < 0.05$ for both) lower in adolescents with ADHD.

Conclusions: This is the first longitudinal study to reveal electrophysiological evidence of a maturational lag associated with ADHD. In addition, our findings revealed basically unaltered sleep macrostructure but altered sleep homeostasis associated with ADHD.

Statement of Significance

Our findings provide the first electrophysiological evidence that, compared to typically developing peers, adolescents diagnosed with attention deficit hyperactivity disorder (ADHD) have similar but delayed brain development trajectories. The study also demonstrates that homeostatic recovery occurs more slowly in adolescents with ADHD and that sleep macrostructure is basically normal in ADHD. These findings hold implications for fundamental and clinical research issues to further our understanding of this prevalent disorder and to reveal critical developmental periods of the underlying processes.

Key words: adolescence; development; ADHD; EEG spectra; homeostasis

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Introduction

It is now recognized that the human brain undergoes a profound reorganization during adolescence [1]. Evidence for and consequences of this reorganization include: the diminished ability to recover function after brain injury and the decreasing ability to learn to speak new languages without an accent (i.e. diminished plasticity); a decrease in brain metabolic rate as great as the decline from normal to senile elderly; a massive decline in the slow-wave electroencephalogram (EEG) of deep non-rapid eye movement (NREM) sleep; and the emergence of adult problem-solving ability (reviewed in [1]). These maturational changes result in part from the late synaptic elimination discovered by Huttenlocher [2].

The idea that sleep EEG could serve as a marker of adolescent brain maturation, proposed decades ago [1], is becoming widely accepted [3–6]. The largest longitudinal study of adolescent sleep [7–9] provides strong evidence that power within the delta band during NREM sleep, i.e. slow-wave EEG activity (SWA) declines by more than 60% between ages 12 and 16.5 years, after which the rate of decline slows markedly. Another major slow-wave component of NREM sleep, theta EEG power, declines earlier than delta EEG power [9].

A major area of research into adolescent brain changes involves magnetic resonance imaging (MRI) studies of cortical thickness. Gray matter thickness and volume decrease across the teenage years [10]. The maturational decline in NREM delta power parallels the decline in cortical gray matter volume [11, 12]. Furthermore, the "back to front" developmental pattern observed in MRI-measured cortical thickness [13] mirrors the pattern of topographical changes in SWA across adolescence [14, 15]. More recently, the role of slow oscillation propagation as a marker of changes in brain connectivity during neurodevelopment has also been advanced [16, 17]. Overall, these studies demonstrate that the sleep EEG can be used as a functional neurodevelopmental measure to gain insights into healthy brain maturation and identify deviations from the typical developmental trajectory.

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder which occurs in about 5%–10% of children, predominantly in males, and is the most common behavioral concern in pediatric settings [18–20]. Sleep problems and sleep-wake instability are frequently reported in children and adolescents with ADHD [21, 22]. The potential impact of these problems on neurocognitive functioning in children with ADHD and on mental well-being of their parents have been described and an interest toward sleep in ADHD population continues to advance [23, 24]. However, differences in several sleep parameters between children with and without ADHD have not been consistent and a relationship of sleep disturbances with ADHD is still unclear [25].

Neuroanatomical studies suggest that ADHD is characterized by a delayed rather than deviant cortical maturation [26–28]. Structural MRI findings provide evidence that maturation in some brain areas is delayed by about 3 years in children with ADHD [27]. Findings on which brain areas show reduced cortical thickness in ADHD subjects are rather variable [27, 29–31]. Delayed brain maturation in children with ADHD has also been evidenced in a reduction of cortical surface area and cortical folding [28, 32].

Despite the sleep EEG providing a valuable tool to investigate the maturation of brain electrophysiology, developmental studies investigating brain functions in ADHD subjects in relation to sleep neurophysiology are scarce, inconsistent, and cross-sectional (reviewed in [20]). High-density EEG studies examining the SWA topography support a neuromaturational delay in children with ADHD [33, 34]. However, other studies did not detect elevated SWA power in subjects diagnosed with ADHD [35–38].

Longitudinal sleep EEG studies examining how brain physiology is altered in ADHD are virtually absent, except our initial report from the current study [39]. In this recent paper, based on sleep EEG data from two time-points (6 months apart), we (1) showed that sleep macrostructure is overall similar in the ADHD (drug-naïve) and control (typically developing) groups; (2) provided suggestive evidence of a brain maturational delay and (3) found altered sleep homeostasis in the ADHD group. Here we extend these data by presenting results from four semiannual recordings of drug-naïve adolescents diagnosed with ADHD and typically developing adolescents, followed from about 12 to 14 years, age range of most rapid developmental changes in slow-wave EEG. The study aimed to determine whether the basic sleep pattern is normal in ADHD, whether the longitudinal changes in adolescent brain electrophysiology corroborate a maturational lag associated with ADHD, and whether within-night slow-wave EEG dynamics are altered in ADHD.

Methods

Study methods details have been published elsewhere [39] and are summarized here.

Subjects

Nine subjects diagnosed with ADHD (two females, mean age 12.39 years at first time-point; range 11.48–13.09), combined presentation according to DSM-V criteria [40], without any additional comorbid chronic diseases, the presence of sleep disorders, or neurodevelopmental and mental disorders including learning disability, intellectual disability, autism spectrum disorder, or anxiety disorders, were included in the analyses. Specifically, comorbidities were screened based on a thorough clinical interviews (both with a parent and a child) and neuropsychological assessments by a clinical neuropsychologist, United States Board Certified Behavioral Analyst (TT). As a part of the assessment process, the Child Behavior Checklist (ages 6–18) from the Achenbach System of Empirically Based Assessment [41], Wechsler Nonverbal Scale of Ability [42], and Comprehensive Executive Function Inventory [43] were administered. Children with prior history of a diagnosed sleep disorder or with any possibility of a sleep disorder were excluded. The presence/history for sleep disturbances were screened by senior sleep researcher via detailed interviews with both participants and parents (e.g. questions regarding snoring, gasps for breath, difficulty in breathing during sleep, nighttime awakenings, daytime sleepiness, jerking of legs while asleep, etc.) and/or assessed by a Georgian translation of the Child Sleep Disturbance Scale [44]. Due to these screening criteria three subjects out of the initially selected 14 potential participants were excluded—two subjects based on the interview and one suspected case based on polysomnography (PSG) recording. Furthermore, two subjects failed to accomplish the first year of the study. The remaining nine subjects, repeatedly assessed by clinical

neuropsychologist/sleep researcher during each recording time-point, completed the study. No further exclusions were necessary. Our efforts to get/keep more subjects in the study were unsuccessful.

The control group consisted of nine subjects (four females, mean age 12.08 years at first time-point, range: 11.69–12.72) without any of the following exclusion criteria: the presence or history of sleep disorders, psychiatric or neurological disorders, head injury, smoking, use of any types of psychotropic medication, a sibling or parent with ADHD, assessed at each recording time-point.

To exclude major differences in overall cognitive performance between the two groups, an inclusion criterion for ADHD was attendance in regular school classes without a status of special educational needs. Furthermore, Raven's Progressive Matrices Test [45] showed no significant difference between the ADHD and control groups ($p > 0.1$).

Parents provided written informed consent and adolescents provided assent. All subjects received monetary compensation for completing each assessment time-point. The study was approved by the Ilia State University ethics committee and was accomplished according to the ethical standards of the Helsinki Declaration.

Experimental design

EEG recordings were performed at approximately 6 month intervals. All subjects were studied in Sleep Lab, Ilia State University, Tbilisi, Georgia on their habitual school day schedules. Subjects were required to avoid napping for 5 days prior to the recording. Actigraphy devices (Philips Respironics, Actiwatch 2) and sleep diaries monitored the subjects' compliance to these requirements. Subjects were additionally asked to restrict their caffeine consumption during this period.

Semiannually, all subjects completed an adaptation night and all-night EEG recording. On the adaptation night, subjects slept in the laboratory to adapt to the environment. The following day they kept regular habitual school/social activities and returned to the laboratory in the evening for the recording night with a nocturnal video-audio PSG. Laboratory personnel monitored the subjects during both nights. Data presented here are from the four semiannual recordings.

EEG recordings and analysis

ALL EEG data were collected on EMBLA N7000 PSG system. EEG electrodes were applied at F3, F4, C3, C4, O1, O2, M1, M2, LOC, ROC, two submental chin locations, reference, and ground electrodes. Impedance, measured at the beginning of the recording, was below 5 kΩ for all electrodes. EEG signals were filtered with a low-cut filter with a –3 dB point at 0.3 Hz and a high-cut filter with a –3dB point at 35 Hz. Data were sampled at 200 Hz.

Thirty second epochs were visually scored as either wake, N1 (stage 1), N2 (stage 2), N3 (stage 3), or rapid eye movement (REM) sleep according to the 2007 American Academy of Sleep Medicine criteria [46]. Each scored recording was checked by a second researcher and discrepancies between scorers were reconciled by the senior scientist (ND). The epochs that had artifacts were identified and marked independently of sleep stage. The central channel with fewer artifacts, C3-M2 or C4-M1, was selected for spectral analysis.

All scored/checked recordings were converted to European Data Format and analyzed at the University of California, Davis with the PASSPLUS sleep analysis system (Delta Software, St. Louis, MO). Fast Fourier Transformation (FFT) analysis for all artifact-free epochs was performed using 5.12 s Welch tapered windows with 2.62 s overlap. The following FFT frequency bands were used for analysis: very low frequency EEG 0.29–1.07 Hz, delta 1.07–4.00 Hz, and theta 4.00–7.91 Hz. All epochs marked with artifact were removed from spectral analysis.

Sleep cycles were calculated based on Feinberg and Floyd criteria [47]. Given that children and adolescents frequently skip the first REM period [5, 48], we divided long first NREM periods (NREMP1) into two cycles if all-night plots of delta EEG power showed two clear peaks separated by a trough ≥ 10 min. All nights that were analyzed included at least four complete NREM periods.

To control for the effect of all-night NREM duration differences, we examined power, as a measure of average activity in a frequency band, only for the first 5 h of NREM sleep. Power was calculated as energy divided by the seconds of artifact-free NREM sleep. Delta and theta power were also calculated in each of four NREM periods. To standardize cycle data, we calculated power in each cycle as a percent of average power in four cycles.

Statistical analysis

Mixed-effects analysis (SAS proc mixed) was used to evaluate age-related changes and group differences in sleep variables as well as age by group interactions. All analyses accounted for sex effects, and the only random term was the intercept.

For EEG power, the initial analyses also used linear mixed-effect analysis of age and group effects with sex effects accounted for. For these initial linear analyses log power was analyzed because log power was more normally distributed. As shown in Figures 1 and 2, the age-related changes in delta and very low frequency power were not linear. Analyzing power, not log power, we used nonlinear mixed-effects analysis to determine if a quadratic model ($y = k + a * (x - h)$ where k is the peak of the parabola and h is the age at which the peak occurs), or a Gompertz model ($D - A * \exp(-\exp(-C * (x - M)))$, where D is the upper asymptote, A is the decrease to the lower asymptote, C is the steepness of the decline, and M is the age of most rapid decline) improved the fit over a linear model. For these analyses, we evaluated whether the age of the quadratic peak and the age of Gompertz most rapid decline differed between groups and between sexes. Alpha was 0.05 and was not adjusted for the multiple analyses conducted.

Analysis of variance (ANOVA) (SAS proc GLM) was used to evaluate cycle data with cycle and recording as repeated measures, group and sex as between factors, and cycle by group interactions. Significant interactions were followed by analyses of group differences in each cycle.

For linear mixed-effects analyses we report effect sizes for group differences and some age by group interactions. The group effect size was calculated as the regression coefficient for the group effect divided by the pooled within group standard deviation ($d = b/\mathrm{SD}$), and the effect size for the age by group interaction was the regression coefficient for the group slope effect divided by 3 (number of recordings minus 1) times the pooled within group standard deviation ($d = b/[(K - 1) * \mathrm{SD}]$) [49].

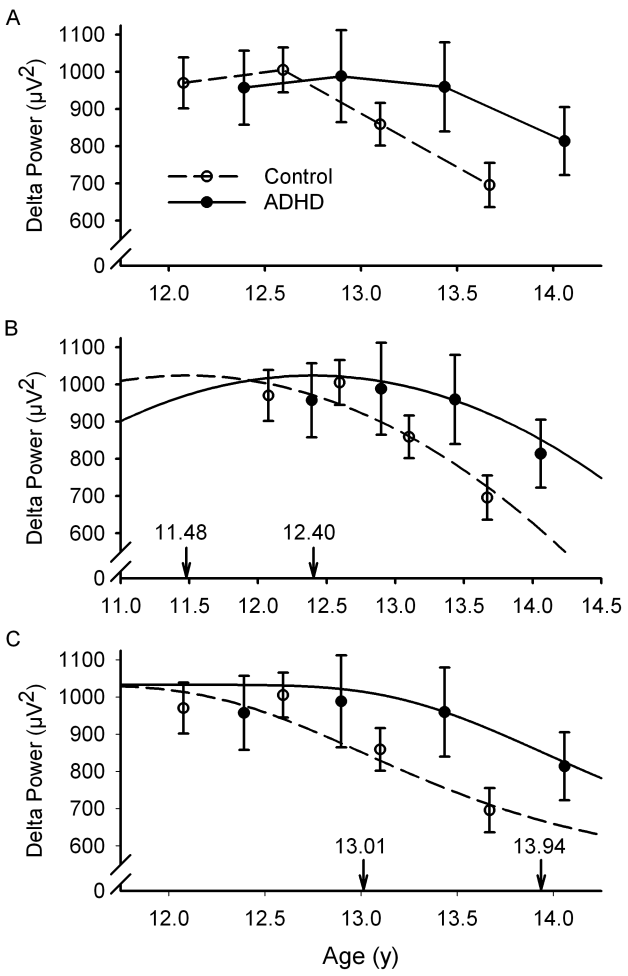

Figure 1. Maturation across ages 12–14 years of delta (1.07–4 Hz) EEG power in the first 5 h of NREM sleep. (A) Mean (± standard error) delta power at each semiannual recording is plotted versus age for the control (open circles, dashed lines) and ADHD groups (filled circles, solid lines). (B) For quadratic functions fit to the data, the delta power peak occurred 0.92 years later in the ADHD group. Ages of the peaks are indicated with arrows on the x-axis. (C) For Gompertz functions fit to the data, the age of most rapid delta power decline (indicated with arrows on the x-axis) occurred 0.93 years later in the ADHD group, but this difference was not significant with sex effects accounted for.

We report partial eta squared as effect sizes for ANOVA results (η^2_p = SSeffect/(SSeffect + SSerror). For d, 0.2, 0.5, and 0.8 are considered small, medium, and large effect sizes respectively; for η^2_p, these values are 0.01, 0.06, and 0.14.

Results

Sleep variables

Table 1 presents sleep variables separately for each group. Mixed-effects analysis with sex effects accounted for showed that the ADHD group had significantly shorter time in bed (TIB) ($F_{1,15}$ = 9.35, p = 0.0080, d = 0.80) and lower total sleep time (TST) ($F_{1,15}$ = 9.39, p = 0.0079, d = 0.91) than the control group. The 41.9 min TST difference between groups was almost entirely comprised of a 39.6 min lower mean N2 duration in the ADHD group ($F_{1,15}$ = 16.6, p = 0.0010, d = 1.22). Latency to REM sleep was shorter in the ADHD group ($F_{1,15}$ = 5.59, p = 0.032, d = 0.60). Sleep efficiency, wake after sleep onset, N1, N3, and REM sleep duration, and number of awakenings per hour of sleep did not differ between groups (p > 0.1 for all, d < 0.6 for all). Expressed as a percent of TST, stage N2 duration % was lower ($F_{1,15}$ = 4.64, p = 0.0048, d = 0.69) and stage N3 duration % was higher ($F_{1,15}$ = 5.75, p = 0.030, d = 0.75) in the ADHD group. Percentages of N1 and REM sleep did not differ between groups (p > 0.5 for both, d < 0.1 for both).

Stage N3 duration and N3 as a percent of TST decreased with age, and N2 as a percent of TST increased with age. N3 duration declined significantly ($F_{1,52}$ = 20.5, p < 0.0001) from an intercept of 115.8 min at the centered age (13.03 year), and N3% decreased at a rate of 2.0%/year ($F_{1,52}$ = 15.4, p = 0.0003) from a centered intercept of 23.4%. N2% increased by 2.3%/year ($F_{1,52}$ = 17.1, p = 0.0001) from a centered intercept of 51.8%. REM latency declined by 4.8 min/year ($F_{1,52}$ = 4.84, p = 0.032) from a centered intercept of 72.9 min.

There were no group differences in the age-related change in any sleep structure measure (age by group interaction p > 0.1 for all).

NREM sleep EEG delta activity

NREM delta power showed complex age trajectories in typically developing adolescents and adolescents with ADHD. Figure 1 shows the age trend for delta (1.07–4 Hz) power in the first 5 h of NREM sleep for both groups. Linear evaluation with mixed-effect analysis of the age trajectory of log delta power (with sex effect accounted for) showed a significant age-related decrease ($F_{1,52}$ = 42.5, p < 0.0001) but no significant group difference ($F_{1,15}$ = 0.05, p = 0.83, d = 0.07) or group by age interaction ($F_{1,52}$ = 0.81, p = 0.37, d = 0.48). As shown in Figure 1, the age trend for delta power does not appear to be a linear decline. The age trajectory for delta power (not log delta power) was better fit with a quadratic equation (Bayesian information criterion (BIC) improved from 973.0 for linear to 965.7 for quadratic). In the quadratic model (Figure 1B), the age at which the peak occurs was 0.92 ± 0.37 (estimate ± SE) years later in the ADHD group (t_{17} = 2.50, p = 0.023) and this difference remained significant with sex effects accounted for (t_{17} = 2.12, p = 0.049). Fitting a Gompertz curve to the age trend for delta power improved the fit a bit more (BIC = 964.8). A Gompertz function fit (Figure 1C) to the data showed that the age of most rapid delta power decline occurred at 13.01 ± 0.48 years in control group and 0.93 ± 0.41 years later in ADHD group, with a significant group difference (t_{17} = 2.27, p = 0.037). This group difference was not significant (t_{17} = 0.89, p = 0.38) when the significant sex difference in the age of most rapid decline (boys 0.86 years later, t_{17} = 2.42, p = 0.027) was accounted for.

NREM sleep EEG activity of very low frequency

Figure 2A and B show the age trends for very low frequency (0.29–1.07 Hz) power in the first 5 h of NREM for the control and ADHD groups. Linear evaluation with mixed-effect analysis of the age trajectory of log power (with sex effect accounted for) showed a significant age-related decrease ($F_{1,52}$ = 32.8, p < 0.0001) but no significant group difference ($F_{1,15}$ = 0.96, p = 0.34, d = 0.37) or group by age interaction ($F_{1,52}$ = 0.43, p = 0.52, d = 0.31). The age trend for very low frequency power does not show a linear decline (Figure 2A). The age-related decline of NREM sleep very low frequency (0.29–1.07 Hz) power was fit with a Gompertz

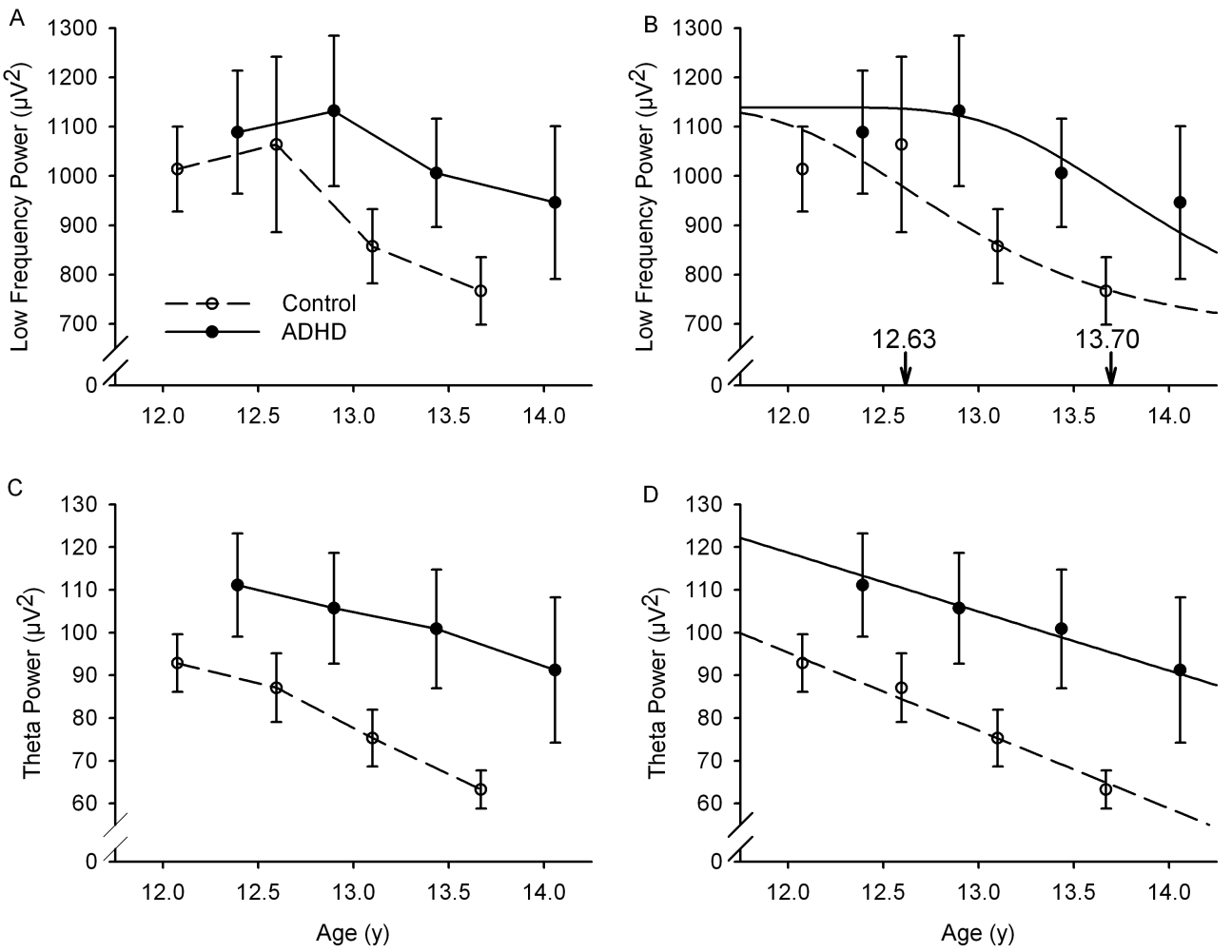

Figure 2. Maturation across ages 12–14 years of very low frequency (A & B, 0.29–1.07 Hz) and theta (C & D, 4–7.91 Hz) EEG power in the first 5 h of NREM sleep. (A) Mean (± standard error) very low frequency power at each semiannual recording is plotted versus age for the control (open circles, dashed lines) and ADHD groups (filled circles, solid lines). (B) For Gompertz functions fit to the very low frequency data, the age of most rapid decline (indicated with arrows on the x-axis) of very low frequency power occurred 1.07 years later in the ADHD group. (C) Using the same format as Figure 2A, mean (± SE) theta power is plotted versus age. (D) Linear functions fit to the theta power data showed a trend toward higher power for the ADHD group but no group difference in the age trend (slope).

Table 1. Group differences and age effects for sleep macrostructure

			Statistics (*p*)	
Sleep variables	ADHD	Control	Group	Age
TIB (min)	518.2 ± 12.2	552.3 ± 9.8	**0.008**	0.36
TST (min)	481.1 ± 13.5	523.1 ± 10.9	**0.008**	0.27
Sleep onset latency (min)	13.6 ± 1.8	8.8 ± 1.4	0.056	0.88
REM latency (min)	68.8 ± 2.7	78.8 ± 3.2	**0.032**	**0.02**
WASO (min)	25.4 ± 4.2	22.5 ± 2.3	0.75	0.81
Sleep efficiency (%)	92.8 ± 0.9	94.7 ± 0.5	0.10	0.44
N1 (%)	4.2 ± 0.4	4.1 ± 0.3	0.72	0.81
N1 (min)	20.3 ± 1.8	21.3 ± 1.5	0.60	0.96
N2 (%)	50.4 ± 1.1	52.9 ± 1.0	**0.048**	**0.0001**
N2 (min)	242.2 ± 5.6	277.0 ± 8.2	**0.001**	0.13
N3 (%)	24.9 ± 1.0	22.4 ± 0.9	**0.03**	**0.0003**
N3 (min)	119.6 ± 7.5	117.1 ± 5.6	0.69	**<0.0001**
REM (%)	20.5 ± 0.7	20.6 ± 0.4	0.88	0.64
REM (min)	99.2 ± 5.1	108.0 ± 2.2	0.09	0.27
Awakening index(#/h)	2.9 ± 0.3	2.2 ± 0.2	0.11	0.051

For group means (± standard error), data were averaged across the four recordings for each subject and then averaged by group. Statistics (*p*) are results of mixed-effects analyses. *P*-values in bold indicate significant differences at $\alpha = 0.05$. Bold and italicized *p*-values indicate significant decrease with age. Group by age interaction was not significant for any variable ($p > 0.20$ for all). TIB, time in bed; TST, total sleep time; Sleep onset latency, latency to the first occurrence of stage 2 sleep; REM, rapid eye movement sleep; REM latency, latency to the first occurrence of stage REM sleep; WASO, wake after sleep onset; N1, stage 1; N2, stage 2; N3, stage 3. Sleep stages are expressed in minutes or as a percentage of total sleep time.

function (Figure 2B) with the parameter C fixed at 1.5. For the ADHD group, the age of most rapid decline of the Gompertz function occurred 1.07 ± 0.42 years later ($t_{17} = 2.58$, $p = 0.019$) than the 12.63 ± 0.34 year age of most rapid decline in typically developing adolescents. For very low frequency EEG, the ADHD lag was significant ($t_{17} = 2.18$, $p = 0.044$) for the Gompertz model even with sex effects accounted for.

NREM sleep EEG theta activity

Theta power declined linearly across age ($F_{1,52} = 74.4$, $p < 0.001$) in both groups. We found a trend toward higher theta power for the ADHD group ($F_{1,15} = 3.99$, $p = 0.064$, $d = 0.64$). There was no group difference in the age-related change in theta power (age by group interaction, $F_{1,52} = 1.53$, $p = 0.22$, $d = 0.54$). Figure 2C and D show the nearly parallel age-related theta power decline for the ADHD and control groups.

Delta and theta EEG activity across the NREM periods

We investigated group and age differences in the across night dynamics of delta and theta EEG activity by analyzing changes in standardized power across the first four NREM periods, again accounting for sex effects. Standardized delta power (Figure 3A) declined across the four NREM periods ($F_{3,45} = 159$, $p < 0.0001$), with a significant cycle by group interaction ($F_{3,45} = 2.89$, $p = 0.046$, $\eta^2_p = 0.16$). Analyzing data for each cycle showed that standardized delta power was significantly lower in cycle 1 ($F_{1,15} = 5.45$, $p = 0.034$, $\eta^2_p = 0.27$) and significantly higher in cycle four ($F_{1,15} = 4.57$, $p = 0.050$, $\eta^2_p = 0.23$) in the ADHD group.

Similarly, standardized theta power (Figure 3B) declined across the four NREM periods ($F_{3,45} = 302$, $p < 0.0001$). The standardized theta decline across cycles showed a clear trend ($F_{3,45} = 2.79$, $p = 0.051$, $\eta^2_p = 0.16$) to differ between groups. Decomposition of the interaction effect showed a significantly lower standardized theta power in cycle 1 ($F_{1,15} = 7.46$, $p = 0.016$, $\eta^2_p = 0.33$) in the ADHD group.

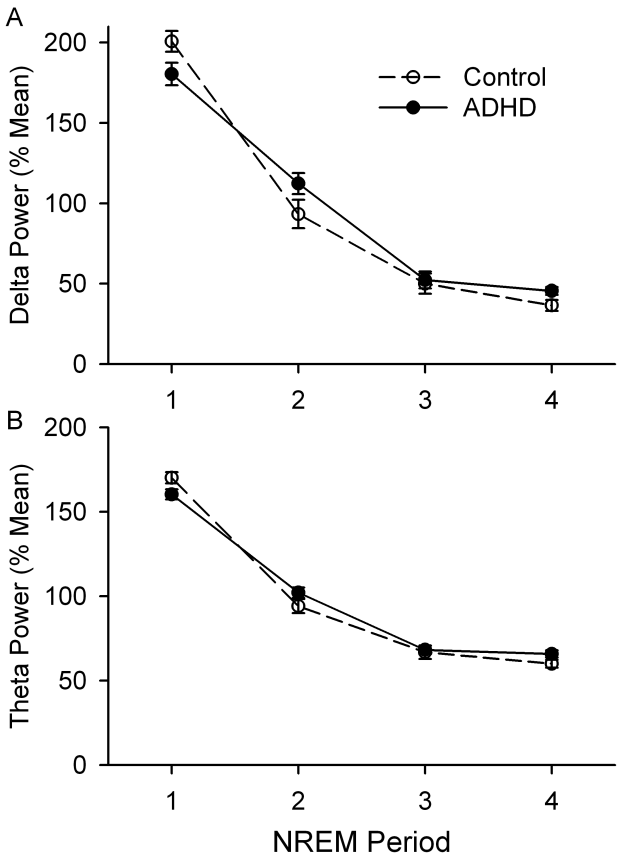

Figure 3. Mean (± standard error) standardized delta (A) and theta (B) power are plotted against NREM period to show the power decline across the night for the control (open circles, dashed lines) and ADHD (filled circles, solid lines) groups. Power in each NREM period was standardized for each recording as a percent of the average power in NREMPs 1 through 4. The trends across the night differed between groups with power in NREMP1 significantly lower in the ADHD group.

Discussion

To our knowledge this study is the first longitudinal study to examine differences in sleep EEG in typically developing adolescents and medication-free adolescents with ADHD across four semiannual recordings. Although study results should be interpreted cautiously due to the small sample size, our findings hold implications for understanding whether electrophysiological data support a maturational lag model of ADHD. With data from four semiannual recordings, we report three main findings which confirm our impressions from the first two recordings: (1) sleep macrostructure is basically similar between groups; (2) Delta and very low frequency EEG power provide evidence of an ADHD-related neurodevelopmental delay in brain maturation. (3) Sleep homeostasis is altered in ADHD.

Sleep structure

Research findings, primarily from cross-sectional studies, are inconclusive regarding ADHD-related differences in sleep macrostructure [20]. Whether or not sleep difficulties are the core impairments of the disorder or originate as a consequences of stimulant medications, is not firmly established [50]. Based on parental reports, sleep difficulties affect as many as 50 per cent of children diagnosed with ADHD [21]. However, objective sleep studies have produced equivocal results. One of the first reports exploring sleep in ADHD disorder revealed that sleep architecture was normal in children with ADHD [51]. Reviews of sleep in children with ADHD report no differences in sleep macrostructure, and conflicting findings regarding TST, TIB, and REM sleep latency/duration and the other measures of sleep architecture [20, 22]. Considering that sleep has a profound impact on cognitive and behavioral functions, it is particularly important to understand the maturational trajectory of sleep macrostructure for children with ADHD. In line with our previously published results from two time-points, we did not find significant alterations in sleep architecture of drug-naïve adolescents with ADHD across four recordings. Sleep macrostructure measures, other than sleep duration and REM sleep latency, were basically similar between groups and age-related changes did not differ between groups. The differences we did detect were for sleep structure measures with large group difference effect sizes. A larger sample size may be able to detect smaller but meaningful differences in the sleep of adolescents with ADHD. The lower sleep duration in the ADHD group was due to the lower stage N2 duration. The small but significant TIB differences

between groups would have small sleep restriction effect that results reduction in stage N2 duration at the end of night [52] and therefore proportionally more time in stage N3.

The significantly shorter REM sleep latency found in our study agrees with some of previous studies [53, 54]. The shorter REM sleep latency suggests a decreased pressure for slow-wave sleep which contradicts data of the higher NREM delta power (discussed below). It may also indicate unstable noradrenergic system and its impaired inhibitory influence on REM sleep [55]. According to a relatively recent attempt to identify sleep phenotypes in ADHD, there is a "primary" form of ADHD which is characterized by a hypoarousal state resembling narcolepsy [56]. Although there were no significant differences in REM sleep quantity in our study, and no reports of daytime sleepiness in study subjects, the consistently shorter REM latency in the ADHD group may support the hypothesis of REM sleep dysregulation in ADHD [57, 58]. Another possibility is that short transitions between NREM and REM sleep oscillation may be associated with a delay of brain maturation [59].

Slow-wave sleep EEG maturation

As already stated, the adolescent decline in slow-wave sleep EEG activity has been interpreted as part of a widespread maturational process driven by synaptic pruning [1, 6, 9, 60]. A delay in cortical pruning that produces an immature brain for a given age fits with a theory of delayed maturation in children with ADHD, and thus should be detectable in sleep slow-wave EEG maturation across adolescence.

The cross-sectional data on ADHD-associated differences in SWA are heterogeneous. Compared to the typically developing children, the increase of SWA in central regions and a less mature topographical distribution of SWA in children with ADHD has been found in a high-density EEG study [34]. Contrary to this finding, SWA in the first hour of NREM sleep was lower in unmedicated ADHD subjects across the whole brain in a study from the same laboratory [61]. The higher level of SWA in ADHD were not reported in other studies focused mainly on cognitive functions [35–38].

Our longitudinal data showing group differences in the age-related decline of delta and very low frequency EEG power strongly suggest a maturational delay in children with ADHD. The quadratic model for the delta power decline showed a maturational lag in the ADHD group even with sex effects accounted for. The ADHD lag for the Gompertz model was significant but the group difference dropped with sex effects accounted for ($p = 0.34$). For very low frequency EEG, the ADHD lag was significant for the Gompertz model even with sex effects accounted for ($p = 0.039$). The earlier maturation in girls adds a confound that hinder making firm conclusions regarding the slow-wave sleep EEG evidence of an ADHD-related neurodevelopmental delay in brain maturation; however, the data do suggest such a delay. The trend toward higher theta power in the ADHD group also suggest a delay. Similar to what we reported for the first two recordings, we again report a trend toward higher theta power without significant group by age interaction. A widespread increase in absolute theta activity was also observed in the ADHD group relative to the healthy control group in a recent study [62]. Since the theta power decline starts at a younger age than that for delta [7], the age range of study participants prevents us to detect the differences in age of most rapid decline for theta power. However, a later start to the theta decline would produce higher theta power across the 12–14 year age range studied here.

Altered sleep homeostasis in ADHD group

The degree to which delta and theta EEG power are concentrated in NREMP1 largely determines the rate of recovery during sleep. We found consistently lower level of standardized delta and theta power in NREMP1 in the ADHD group suggestive of altered sleep homeostatic regulation in those adolescents. Effect sizes were large for both the group by cycle interaction and the group differences in NREMP1. Similar to our findings, Miano et al. [33] reported that the SWA decrease across the night from early to late hour of NREM sleep was more evident in controls than in the ADHD group. Furrer et al. [61] also reported lower SWA across the whole brain in the first hour of sleep that most likely correspond to the NREMP1. Lower delta in NREMP1 differs from what would be expected from delayed brain maturation. A less mature brain with higher synaptic density would accumulate greater synaptic weight across a day of waking, be positioned higher on the recuperation curve, and have greater slow-wave power in NREMP1. Indeed, the proportion of delta in NREMP1 decreases across adolescence [7]. The lower delta in NREMP1 also differs from the predicted response from the shorter sleep duration that we observed in the ADHD group. Instead, significantly lower normalized delta and theta power in the NREMP1 is indicative of altered sleep homeostasis in adolescents with ADHD.

Whether altered sleep homeostasis reflects a reduced capacity or reduced need to produce high levels of slow-wave EEG during NREMP1 needs further exploration. A reduced need for recuperation would be shown in lower total delta and theta power which we did not find. We speculate that reduced capacity to produce slow-wave EEG may result from the altered white matter microstructure described in ADHD [63, 64]. Recent findings indicate that high axial diffusivity in young adults is associated with a steeper rising slope of the sleep slow-waves [65] which is a very sensitive marker of sleep homeostasis [66, 67]. Whether or not altered myelination affects the slopes of slow-waves and by this way the capacity of homeostatic recuperation in children with ADHD needs further investigation. Another possibility to explain a reduced capacity of high amplitude slow-wave EEG generation during NREMP1 in ADHD could be the altered efficacy of cortico-cortical connectivity which in turn may be associated with the maturational delay of slow oscillation found in the present study.

Data from adults indicate that homeostatic sleep pressure buildup did not differ in ADHD and control subjects [68]. To place this finding in context of our data, we may suggest that homeostatic recovery in sleep occurs more slowly in adolescents with ADHD compared to typically developing peers, with a delta debt compensated in the later cycles.

Cortical and white matter maturation reflect separate, but complimentary, neurodevelopmental processes. ADHD might be caused by abnormal persistence of too many synapses along with altered microstructural properties of white matter. We note that, at least metaphorically, perturbed axonal integrity in addition to excessive "choice points" (slow synaptic pruning) might produce the distractibility often present in this condition.

Limitations

The main limitation of the study is the small number of adolescents. However, the longitudinal design of the study increased the statistical power and detected existing differences. Although sleep disorders were screened very attentively, recordings without respiratory and leg movements channels to objectively assess sleep disordered breathing and periodic limb movements during sleep, are study limitations. Another limitation, although controlled statistically, is the different number of girls in the ADHD and control groups. A larger longitudinal study, covering a wider age range and having age and sex matched controls, is needed to firmly address sleep EEG maturational lag in ADHD and to detect critical developmental periods for intervention. Nevertheless, the longitudinal design and drug-naïve ADHD subjects are strengths of the study that provide a strong framework for studying the real maturation pattern of purely nonmedicated children diagnosed with ADHD. However, the exclusion of medicated participants may also be considered a limitation because the findings here may not be applicable to the vast majority of ADHD patients who take stimulant medication.

Conclusion

This is the first longitudinal study to reveal electrophysiological evidence of a maturational lag associated with ADHD in medication-free adolescents. Study findings on group differences in the age-related power decline of delta and very low frequency EEG strongly suggest a maturational delay in ADHD and support the idea of delayed brain maturation as the underlying cause of the disorder. Such evidence may elucidate the extent to which delayed brain maturation relate to the spectrum of neurocognitive and behavioral deficits common to ADHD and the extent to which coexisting conditions (including sleep disorders) and medications, contribute/exacerbates those deficits. This may lead to more precise diagnostic measures and effective treatment strategies.

Study results also show altered sleep homeostasis in adolescents with ADHD with a homeostatic recovery occurring more slowly which indicate that altered recuperative process is associated with the disorder. Further, our data support the preponderant evidence that basic sleep structure is unaltered with ADHD. These findings hold implications for fundamental and clinical research issues to distinguish the sleep architecture of ADHD itself from the sleep architecture associated with sleep disorders. This may affect interventions targeting sleep neurophysiology leading to the improved therapeutic options.

Finally, a broad area for further investigations are evident. As we noted in our initial report it would be interesting to determine differences in the maturational EEG trajectories between individuals with ADHD whose condition improves with age and those whose do not. Another important research area would be the investigation of the relationship between slow dynamic of across night slow-wave sleep downscaling in adolescents with ADHD and cognitive deficits seen in those adolescents.

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None declared.

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Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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