Journal of Clinical Child & Adolescent Psychology, 46(2), 188–197, 2017

ISSN: 1537-4416 print/1537-4424 online
DOI: 10.1080/15374416.2016.1157756

Stage 2 Sleep EEG Sigma Activity and Motor Learning in Childhood ADHD: A Pilot Study

Jared M. Saletin

Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University and Sleep for Science Research Laboratory, E.P. Bradley Hospital

William G. Coon

Sleep for Science Research Laboratory, E.P. Bradley Hospital and National Center for Adaptive Neurotechnologies, New York State Department of Health

Mary A. Carskadon

Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, Sleep for Science Research Laboratory, E.P. Bradley Hospital and Centre for Sleep Research, University of South Australia

Attention deficit hyperactivity disorder (ADHD) is associated with deficits in motor learning and sleep. In healthy adults, overnight improvements in motor skills are associated with sleep spindle activity in the sleep electroencephalogram (EEG). This association is poorly characterized in children, particularly in pediatric ADHD. Polysomnographic sleep was monitored in 7 children with ADHD and 14 typically developing controls. All children were trained on a validated motor sequence task (MST) in the evening with retesting the following morning. Analyses focused on MST precision (speed–accuracy trade-off). NREM Stage 2 sleep EEG power spectral analyses focused on spindle-frequency EEG activity in the sigma (12–15 Hz) band. The ADHD group demonstrated a selective decrease in power within the sigma band. Evening MST precision was lower in ADHD, yet no difference in performance was observed following sleep. Moreover, ADHD status moderated the association between slow sleep spindle activity (12–13.5 Hz) and overnight improvement; spindle-frequency EEG activity was positively associated with performance improvements in children with ADHD but not in controls. These data highlight the importance of sleep in supporting next-day behavior in ADHD while indicating that differences in sleep neurophysiology may contribute to deficits in this population.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is associated with simultaneous deficits in daytime learning (Adi-Japha, Fox, & Karni, 2011) and nocturnal sleep (Owens et al., 2013). Whereas sleep supports learning in adults, particularly for motor skills (Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002), this association is less well understood in adolescents, particularly for those with ADHD. This pilot study examines whether distinct profiles of sleep-dependent learning are observed in ADHD and in typically developing children.

The current study focused on a procedural memory paradigm known to demonstrate sleep-dependent improvement in adults. Whereas sleep deprivation impairs overnight improvement in motor skill learning (Fischer, Hallschmid, Elsner, & Born, 2002), both nocturnal sleep (Walker et al., 2002) and daytime naps (Nishida & Walker, 2007) consolidate and stabilize performance. A neural marker of sleep-related overnight improvement is

Correspondence should be addressed to Jared M. Saletin, Sleep for Science Research Laboratory, 300 Duncan Drive, Providence, RI 02906. E-mail: jared_saletin@brown.edu
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/hcap.

found in the non-rapid eye movement Stage 2 Sleep Electroencephalogram (EEG): the thalamocortical sleep spindle (a synchronous burst in the 12–15 Hz range; Nishida & Walker, 2007). Sleep-spindle-frequency EEG activity in the sigma band (12–15 Hz) over motor cortex predicts overnight gains in motor learning in healthy adults, and indexes the degree of motor skill learning deficits in circumstances such as schizophrenia (Wamsley et al., 2013).

Although one recent study examined sleep-dependent procedural motor skill learning in pediatric ADHD (Prehn-Kristensen et al., 2011), the authors did not perform spectral analysis of the sleep EEG. Indeed, whether sleep spindles are atypical in children with ADHD is unclear. When compared to traditional polysomnography, relatively little is known about the microfeatures of the sleep EEG in this population. Whereas one recent study identified lower slow wave activity and higher spindle-frequency sigma activity in ADHD (Prehn-Kristensen et al., 2013), another group demonstrated a converse increase in slow wave activity over central cortices (Ringli et al., 2013). Neither of these studies involved a motor-learning paradigm. Thus, the current pilot study aimed to add to this growing literature, while testing the hypothesis that overnight motor learning ability in ADHD may be sensitive to spindle-frequency EEG activity expressed during sleep.

MATERIALS AND METHODS

The local Institutional Review Board approved the study. Informed consent was obtained from all parents, with assent from all children. Each child received monetary compensation for participating in the study.

Participants

Twenty-six children (10–12.9 years of age) entered the study. Five children were excluded from analysis for technical issues ($n = 2$) or attrition ($n = 3$), yielding a final sample of seven children with ADHD and 14 typically developing controls (TDC). The sample was primarily male yet was balanced for gender, with two girls in the ADHD group and four girls in the TDC group. Complete demographics are reported in Table 1.

A brief parental telephone interview screened for current past medical/psychiatric conditions, family history of medical/psychiatric conditions, current use of psychoactive agents, and abnormal sleep habits. Diagnosis of ADHD was confirmed using the "ADHD" and "other DSM-IV Diagnostic Categories" of the Diagnostic Interview Schedule for Children, Fourth Edition (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000; Table 1). Exclusion criteria included parental or child report of irregular sleep patterns (e.g., self-reported sleep schedules that

TABLE 1
Demographic Variables

	ADHD[a]	*Controls*[b]	*p*
Gender (No. of Girls)	2	4	1.000
Age (Years)	11.9 ± 0.9	11.7 ± 0.9	.62
DISC-IV			
ADHD Symptoms	11.3 ± 3.4	0.86 ± 1.2	< .001
Behavioral Impairments	6.6 ± 1.9	0.00 ± 0.0	< .001
Symptoms + Impairments	17.9 ± 4.1	0.86 ± 1.2	< .001
BDI			
Raw Score	5.1 ± 4.0	5.00 ± 4.0	.94
T-Score	39.2 ± 4.3	39.15 ± 4.2	.95
WRAML-2			
Verbal Memory	112.3 ± 9.8	116.21 ± 10.5	.42
Visual	98.7 ± 15.1	97.64 ± 11.5	.86
Screening Memory	106.9 ± 11.3	108.86 ± 11.3	.71
KBIT-2			
Verbal	111.6 ± 13.3	119.21 ± 10.6	.17
Nonverbal	105.9 ± 13.3	115.05 ± 9.3	.079
IQ	110.3 ± 14.1	120.07 ± 9.4	.072
WRAT4			
Word Reading	99.2 ± 15.2	115.21 ± 15.9	.067
Spelling	107.0 ± 12.7	116.29 ± 16.3	.31
Math Computation	101.8 ± 18.4	120.20 ± 11.6	.018

Note. Data reported as $M \pm SD$. Significance from two-tailed chi-square tests, or independent samples t–tests as appropriate. DISC-IV = Diagnostic Interview Schedule for Children Version IV; WRAML-2 = Wide Range Assessment of Memory and Learning, Second Edition; KBIT-2 = Kaufman Brief Intelligence Test, Second Edition; WRAT4 = Wide Range Achievement Test 4.

[a]$n = 7$.

[b]$n = 14$.

vary by greater than 3 hours across a week, self-reported excessive daytime sleepiness, frequent napping [≥ three times/week], a morningness/eveningness score [Smith, Reilly, & Midkiff, 1989] of greater than 2 standard deviations above or below the mean values of subjects in the same grade [age] and of the same sex, based on our laboratory normative data pool); travel beyond two time zones within 2 months of the study; and diagnosis of a learning disability, mental retardation, dyslexia, pervasive developmental disorder; and a personal and/or family history of narcolepsy.

Neuropsychological assessment characterized children on intelligence/achievement, attention/impulse control, learning/memory, response speed/productivity, and problem solving/cognitive control. Trained staff administered the Kaufman Brief Intelligence Test, Second Edition (Kaufman & Kaufman, 2004), the Wide Range Assessment of Memory and Learning, Second Edition (Sheslow & Adams, 2003), and the Wide Range Achievement Test, Fourth Edition (Wilkinson & Robertson, 2006). Both groups were in normative ranges (Table 1), although TDC children had higher math computation scores compared to ADHD peers ($p = .018$).

PROCEDURES

At-Home Protocol

Participants were monitored by wrist actigraphy (Sadeh, Sharkey, & Carskadon, 1994) and completed a sleep-wake diary for 1 week before and throughout the study. During this time participants were asked to maintain a 10-hr sleep schedule set to habitual rise time (call-ins to a laboratory answering machine ensured compliance) to ensure stable sleep patterns prior to the start of the study for all children. Participants abstained from caffeine 12 hr before bedtime for the entire course of the study. Those in the ADHD group were withdrawn from psychostimulants for 2 weeks before and throughout the in-lab study.

In-Lab Protocol

Participants spent 2 consecutive nights in the laboratory on the same schedule as at home: (a) an adaptation night to acclimate to the laboratory and screen for sleep-disordered breathing; (b) the primary experimental night. On the adaptation night participants arrived approximately 3.5 hr before scheduled bedtime and were monitored overnight using polysomnography (see next). Participants returned the next evening, were provided dinner, and again prepared for polysomnography. Approximately 80 min before bedtime, each participant began a cognitive test battery including a declarative memory assessment (Ellenbogen, Hulbert, Stickgold, Dinges, & Thompson-Schill, 2006) (declarative memory performance not examined in the current report), followed by the Motor Sequence Task (MST) (Nishida & Walker, 2007; Walker et al., 2002; Walker et al., 2003), described in detail next. MST training occurred approximately 60 min before bed; morning testing on the MST began after breakfast, approximately 75 min after waking.

Motor Sequence Task

To assess procedural skill learning, participants completed the MST (Figure 2, upper-panel), well-documented as sleep-dependent in adults (Nishida & Walker, 2007; Walker et al., 2002). The MST required participants to tap a five-element sequence (4–1–3–2–4) on the numeric keys of a computer keyboard with the fingers of their nondominant hand "as quickly and accurately as possible" for 30 s. Participants could see the sequence on the screen; however, no feedback was given with respect to accuracy. Evening training consisted of twelve 30-s trials alternating with 30-s periods of rest. Morning testing consisted of four 30-s trials, with equivalent intervening rest. "MST Precision" was calculated as the proportion of total keystrokes that were not errors. This metric represents a trade-off between speed (number of correct five-digit sequences typed) and accuracy (number of errors made). As in prior studies, evening performance was defined as the average of the final two evening trials; morning performance was defined as the average of the first two trials (Nishida & Walker, 2007; Walker et al., 2002, Walker et al., 2003; Walker & Stickgold, 2005; Walker, Stickgold, Alsop, Gaab, & Schlaug, 2005; Walker, Stickgold, Jolesz, & Yoo, 2005). A within-subject measure of overnight improvement was derived as the absolute difference between morning and evening scores.

Polysomnographic Recording

Sleep on both nights was monitored by polysomnography using a Grass Comet XL system (Astro-Med, Inc., West Warwick, RI) measuring the EEG at central and occipital derivations (C3/A2, C4/A1, O1/A2, and O2/A1), right and left electrooculogram, electromyogram, and electrocardiogram. Sleep stages were visually scored by trained technicians (blind to ADHD condition; interrater reliability ≥ 85%) in 30-s epochs from C3/A2 according to standard criteria (Rechtschaffen & Kales, 1968). Respiratory measures were applied on the adaptation night to screen for sleep-disordered breathing. An Apnea-Hypopnea Index (the number of apnea or hypopnea events per hour of sleep) was derived according to standard criteria (Iber, Ancoli-Israel, Chesson, & Quan, 2007).

Power Spectral Analysis of Sleep EEG

The current analyses focus on sleep spindle frequencies in Stage 2 sleep due to their documented role in supporting overnight MST improvement (Nishida & Walker, 2007; Walker et al., 2002). A power spectral analysis of the Stage 2 NREM sleep EEG was performed following established procedures (Kurth et al., 2010; Mander, Santhanam, Saletin, & Walker, 2011; Ringli et al., 2013; van Der Helm et al., 2011). In short, following semiautomated artifact detection fast fourier transforms on hamming-windowed 5-s segments yielded power spectral densities with 0.2 Hz resolutions. To normalize amplitude differences among individuals, the power spectrum of each channel was divided by the total integrated power (0.6–32 Hz), resulting in relative power spectral densities, which were matched with corresponding sleep stages.

Relative power was assessed for the average of the C3/A2 and C4/A1 derivations, reflecting activity over primary motor cortex, motivated by prior associations with overnight MST improvement (Nishida & Walker, 2007). Group differences in sleep EEG spectra were first examined across the entire frequency range (0.6–32 Hz), and subsequently using a priori defined bands of interest in the sigma band: slow sleep spindle activity (12–13.5 Hz) and fast sleep spindle activity (13.5–15 Hz). Although the primary focus of this analysis was placed on sleep spindle frequency activity, slow wave activity (1–4.6 Hz) was also derived as a comparison and to test prior reports of slow wave activity changes in ADHD (Ringli et al., 2013).

Statistical Analysis

Group differences in the EEG power density spectra were examined using bootstrapped independent-sample *t* tests. This method makes no assumptions regarding the distributional qualities of the EEG frequency spectrum and is described in detail elsewhere (Tarokh & Carskadon, 2010a, 2010b). In short, for each 0.2 Hz frequency bin, 5,000 random group assignments were sampled with replacement from the data, yielding a bootstrapped distribution for each group. A difference distribution, S_2-S_1 was used to test statistical significance of the actual difference between groups. If the true difference exceeded the 97.5th percentile of the bootstrapped distribution, it was considered statistically significant (equivalent to a two-tailed alpha level of .05). To limit erroneous Type 1 errors from testing many frequencies, significant frequencies not surrounded by at least two other significant frequencies were discarded.

Performance data were analyzed in StataSE 13.0 (StataCorp LP, College Station, TX) using mixed-effects models including a within-subjects factor condition (Evening/Morning) and a between-subjects factor group (ADHD/TDC). Primary focus was placed upon the interaction of group and condition: whether ADHD status moderates the impact of sleep. Exploratory simple main effects decomposed the interaction to examine (a) whether the groups differed statistically in the morning or evening conditions and (b) whether overnight changes occurred within-each group independently. Effect sizes are reported as appropriate.

Multiple regression analyses were used to test whether the relationship between prior night sleep EEG activity and overnight behavioral change differed between the ADHD and TDC groups. Each model included three parameters: Relative EEG power, Group (ADHD/TDC), and the interaction of group and EEG power: whether ADHD status moderate the relationship between sleep EEG activity and overnight learning. Simple-slopes decomposed the interaction. Robust standard errors accommodated potential effects of outliers in a heterogeneous and small sample.

RESULTS

Group Sleep Variables

Polysomnographic sleep variables are reported in Table 2. The ADHD group spent less time in bed as evident by a lower Total Dark Time (p = .025). Despite this difference, both groups demonstrated total sleep times of nearly 10 hours, indicating no major differences in sleep opportunity. A nonsignificant trend suggested fewer minutes in REM sleep in the ADHD group (p = .069); however, this trend was eliminated when expressed as a percentage of total sleep time (p = .10). No other differences in sleep were observed. No evidence for sleep-disordered breathing was observed in these participants; AHI was low for both the TDC (1.21 ± 0.22) and ADHD (1.41 ± 0.16) groups; further, AHI did not distinguish the groups (p = .54).

Sleep Power Spectra by Group

Stage 2 EEG analyses revealed a suppression of power in the spindle-related sigma band (12.4–16.4 Hz) in ADHD relative to TDC (Figure 1, bootstrapped ps < .05). Although theta activity (~4–8 Hz) was marginally higher in ADHD, this difference was not statistically significant. No other significant differences in the power spectra occurred between the ADHD and TDC groups. These results were confirmed by examining a priori bands of interest. Slow wave activity did not differentiate groups, $t(19) = –0.01$, $p = .99$, $d = –0.0048$, whereas the ADHD group expressed lower power in the slow, $t(19) = –2.48$, $p = .023$, $d = –1.15$, and fast, $t(19) = –2.11$, $p = .049$, $d = –0.98$, spindle bands, with the greatest deficit observed for slow spindle activity.

MST Behavioral Performance

MST precision—representing the trade-off between speed and accuracy—improved following sleep (Figure 2), as indicated by a main-effect of condition, Wald-χ^2 = 17.56, $p < .0001$, $d = .67$. The magnitude of this overnight improvement in precision differed by ADHD status, as

TABLE 2
Polysomnographic Sleep Statistics

	ADHD[a]	*Controls*[b]	*p*
Total Dark Time (min)	590 ± 15	602 ± 9	.025
Sleep Period Time (min)	563 ± 11	579 ± 19	.051
Total Sleep Time (min)	541 ± 21	561 ± 23	.064
Sleep Efficiency (%)	96.0 ± 3.0	96.8 ± 1.7	.44
Latency to Sleep Onset (min)	18 ± 15	17 ± 10	.76
Latency to REM Sleep (min)	144 ± 64	124 ± 55	.48
Wake After Sleep Onset (min)	16 ± 16	10 ± 9	.28
Wake After Final Awakening (min)	8 ± 17	6 ± 16	.76
Wake (min)	42 ± 28	32 ± 18	.33
NREM Stage 1 (min)	35 ± 19	30 ± 9	.38
NREM Stage 2 (min)	205 ± 29	222 ± 41	.36
NREM Stage 3 (min)	74 ± 28	66 ± 22	.56
NREM Stage 4 (min)	125 ± 21	124 ± 30	.95
REM Sleep (min)	108 ± 22	119 ± 18	.069
Slow Wave Sleep (min)	199 ± 41	190 ± 40	.66
Wake (% TST)	9.0 ± 5.7	5.9 ± 3.6	.31
NREM Stage 1 (% TST)	6.5 ± 3.5	5.3 ± 1.5	.28
NREM Stage 2 (% TST)	38.1 ± 6.4	39.5 ± 6.9	.65
NREM Stage 3 (% TST)	13.5 ± 6.8	11.7 ± 3.6	.43
NREM Stage 4 (% TST)	23.2 ± 4.3	22.3 ± 5.9	.72
REM Sleep (% TST)	17.3 ± 3.7	19.8 ± 2.9	.10
Slow Wave Sleep (% TST)	36.7 ± 7.0	34.0 ± 7.3	.43
Stage 2 EEG Spectral Power			
Slow Wave Activity (% μV^2)	.57 ± .058	.57 ± .031	.99
Slow Sleep Spindle Activity (% μV^2)	.024 ± .012	.037 ± .011	.023
Fast Sleep Spindle Activity (% μV^2)	.0059 ± .0014	.011 ± .0062	.049

Note: Data reported as *M* ± *SD*. Significance from two-tailed independent-samples *t*–tests. Time in Bed = elapsed time from lights out to lights on; Sleep Period Time = elapsed time from sleep onset to final awakening; Total Sleep Time (TST) = total time scored sleep within SPT; Sleep Efficiency = (TST/SPT) × 100; Slow Wave Sleep = Stages 3 + 4 collapsed. EEG = electroencephalogram.

[a]n = 7.

[b]n = 14.

shown by an interaction of group and condition, Wald-χ^2 = 6.08, p = .014, d = 1.14. Specifically, MST precision improved overnight for the ADHD group, Wald-χ^2 = 16.61, p < .0001, d = 1.33, but not for TDCs, Wald-χ^2 = 2.23, p = .14, d = .079. As a result, despite the ADHD group having impaired MST precision in the evening vis-à-vis TDC, Wald-χ^2 = 3.90, p = .048, d = 1.33, this effect was ameliorated in the morning: simple effect, Wald-χ^2 = 0.02, p = .88, d = .34.

Sleep–Behavior Relationships

We next examined whether the group differences in slow and fast spindle-frequency activity accounted for differential overnight improvement in MST precision in ADHD; these results are illustrated in Figure 3. ADHD status significantly moderated the association between slow spindle EEG frequency activity and overnight improvement in MST precision (β = −8.22, p = .023). Specifically, MST precision was positively associated with slow spindle activity for the ADHD group (β = 8.71, p = .003), but not for TDCs (β = .50, p = .82). Despite having lower slow spindle activity, children with ADHD appear more sensitive than TDCs to the cognitive benefits it supports. These associations were not mirrored for fast spindle activity (ps > .05). In light of the potential (albeit not statistically significant) group difference in IQ (ADHD group: 110.3 ± 14.1; TDCs: 120.07 ± 9.4), we repeated this analysis with IQ included as a covariate in the model. Despite controlling for IQ, we confirmed the moderating effect of ADHD status on the association between slow sleep spindle activity and overnight gains in MST precision (β = –8.72, p = .026); thus, a significant effect remained in the ADHD group with no effect for the TDC group (β = .435, p = .85).

DISCUSSION

These initial findings provide a series of novel insights. First, despite no differences in sleep structure, sleep spindle EEG activity appears attenuated in 10- to 13-year-old children with ADHD. Second, despite deficits in motor skill precision present in children with ADHD prior to sleep (Adi-Japha et al., 2011), no group difference was observed

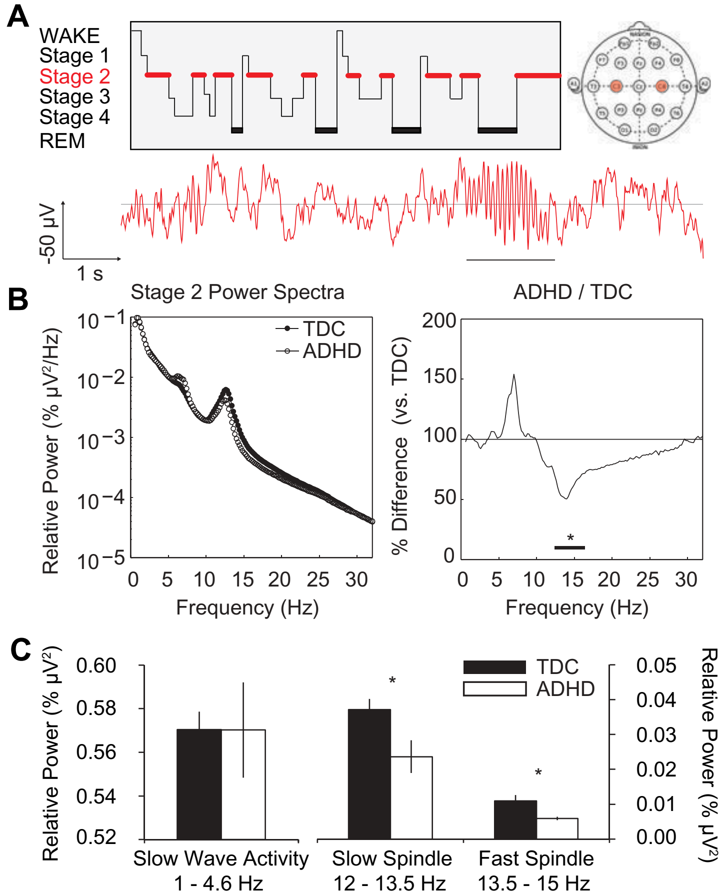

FIGURE 1 All-night NREM Stage 2 power spectra. (**A**) *Top-Left*: A schematic "hypnogram" (adapted, with permission, from Abel, Havekes, Saletin, & Walker, 2013) demonstrating a prototypical night of sleep, as staged by polysomnography. Red highlights NREM Stage 2 sleep, from which all electroencephalogram (EEG) analyses derive. *Top-Right*: A pictorial depiction of the standard electrode placements for EEG. Power spectra are averaged for the left and right central derivations (C3 and C4, labeled in red), respectively, corresponding to primary motor cortex. *Bottom*: Representative 10 s of Stage 2 NREM EEG. Time and amplitude scale as indicated. Underlined portion highlights a prototypical sleep spindle frequency event. (**B**) *Left*: Relative EEG power during Stage 2 sleep for the typically developing controls (black circles) and attention deficit hyperactivity disorder (ADHD) group (white circles), respectively from 0.6 Hz to 32 Hz at 0.2 Hz resolution (frequency on abscissa). Each participant's power spectrum is normalized to his or her total power across this range yielding relative (%) values, plotted here on a base-10 logarithmic scale. *Right*: Stage 2 power in the ADHD group plotted as a percentage of the typically developing group; frequency axis as before. Black bar indicates frequencies of significant difference between groups. (**C**) Integrated Stage 2 power extracted for the slow wave, slow spindle, and fast spindle bands, respectively, using a priori frequency definitions. Significance values are derived from appropriate statistics reported in the text and are indicated as $+p < .10$, $*p < .05$.

in the morning. Third, the degree of successful overnight improvement in ADHD children is associated with the magnitude of sleep spindle EEG frequency activity retained. Together these data underscore a necessity to ensure healthy sleep in this population while indicating a need for future research examining mechanisms underlying these associations.

Traditional polysomnography has yet to reveal a consistent sleep signature of ADHD (Gruber, 2009; Owens et al., 2013). Our finding of reduced spindle-frequency EEG activity adds to recent quantitative spectral analyses (Prehn-Kristensen et al., 2013; Ringli et al., 2013) which demonstrate that microfeatures of the sleep EEG may aid in distinguishing children with ADHD. One limitation of early, inconsistent reports of fewer spindles in ADHD (Khan & Rechtschaffen, 1978; Kiesow & Surwillo, 1987) is that sleep EEG sigma frequencies shift during development (Jenni & Carskadon, 2004; Kurdziel, Duclos, & Spencer, 2013) making automated spindle detection in this age range challenging. The current study examined the entire range of EEG frequencies, circumventing this limitation. Further studies will continue to elucidate how sleep EEG may differentiate children with and without ADHD.

It is intriguing that no associations emerged between overnight gains in MST precision and spindle-frequency EEG activity for the typically developing children—despite

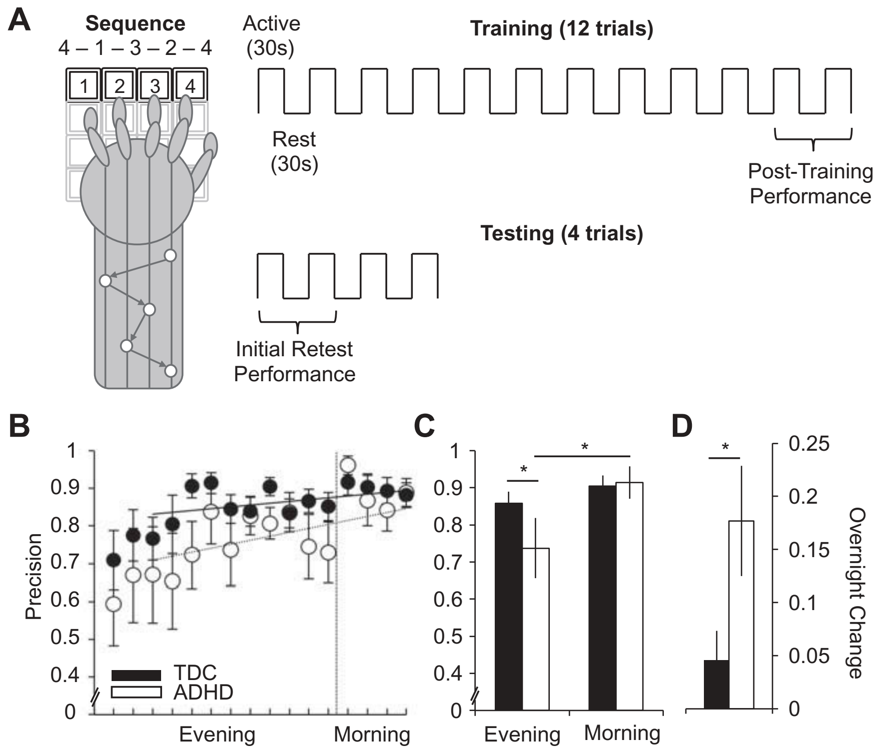

FIGURE 2 Motor Sequence Task (MST) behavior. Motor learning was measured using the Motor Sequence Task (MST). (**A**) MST protocol: Evening training (right-top panel) consisted of 12 rounds of 30-s trials of repeatedly tapping the motor sequence "4–1–3–2–4" on the numeric keys of the keyboard with the nondominant hand (schematic shown in left panel), alternating with 30-s bouts of rest. Morning testing consisted of four rounds of tapping and rest, as before. Evening performance was quantified as the average of the final two training trials, and morning performance as the average of the first two testing trials. MST schematic adapted and redrawn from Walker et al. (2003). (**B**) MST precision is reported trial-by-trial (left panel) and using evening and morning summary scores (right panel) for the typically developing controls (TDC; black-fill) and attention deficit hyperactivity disorder (ADHD; white-fill) groups, respectively. Lines of best fit for ADHD (dotted) and TDC (solid) are fit to the final 10 trials of training, and project forward to predict morning precision gains based on practice alone. (**C-D**) Histograms plotting evening and morning summary scores for each group (**C**), and within-subject overnight change scores (**D**). All error bars indicate standard error of the mean. Significance values are derived from appropriate statistics reported in the text and are indicated as $+p < .10$, $*p <$ x.05.

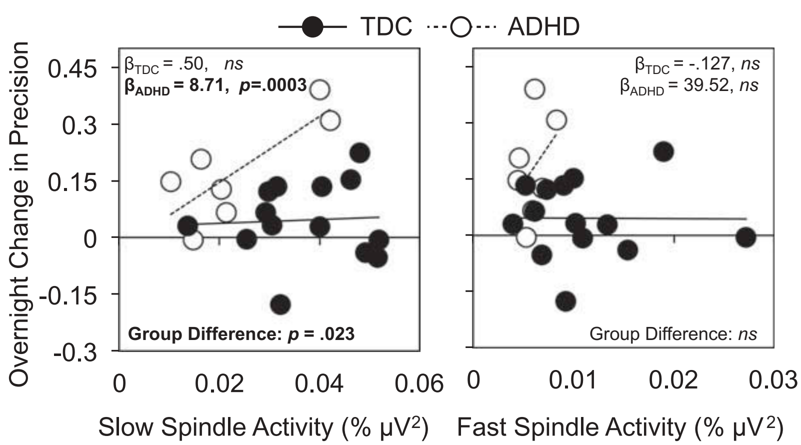

FIGURE 3 Association between electroencephalogram (EEG) spindle activity and overnight precision gains. Scatterplots of the association between individual levels of slow (12–13.5 Hz; left) and fast (13.5–15 Hz; right) spindle activity during NREM Stage 2 sleep and overnight change in Motor Sequence Task (MST) precision (proportion of keystrokes not associated with errors). Lines of best fit for the typically developing controls (TDC) group (black circles) are plotted as solid lines with those for the attention deficit hyperactivity disorder (ADHD) group (white circles) plotted as dotted lines. Groupwise simple slopes and the difference between these slopes are extracted from the regression models reported in the text; *ns* = $p > .05$.

spindle-dependent effects in healthy adults (Nishida & Walker, 2007; Wamsley et al., 2013)—consistent with other sleep-dependent memory studies in children (Wilhelm, Diekelmann, & Born, 2008). Despite this null finding in typically developing children, those with ADHD demonstrated an adultlike relationship despite an overall decrease in sleep spindle activity. Thus, the success of spindle production may be functionally protective in children with ADHD, as those with higher (more TDC-like) spindle activity benefited by exhibiting a concomitantly higher improvement in MST precision the next day. Conversely, those with a greater spindle deficit demonstrated lower overnight improvement in MST precision. The magnitude of the spindle activity deficit in a child with ADHD may therefore provide an index of their behavioral deficits while also providing a mechanistic target within sleep for intervention. For example, noninvasive stimulation of the brain using techniques such as transcranial direct current stimulation (Prehn-Kristensen et al., 2014) or sensorimotor rhythm neurofeedback (Hoedlmoser et al., 2008) can manipulate sleep EEG in a nonpharmacological manner, potentiating slow wave as well as sleep spindle frequency activity above baseline levels. These studies have demonstrated benefits in declarative memory from this modulation of the sleep EEG; however, they have not yet been extended to the motor learning domain described here.

This study is not without limitations. First, as the adaptation night may include EEG-altering first-night effects (Agnew, Webb, & Williams, 1966), the current study cannot preclude the possibility that the differences in sleep EEG reported reflect not a stable difference in ADHD but rather a difference in learning-dependent changes in EEG (Huber, Ghilardi, Massimini, & Tononi, 2004). Second, the current sample was unable to dissociate between symptom presentations of ADHD. To do so will require sample sizes greater than those here or elsewhere (Prehn-Kristensen et al., 2011; Prehn-Kristensen et al., 2014). In the context of the small sample size of the current study, we note that the strength of the effects reported (e.g., $d = 1.14$ with respect to the group difference in overnight performance gains) indicate a potentially powerful difference in sleep-dependent cognition in ADHD, meriting a more robust sample. Specifically, a large within-group effect of sleep was observed in the ADHD group ($d = 1.33$), yet a small effect was observed for TDCs ($d = 0.079$). Third, our subjects were recruited to be free of disordered sleep. Thus, the current study cannot address how sleep disorders in ADHD (e.g., sleep disordered breathing; Sedky, Bennett, & Carvalho, 2014) or atypical Cyclic Alternating Pattern (Akinci et al., 2015)) may impact overnight improvements in motor learning. Fourth, the current study does not replicate a group difference in slow wave activity (Ringli et al., 2013). The lack of frontal EEG derivations limits our present ability to address whether a stable slow wave activity difference is present in ADHD. Slow wave activity transitions from posterior dominance to anterior dominance during adolescence (Kurth et al., 2012); thus, future studies employing denser EEG montages will be necessary to more adequately address this issue. Finally, the current participants were withdrawn from psychostimulants throughout the protocol, limiting the ecological validity of our participants' sleep. Stimulants prescribed for ADHD (e.g., dextroamphetamine) may disrupt sleep (Andersen et al., 2009), although the nature of this disruption, particularly with respect to the frequencies described here, is unclear (Surman & Roth, 2011). More generally, the potential interaction of ADHD medications and sleep in mitigating behavioral deficits in ADHD warrants further examination.

In conclusion, although sleep disturbance is a common complaint in childhood ADHD, traditional polysomnography has been inconclusive in identifying a neurophysiological signature in sleep that indexes cognitive and behavioral deficits. These data join with other recent reports to indicate that microstructural properties of the sleep EEG not commonly examined in a clinical study—here, sleep spindle frequency activity—may, in part, regulate next-day behavioral function in ADHD. Future clinical and basic studies will elucidate the extent to which these sleep EEG oscillations relate to the broader spectrum of symptoms common to ADHD, and, furthermore, whether interventions targeting such sleep neurophysiology may therapeutically aid in the treatment of this and other neurodevelopmental disorders.

ACKNOWLEDGMENTS

We thank Robert Daly of the Periodic Breathing Foundation, as well as Drs. Jeffrey Ellenbogen, Robert Stickgold, and Robert Thomas for their guidance in study design; Drs. Tifenn Raffray, Eliza Van Reen, Bryce Mander, and Matthew Walker for thoughtful discussions in preparation of this manuscript; and laboratory staff—particularly Henry Arantes, Dave Bushnell, Jennifer King, Denise Maceroni, and Erin McInrue—for assistance in collecting the data. We finally offer thanks to the participants in this study and their families for the contribution of their time and effort.

FUNDING

This work was funded by support from the Periodic Breathing Foundation (to MAC), the Johns Hopkins Second Decade Society (to JMS) and NIMH T32MH019927 (to JMS).

ORCID

Jared M. Saletin http://orcid.org/0000-0002-8547-0161
William G. Coon http://orcid.org/0000-0002-2008-8041

REFERENCES

Abel, T., Havekes, R., Saletin, J. M., & Walker, M. P. (2013). Sleep, plasticity and memory from molecules to whole-brain networks. *Current Biology*, *23*(17), R774–788. doi:10.1016/j.cub.2013.07.025

Adi-Japha, E., Fox, O., & Karni, A. (2011). Atypical acquisition and atypical expression of memory consolidation gains in a motor skill in young female adults with ADHD. *Research in Developmental Disabilities*, *32*(3), 1011–1020. doi:10.1016/j.ridd.2011.01.048

Agnew, H. W., Jr., Webb, W. B., & Williams, R. L. (1966). The first night effect: An EEG study of sleep. *Psychophysiology*, *2*(3), 263–266. doi:10.1111/psyp.1966.2.issue-3

Akinci, G., Oztura, I., Hiz, S., Akdogan, O., Karaarslan, D., Ozek, H., & Akay, A. (2015). Sleep structure in children with Attention-Deficit/Hyperactivity disorder. *Journal of Child Neurology*, *30*(11), 1520–1525. doi:10.1177/0883073815573318

Andersen, M. L., Margis, R., Frey, B. N., Giglio, L. M., Kapczinski, F., & Tufik, S. (2009). Electrophysiological correlates of sleep disturbance induced by acute and chronic administration of D-amphetamine. *Brain Research*, *1249*, 162–172. doi:10.1016/j.brainres.2008.10.023

Ellenbogen, J. M., Hulbert, J. C., Stickgold, R., Dinges, D. F., & Thompson-Schill, S. L. (2006). Interfering with theories of sleep and memory: Sleep, declarative memory, and associative interference. *Current Biology*, *16*(13), 1290–1294. doi:10.1016/j.cub.2006.05.024

Fischer, S., Hallschmid, M., Elsner, A. L., & Born, J. (2002). Sleep forms memory for finger skills. *Proceedings of the National Academy of Sciences*, *99*(18), 11987–11991. doi:10.1073/pnas.182178199

Gruber, R. (2009). Sleep characteristics of children and adolescents with attention deficit-hyperactivity disorder. *Child and Adolescent Psychiatric Clinics of North America*, *18*(4), 863–876. doi:10.1016/j.chc.2009.04.011

Hoedlmoser, K., Pecherstorfer, T., Gruber, G., Anderer, P., Doppelmayr, M., Klimesch, W., & Schabus, M. (2008). Instrumental conditioning of human sensorimotor rhythm (12-15 Hz) and its impact on sleep as well as declarative learning. *Sleep*, *31*(10), 1401–1408.

Huber, R., Ghilardi, M. F., Massimini, M., & Tononi, G. (2004). Local sleep and learning. *Nature*, *430*(6995), 78–81. doi:10.1038/nature02663

Iber, C., Ancoli-Israel, S., Chesson, A., & Quan, S. (Eds.). (2007). *The AASM manual for the scoring of sleep and associated events: Rules, terminology, and technical specification* (1st ed.). Westchester, IL: American Academy of Sleep Medicine.

Jenni, O. G., & Carskadon, M. A. (2004). Spectral analysis of the sleep electroencephalogram during adolescence. *Sleep*, *27*(4), 774–783.

Kaufman, A. S., & Kaufman, N. L. (2004). *Kaufman Brief Intelligence Test* (2nd ed.). Bloomington, MN: Pearson.

Khan, A., & Rechtschaffen, A. (1978). Sleep patterns and sleep spindles in hyperkinetic children. *Sleep Research*, *7*, 137.

Kiesow, N. A., & Surwillo, W. W. (1987). Sleep spindles in the EEGs of hyperactive children. *Psychological Reports*, *60*(1), 139–144. doi:10.2466/pr0.1987.60.1.139

Kurdziel, L., Duclos, K., & Spencer, R. M. (2013). Sleep spindles in midday naps enhance learning in preschool children. *Proceedings of the National Academy of Sciences*, *110*(43), 17267–17272. doi:10.1073/pnas.1306418110

Kurth, S., Jenni, O. G., Riedner, B. A., Tononi, G., Carskadon, M. A., & Huber, R. (2010). Characteristics of sleep slow waves in children and adolescents. *Sleep*, *33*(4), 475–480.

Kurth, S., Ringli, M., Lebourgeois, M. K., Geiger, A., Buchmann, A., Jenni, O. G., & Huber, R. (2012). Mapping the electrophysiological marker of sleep depth reveals skill maturation in children and adolescents. *Neuroimage*, *63*(2), 959–965. doi:10.1016/j.neuroimage.2012.03.053

Mander, B. A., Santhanam, S., Saletin, J. M., & Walker, M. P. (2011). Wake deterioration and sleep restoration of human learning. *Current Biology*, *21*(5), R183–184. doi:10.1016/j.cub.2011.01.019

Nishida, M., & Walker, M. P. (2007). Daytime naps, motor memory consolidation and regionally specific sleep spindles. *PLoS One*, *2*(4), e341. doi:10.1371/journal.pone.0000341

Owens, J., Gruber, R., Brown, T., Corkum, P., Cortese, S., O'Brien, L. … Weiss, M. (2013). Future research directions in sleep and ADHD: Report of a consensus working group. *Journal of Attention Disorders*, *17*(7), 550–564. doi:10.1177/1087054712457992

Prehn-Kristensen, A., Molzow, I., Munz, M., Wilhelm, I., Muller, K., Freytag, D. … Baving, L. (2011). Sleep restores daytime deficits in procedural memory in children with attention-deficit/hyperactivity disorder. *Research in Developmental Disabilities*, *32*(6), 2480–2488. doi:10.1016/j.ridd.2011.06.021

Prehn-Kristensen, A., Munz, M., Goder, R., Wilhelm, I., Korr, K., Vahl, W., & Baving, L. (2014). Transcranial oscillatory direct current stimulation during sleep improves declarative memory consolidation in children with attention-deficit/hyperactivity disorder to a level comparable to healthy controls. *Brain Stimulation*, *7*(6), 793–799. doi:10.1016/j.brs.2014.07.036

Prehn-Kristensen, A., Munz, M., Molzow, I., Wilhelm, I., Wiesner, C. D., & Baving, L. (2013). Sleep promotes consolidation of emotional memory in healthy children but not in children with attention-deficit hyperactivity disorder. *PLoS One*, *8*(5), e65098. doi:10.1371/journal.pone.0065098

Rechtschaffen, A., & Kales, A. (Eds.). (1968). *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects*. Los Angeles: Brain Information Service/Brain Research Institute, University of California.

Ringli, M., Souissi, S., Kurth, S., Brandeis, D., Jenni, O. G., & Huber, R. (2013). Topography of sleep slow wave activity in children with attention-deficit/hyperactivity disorder. *Cortex*, *49*(1), 340–347. doi:10.1016/j.cortex.2012.07.007

Sadeh, A., Sharkey, K. M., & Carskadon, M. A. (1994). Activity-based sleep-wake identification: An empirical test of methodological issues. *Sleep*, *17*(3), 201–207.

Sedky, K., Bennett, D. S., & Carvalho, K. S. (2014). Attention deficit hyperactivity disorder and sleep disordered breathing in pediatric populations: A meta-analysis. *Sleep Medicine Reviews*, *18*(4), 349–356. doi:10.1016/j.smrv.2013.12.003

Shaffer, D., Fisher, P., Lucas, C. P., Dulcan, M. K., & Schwab-Stone, M. E. (2000). NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): Description, differences from previous versions, and reliability of some common diagnoses. *Journal of the American Academy of Child & Adolescent Psychiatry*, *39*(1), 28–38. doi:10.1097/00004583-200001000-00014

Sheslow, D., & Adams, W. (2003). *Wide range assessment of memory and learning, second edition administration and technical manual*. Lutz, FL: Psychological Assessment Resources.

Smith, C. S., Reilly, C., & Midkiff, K. (1989). Evaluation of three circadian rhythm questionnaires with suggestions for an improved measure of morningness. *Journal of Applied Psychology*, *74*(5), 728–738. doi:10.1037/0021-9010.74.5.728

Surman, C. B., & Roth, T. (2011). Impact of stimulant pharmacotherapy on sleep quality: Post hoc analyses of 2 large, double-blind, randomized, placebo-controlled trials. *The Journal of Clinical Psychiatry*, *72*(7), 903–908. doi:10.4088/JCP.11m06838

Tarokh, L., & Carskadon, M. A. (2010a). Developmental changes in the human sleep EEG during early adolescence. *Sleep*, *33*(6), 801–809.

Tarokh, L., & Carskadon, M. A. (2010b). Sleep electroencephalogram in children with a parental history of alcohol abuse/dependence. *Journal of Sleep Research*, *19*(1 Pt 2), 165–174. doi:10.1111/j.1365-2869.2009.00763.x

van Der Helm, E., Yao, J., Dutt, S., Rao, V., Saletin, J. M., & Walker, M. P. (2011). REM sleep depotentiates amygdala activity to previous emotional experiences. *Current Biology*, *21*(23), 2029–2032. doi:10.1016/j.cub.2011.10.052

Walker, M. P., Brakefield, T., Morgan, A., Hobson, J. A., & Stickgold, R. (2002). Practice with sleep makes perfect: Sleep-dependent motor skill learning. *Neuron*, *35*, 205–211. doi:10.1016/S0896-6273(02)00746-8

Walker, M. P., Brakefield, T., Seidman, J., Morgan, A., Hobson, J. A., & Stickgold, R. (2003). Sleep and the time course of motor skill learning. *Learning & Memory*, *10*(4), 275–284. doi:10.1101/lm.58503

Walker, M. P., & Stickgold, R. (2005). It's practice, with sleep, that makes perfect: Implications of sleep-dependent learning and plasticity for skill performance. *Clinics in Sports Medicine*, *24*(2), 301–317, ix. doi:10.1016/j.csm.2004.11.002

Walker, M. P., Stickgold, R., Alsop, D., Gaab, N., & Schlaug, G. (2005). Sleep-dependent motor memory plasticity in the human brain. *Neuroscience*, *133*(4), 911–917. doi:10.1016/j.neuroscience.2005.04.007

Walker, M. P., Stickgold, R., Jolesz, F. A., & Yoo, S. S. (2005). The functional anatomy of sleep-dependent visual skill learning. *Cerebral Cortex*, *15*(11), 1666–1675. doi:10.1093/cercor/bhi043

Wamsley, E. J., Shinn, A. K., Tucker, M. A., Ono, K. E., McKinley, S. K., Ely, A. V., & Manoach, D. S. (2013). The effects of eszopiclone on sleep spindles and memory consolidation in schizophrenia: A randomized placebo-controlled trial. *Sleep*, *36*(9), 1369–1376. doi:10.5665/sleep.2968

Wilhelm, I., Diekelmann, S., & Born, J. (2008). Sleep in children improves memory performance on declarative but not procedural tasks. *Learning & Memory*, *15*(5), 373–377. doi:10.1101/lm.803708

Wilkinson, G. S., & Robertson, G. J. (2006). *Wide Range Achievement Test 4 professional manual*. Lutz, FL: Psychological Assessment Resources.