



## Temporal Characteristics of the Sleep EEG Power Spectrum in Critically Ill Children

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**Study Objectives:** Although empirical evidence is limited, critical illness in children is associated with disruption of the normal sleep-wake rhythm. The objective of the current study was to examine the temporal characteristics of the sleep electroencephalogram (EEG) in a sample of children with critical illness.

**Methods:** Limited montage EEG recordings were collected for at least 24 hours from 8 critically ill children on mechanical ventilation for respiratory failure in a pediatric intensive care unit (PICU) of a tertiary-care hospital. Each PICU patient was age- and gender-matched to a healthy subject from the community. Power spectral analysis with the fast Fourier transform (FFT) was used to characterize EEG spectral power and categorized into 4 frequency bands:  $\delta$  (0.8 to 4.0 Hz),  $\theta$  (4.1 to 8.0 Hz),  $\alpha$  (8.1 to 13.0 Hz), and  $\beta_1/\beta_2$  (13.1 to 20.0 Hz).

**Results:** PICU patients did not manifest the ultradian variability in EEG power spectra including the typical increase in  $\delta$ -power during the first third of the night that was observed

in healthy children. Differences noted included significantly lower mean nighttime  $\delta$  and  $\theta$  power in the PICU patients compared to healthy children ( $p < 0.001$ ). Moreover, in the PICU patients, mean  $\delta$  and  $\theta$  power were higher during daytime hours than nighttime hours ( $p < 0.001$ ).

**Conclusions:** The results presented herein challenge the assumption that children experience restorative sleep during critical illness, highlighting the need for interventional studies to determine whether sleep promotion improves outcomes in critically ill children undergoing active neurocognitive development.

**Keywords:** sleep, critical illness, intensive care unit, mechanical ventilation, children, pediatric critical care, sedation, circadian rhythm, electroencephalogram

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During infancy, childhood, and adolescence, the sleep experience evolves over time, reflecting ongoing neurologic maturation.<sup>1</sup> Sleep plays an integral role in homeostasis of multiple organ systems, including the respiratory, cardiac, gastrointestinal, endocrine, and neurologic systems. Critically ill children in the pediatric intensive care unit (PICU) are exposed to a multitude of risk factors for sleep disruption, during a time when the restorative benefits of sleep are of fundamental importance for neurocognitive development. In fact, a number of studies in children have shown that slow wave activity in the sleep electroencephalogram (EEG) is associated with high levels of synaptic density and activity, a vital component of neurologic maturation.<sup>2–4</sup> Critically ill children are at higher risk for altered sleep-wake homeostasis resulting from not just the underlying illness but also from exposure to the PICU environment. In addition, centrally acting medications used for sedation in critically ill children are detrimental to the biology of sleep.<sup>5–7</sup> Internationally, the most common combination of medications used for sedation of mechanically ventilated

### BRIEF SUMMARY

**Current Knowledge/Study Rationale:** Although sleep in critically ill adults has been a recent focus of clinical investigation, there is a paucity of data surrounding sleep disturbances in critically ill children who are undergoing active neurocognitive development. The primary objective of this study is to characterize the sleep EEG in previously healthy children admitted to the pediatric intensive care unit (PICU) with respiratory failure.

**Study Impact:** The results of this study challenge the common paradigm among pediatric intensivists that children are experiencing restorative, natural sleep in the PICU environment. Children in the PICU demonstrate no day-night organization of sleep, highlighting the need for ongoing research and interventions to promote sleep-wake homeostasis during critical illness in the developing brain.

children is opioid and benzodiazepine.<sup>8,9</sup> Thus, given the number of environmental and iatrogenic exposures in the PICU, the normal ultradian variability of sleep EEG activity is likely to be absent. However, empirical evidence on whether the temporal organization of sleep is indeed disrupted is lacking.

Sleep is traditionally assessed using visual inspection of the sleep EEG from polysomnography (PSG).<sup>10,11</sup> Although conventional sleep staging is clinically useful for assessing sleep architecture, its use in characterizing sleep of patients admitted to the ICU is of limited value.<sup>12,13</sup> The EEG of a critically ill child is confounded by the derangements induced by the critical illness and by the central effects of various medications that are typically administered for sedation. Furthermore, neuromuscular blockade limits the use of PSG, as muscle activity is pharmacologically inhibited. Children add an additional layer of variability in normative sleep depending on age. Given these factors, alternative methods for characterizing the sleep EEG in critically ill children are needed.<sup>14</sup> Additionally, sleep may occur any time during the day or night while in the PICU; therefore, assessment of a 24-hour period is necessary to capture the temporal characteristics of sleep in these patients. The objective of the current study was to characterize the sleep EEG in a sample of critically ill children without baseline neurologic disease. It was hypothesized that critically ill children will not demonstrate day-night organization of sleep and will lack the normal characteristics of the sleep EEG that are typical in healthy children.

## METHODS

### Study Sample

Children with respiratory failure requiring mechanical ventilation were recruited from the PICU of the Johns Hopkins Children's Center. Each bed in the PICU is positioned adjacent to a window with adjustable shades. Patients were eligible for the study on the first day of mechanical ventilation if ventilator support was expected to continue for least 24 hours. Exclusion criteria included a history of sleep disordered breathing (SDB), surgery within the last 7 days, seizures, neurological injury, and severe developmental delay. To rule out SDB, a detailed history was obtained from the parent(s) including a history of snoring. In addition, the medical record was reviewed for previous sleep studies and parents were asked to complete the Children's Sleep Habits Questionnaire.<sup>15</sup> Finally, patients were excluded if it was deemed that the monitoring would interfere with medical care. Eligible patients underwent informed consent with a parent or legal guardian. To compare the data collected during critical illness, healthy age- and gender-matched children without central or obstructive sleep apnea (OSA) from the Tucson Children's Assessment of Sleep Apnea (TuCASA) study were used. The TuCASA study is a community-based study aimed at assessing the prevalence of sleep apnea in children.<sup>16</sup> OSA was defined if the respiratory disturbance index, using the 3% desaturation criteria, was  $\geq 1$  event per hour of total sleep time. Hypopneas were scored if the magnitude of any ventilation signal decreased to below approximately 70% of the baseline amplitude  $\geq 6$  s or for  $\geq 2$  consecutive breaths. The study protocol was approved by the Institutional Review Board (IRB) on human subjects research of the Johns Hopkins University School of Medicine.

### EEG Monitoring and Power Spectral Analysis

The recording montage for the PICU patients included bilateral central and occipital EEG leads sampled at 125 Hz,

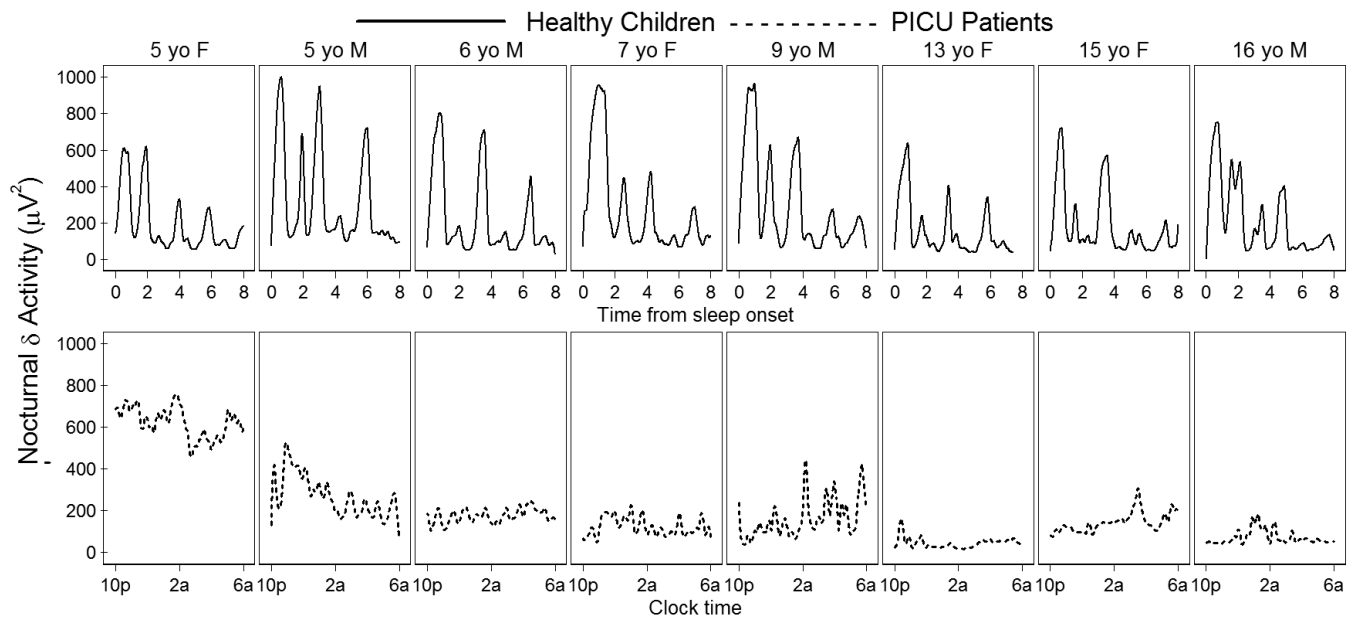
right and left-sided electrocuculograms (EOG), and submental electromyogram (EMG) using the Embla N7000 system (Embla, Denver, Colorado, USA). The montage was accompanied by high-resolution video monitoring for assessing medical interventions (e.g., suctioning, dressing changes) and occurrence of movement or activity. The recording was continued for  $\geq 24$  h and discontinued when the patient was extubated or at 72 h after the initiation of data collection. Home nocturnal PSG for the healthy children in the TuCASA sample included central leads as well as bilateral EOG leads and chin EMG. Detailed methodology for the TuCASA cohort has been previously described.<sup>17</sup> Power spectral analysis of EEG recordings from the PICU and age- and gender-matched subjects was conducted using the fast Fourier transform (FFT) in Matlab (Ver. R2014A, Matlab, Inc.). The FFT was conducted on an EEG record length of 5 s to obtain a frequency resolution of 0.2 Hz. The power content (expressed as  $\mu\text{V}^2$ ) for each 30-s epoch of sleep was determined as the average power across the six 5-s segments of the EEG. The resulting spectral distribution from the FFT was categorized into the following frequency bands:  $\delta$  (0.8 to 4.0 Hz);  $\theta$  (4.1 to 8.0 Hz);  $\alpha$  (8.1 to 13.0 Hz);  $\beta_1$  (13.1 to 16.0 Hz); and  $\beta_2$  (16.1 to 20.0 Hz). The power in each frequency bandwidth was expressed as absolute power in each 30-s epoch of sleep. Frequencies  $< 0.8$  Hz were excluded to remove the effects of low-frequency artifacts (e.g., sweating and respiration).

### Statistical Analysis

Data are summarized as means  $\pm$  standard deviation or medians (interquartile range) as appropriate. Differences in mean nocturnal EEG power between the PICU patients and matched healthy children were tested using the Wilcoxon signed-rank test given the small sample size and skewed distribution of EEG spectral power. Matching was performed using the cmatch command in Stata 12 (Statacorp; College Station, TX). The nocturnal period was defined as the time from sleep onset for healthy children, and the hours of 22:00–06:00 for the PICU patients. Given well-established temporal patterns in the EEG spectra during the night in healthy children, analyses were also undertaken to characterize temporal patterns of EEG spectral power for each frequency band using a locally weighted scatterplot smoothing (LOWESS) spline technique for both the PICU patients and healthy children. The LOWESS method depicts the association between 2 variables (i.e., EEG  $\delta$  power activity vs. time) using a smoothing coefficient to provide a robust fit to the data without eliminating changes in slope over time. Statistical tests were 2-sided, and a p value less than 0.05 was defined as statistically significant. All calculations were performed in Stata 12 (StatacorpLP; College Station, TX).

## RESULTS

Eight critically ill PICU patients with respiratory failure (median age 8 years, range 6–16 years) underwent limited montage EEG monitoring. Each patient was receiving a continuous background infusion of both opioid and benzodiazepine at the time of enrollment and monitoring, with a goal State Behavioral Score between  $-1$  and  $1$ .<sup>18</sup> Demographic data and diagnoses for the study sample are shown in **Table 1**. Two of the 8

**Figure 1**—Nocturnal EEG  $\delta$  power in PICU patients and age and gender-matched healthy children.

Values plotted were derived using a Lowess smoothing function.

**Table 1**—Demographics of PICU sample.

Patient	Gender	Age	Diagnosis	Morphine Dose (mg/kg/day)*	Midazolam Dose (mg/kg/day)*
A	Female	5	Pneumonia with ARDS	2.4	0.1
B	Male	5	Pneumonia with ARDS	2.3	0.2
C	Male	6	CVID with ARDS	2.6	3.2
D	Female	7	Sepsis and ARDS	1.3	0.1
E	Male	9	HLH with ARDS	0.4	0.1
F	Female	13	MAS with ARDS	0.8	0.04
G	Female	15	Pneumonia with ARDS	3.4	0.4
H	Male	16	Sarcoma with ARDS	6.3	2.5

\*Opioid and benzodiazepine dose received during 24-h sleep EEG recording period in morphine and midazolam equivalents. ARDS, acute respiratory distress syndrome; CVID, common variable immunodeficiency; HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome.

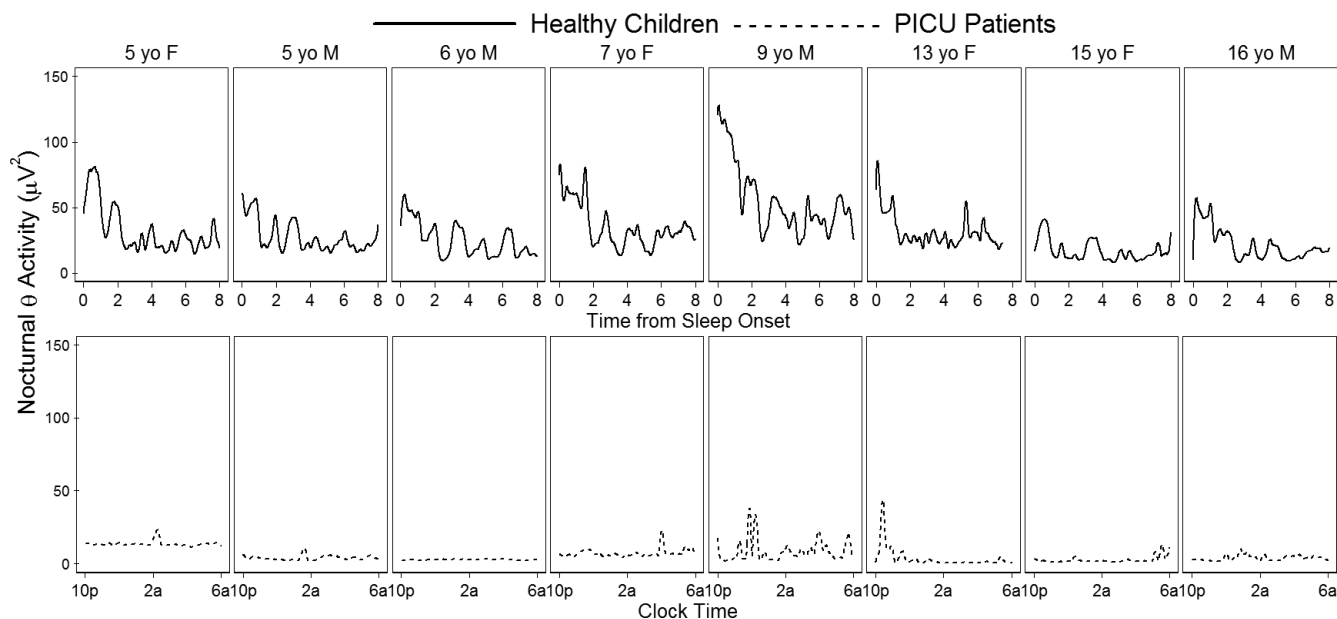
patients were receiving a low-dose infusion of one sympathomimetic agent for hemodynamic support. Patient D received dopamine at 5 mcg/kg/h while Patient F received phenylephrine at 2 mcg/kg/h during the 24-h EEG recording period. Although the full 24-h period was recorded in all patients, only 18 h were included in 2 patients due to clinical instability. However, EEG power spectral analysis included the recordings of the full nocturnal period in all patients. EEG data from the first 8 consecutive nocturnal hours (22:00–06:00) were analyzed for each PICU patient and compared to nocturnal EEG of an age- and gender-matched healthy child. The average EEG power in each of the frequency bands (i.e.,  $\delta$ ,  $\theta$ ,  $\alpha$ ,  $\beta_1$ , and  $\beta_2$ ) was lower in PICU patients than healthy patients (**Table 2**). Furthermore, unlike healthy children, PICU patients did not demonstrate the characteristic temporal EEG patterns in  $\delta$  or  $\theta$  power spectral bands during the night as evident in the healthy children. As shown in **Figure 1**, healthy children demonstrated the typical ultradian pattern in EEG activity with an increase in  $\delta$  power during NREM sleep, particularly in the first third of the night.

**Table 2**—Average EEG spectral power during nocturnal period, expressed as  $\mu\text{V}^2$  (mean  $\pm$  SD).

EEG Frequency Band	Healthy Children	PICU Patients	p value
$\delta$ (0.8–3.9 Hz)	203.1 $\pm$ 210.5	174.7 $\pm$ 201.5	< 0.001
$\theta$ (4.0–7.9 Hz)	30.7 $\pm$ 23.9	5.6 $\pm$ 13.1	< 0.001
$\alpha$ (8.0–11.9 Hz)	6.6 $\pm$ 4.9	1.6 $\pm$ 4.8	< 0.001
$\beta_1$ (12.0–15.9 Hz)	0.8 $\pm$ 1.1	0.6 $\pm$ 1.74	< 0.001
$\beta_2$ (16.0–20. Hz)	1.1 $\pm$ 2.4	1.2 $\pm$ 3.4	0.017

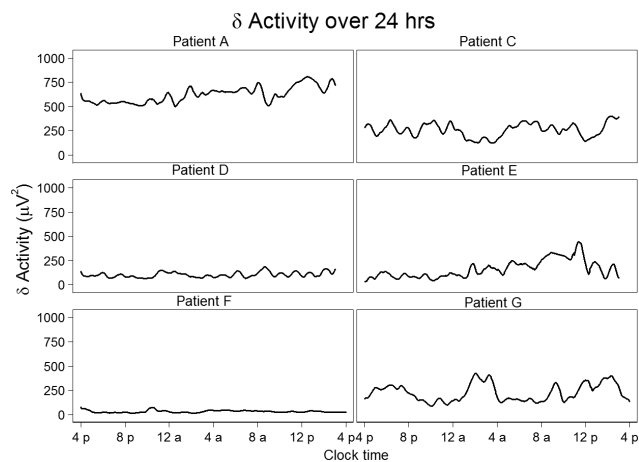
Moreover, healthy children demonstrated a decline in overall EEG  $\delta$  power over the course of the night, while PICU patients demonstrate little variability as evidenced by their flattened profiles. Subject A's profile differed from the other PICU patients in that the baseline delta activity was maintained at a high level throughout the recording period. All other patients had peaks in EEG  $\delta$  power well below 500  $\mu\text{V}^2$ .

**Figure 2**—Nocturnal EEG  $\theta$  power in PICU patients and age and gender-matched healthy children.



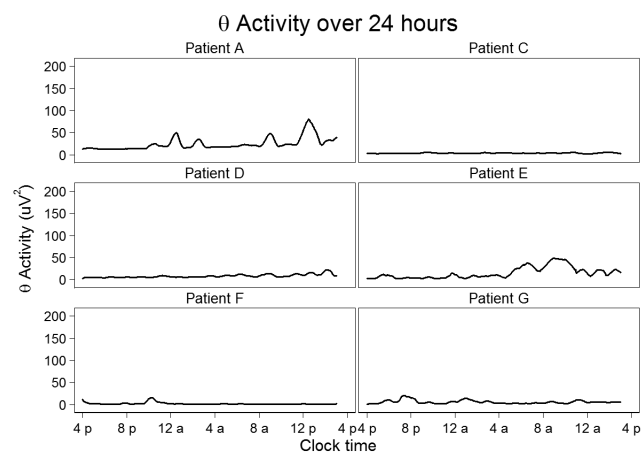
Values plotted were derived using a Lowess smoothing function.

**Figure 3**—Twenty-four-hour EEG  $\delta$  power in PICU patients.



Values plotted were derived using a Lowess smoothing function.

**Figure 4**—Twenty-four-hour EEG  $\theta$  power in PICU patients.



Values plotted were derived using a Lowess smoothing function.

Alterations in the nocturnal EEG  $\theta$  power profile (4–7 Hz) were similar to the findings for  $\delta$  power, with lack of an ultradian rhythm during the night (**Figure 2**). Healthy children demonstrated the expected temporal variability in EEG  $\theta$  power, which gradually declined in the latter part of the night. In contrast,  $\theta$  power in the EEG was at very low levels and did not display temporal variability in PICU patients. Mean absolute  $\theta$  power in the EEG in the healthy children was  $30.7 \mu\text{V}^2$ , while mean EEG  $\theta$  power in PICU patients was  $5.6 \mu\text{V}^2$  ( $p < 0.001$ ). Given that critically ill children in the PICU may experience sleep during any part of the day or night, EEG  $\delta$  and  $\theta$  power were evaluated in the 6 children with complete 24-h data. As seen in **Figure 3**, there was evidence of oscillations in EEG  $\delta$  power over the 24-h period for PICU patients,

most obvious for Patient G. In contrast, with the exception of Patients A and E, most PICU patients did not demonstrate ultradian variability in EEG  $\theta$  power (**Figure 4**). Mean EEG  $\delta$  and  $\theta$  power of PICU patients were compared between the day (07:00 through 19:00) and night (19:00 through 07:00) hours. Mean EEG  $\delta$  power was higher during the day ( $237 \pm 243 \mu\text{V}^2$ ) than night ( $211 \pm 223 \mu\text{V}^2$ ;  $p < 0.001$ ). Similarly, EEG  $\theta$  power during the day was higher than the night ( $10 \pm 31$  vs.  $8 \pm 17 \mu\text{V}^2$ ,  $p < 0.001$ ). Among PICU patients, nocturnal  $\delta$  and  $\theta$  power was not associated with cumulative nocturnal morphine ( $p = 0.4$  and  $0.5$ , respectively) or midazolam equivalents ( $p = 0.6$  and  $0.3$ , respectively). There was also no significant association among the PICU patients between cumulative 24-h morphine and midazolam equivalents and mean 24-h  $\delta$  and  $\theta$  power.

## DISCUSSION

The results of this study demonstrate that, over a 24-hour period, there are significant differences in the EEG power spectra between critically ill and healthy children. Critically ill children have no day-night organization of sleep and exhibit decreases in slow wave activity (i.e.,  $\delta$  power) during the nighttime hours when compared to healthy children. Although sleep has previously been investigated in PICU patients, available studies have relied on subjective assessment with visual scoring of the polysomnogram.<sup>5</sup> In a recent systematic review on sleep in critically ill children, nine studies were identified, with four resulting from the same randomized controlled trial. Of the studies which focused on critically ill children and utilized objective measurements of sleep, common findings included decreases in REM sleep and slow wave sleep, with evidence of frequent nocturnal arousals.<sup>19,20</sup> The findings of the current study add to the existing body of evidence by providing insights regarding the temporal trends of sleep EEG power spectral activity in critically ill children without baseline neurologic disease who are admitted with respiratory failure.

Although the true function of sleep remains elusive, a great deal is now known regarding the physiologic effects and consequences of altered sleep including effects on protein synthesis, cellular and humoral immunity, and increased catabolism.<sup>7</sup> Much research has been devoted to characterizing sleep in the adult ICU.<sup>13,14,21–23</sup> Yet, the negative impact of sleep disruption in the critically ill pediatric patient undergoing rapid advances in growth, cognition, and behavior has not been well characterized. Infancy and childhood are marked by sleep as the predominant behavioral state, and sleep structure and organization are in a constant state of change, paralleling central nervous system (CNS) growth and differentiation.<sup>24</sup> However, the ontogeny of sleep may not only be a correlate of CNS development, but a reflection of the reciprocal interactions between brain plasticity and sleep.<sup>25</sup> Indeed, natural sleep may play a dynamic role in brain development, laying the groundwork for future learning.

Healthy children demonstrate a well-characterized temporal pattern of slow wave activity (EEG  $\delta$  power) activity when asleep, with a significant concentration of  $\delta$  power in the first NREM period, which generally occurs within the first two hours after sleep onset.<sup>26</sup> Data from the age- and gender-matched healthy children in this investigation demonstrate that consistent pattern. With increasing age, EEG  $\delta$  power exhibits a steep decline across adolescence after reaching a peak in childhood, again reflecting the role of NREM sleep in brain function.<sup>27</sup> Findings from the patient sample in the current investigation show that critically ill children demonstrate major differences in nocturnal EEG patterns when compared to normal children, despite demonstrating a behavioral state (eyes closed, resting state) that is characteristic of sleep. The observed differences including the lack of day-night organization among sedated, critically ill children may, in part, be related to use of sedative medications. Pharmacologic management of sedation and analgesia for intubated children in the PICU primarily consists of opioids and benzodiazepines.<sup>8,9</sup> A recent international survey of pediatric intensivists determined that fentanyl is the most commonly used opioid and midazolam is the most commonly

used benzodiazepine. Although opioids increase total sleep time in healthy subjects, they decrease slow wave and REM sleep.<sup>7</sup> Benzodiazepines also significantly suppress slow wave and REM sleep and are known independent risk factors for the development of ICU delirium in adults.<sup>28</sup> The risks of continuous sedative and analgesic exposure are compounded by polypharmacy and environmental factors such as noise, light, and patient care interventions, leading to further negative effects on sleep architecture. Additionally, sympathomimetic medications frequently used in the critically ill setting are known to decrease both REM and slow wave sleep.<sup>7,29</sup>

Poor sleep quality is a risk factor for delirium, which can lead to a vicious cycle of increasing sedation to maintain safety and help the patient “sleep.” The results of our study challenge the general notion that children in the PICU are experiencing natural, restorative sleep.<sup>9</sup> Lack of day-night cycles in conjunction with loss of natural sleep among PICU patients is an important area for future research. Simple nonpharmacologic interventions such as earplugs and eye masks at night, consistently opening shades to achieve sunlight exposure during the day, and implementation of noise reduction protocols may go a long way to promote sleep and decrease sedation needs.<sup>9,30–32</sup> Therefore, it is essential that future studies investigating sleep in the PICU include continuous noise and light measurements. Before pharmacologic interventions such as melatonin are considered, it is imperative to further characterize dim light melatonin onset (DLMO) in critically ill children to better delineate the underlying pathophysiology of altered sleep in the PICU. Furthermore, sleep-wake problems that begin in the PICU may persist long after discharge from the PICU and hospital into the home setting, a long-term consequence that deserves further investigation as it relates to neuropsychological outcomes.

There are several limitations in the current study. First, the use of healthy children as a comparison group for patients in the PICU may not be the most suitable given that healthy children were monitored only overnight and not for the extended period as the PICU sample. The second limitation is a small sample size and all of the children in the PICU had respiratory failure. Therefore, the results of the current study may not be generalizable to pediatric patients with other causes of critical illness. The same sample size may also explain the lack of an association between  $\delta$  and  $\theta$  power with sedative medication doses among PICU patients. Third, the sample of healthy children from the TuCASA cohort likely had greater exposure to sunlight than the PICU patients, which was not measured. Fourth, differences in the platform used to record the EEG in the PICU patients (Embla) and the TuCASA cohort (Compumedics) may lead to quantitative differences in EEG power spectra between the two groups. Finally, the results presented herein need to be interpreted with the knowledge that there are unmeasurable confounders that may affect the EEG recordings, including the severity of critical illness and underlying neurobiologic activity of the patients.

In summary, critically ill children in the PICU demonstrate differences in the EEG including the lack of ultradian increase in slow wave activity during the nighttime hours. The importance of sleep during recovery from critical illness deserves continued attention, particularly for children who are undergoing active neurologic maturation when sleep plays a vital role

in normal development. Furthermore, disruption in sleep architecture has implications for how children are cared for during the most acute phase of their illness. Future research must focus on the modifiable risk factors for sleep disturbances in the critically ill child, including sedative approaches and non-pharmacologic behavioral interventions to promote natural sleep during recovery.

## REFERENCES

1. Curcio G, Ferrara M, De Gennaro L. Sleep loss, learning capacity and academic performance. *Sleep Med Rev* 2006;10:323–37.
2. Tarokh L, Van Reen E, LeBourgeois M, Seifer R, Carskadon MA. Sleep EEG provides evidence that cortical changes persist into late adolescence. *Sleep* 2011;34:1385–93.
3. Feinberg I, Campbell IG. Sleep EEG changes during adolescence: an index of a fundamental brain reorganization. *Brain Cogn* 2010;72:56–65.
4. Kurth S, Jenni OG, Riedner BA, Tononi G, Carskadon MA, Huber R. Characteristics of sleep slow waves in children and adolescents. *Sleep* 2010;33:475–80.
5. Kudchadkar SR, Aljohani OA, Punjabi NM. Sleep of critically ill children in the pediatric intensive care unit: a systematic review. *Sleep Med Rev* 2014;18:103–10.
6. Huupponen E, Maksimov A, Lapinlampi P, et al. Electroencephalogram spindle activity during dexmedetomidine sedation and physiological sleep. *Acta Anaesthesiol Scand* 2008;52:289–94.
7. Kudchadkar S, Sterni L, Yaster M, Easley RB. Sleep in the Intensive Care Unit. *Contemp Crit Care* 2009;7:1–12.
8. Curley MA, Wypij D, Watson RS, et al. Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: a randomized clinical trial. *JAMA* 2015;313:379–89.
9. Kudchadkar SR, Yaster M, Punjabi NM. Sedation, sleep promotion, and delirium screening practices in the care of mechanically ventilated children: a wake-up call for the pediatric critical care community. *Crit Care Med* 2014;42:1592–600.
10. Grigg-Damberger M, Gozal D, Marcus, et al. The visual scoring of sleep and arousal in infants and children. *J Clin Sleep Med* 2007;3:201–40.
11. Iber C, American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specifications. Westchester, IL: American Academy of Sleep Medicine, 2007.
12. Pisani MA, Friese RS, Gehlbach BK, Schwab RJ, Weinhouse GL, Jones SF. Sleep in the intensive care unit. *Am J Respir Crit Care Med* 2015;191:731–8.
13. Ambrogio C, Koebnick J, Quan SF, Ranieri M, Parthasarathy S. Assessment of sleep in ventilator-supported critically ill patients. *Sleep* 2008;31:1559–68.
14. Watson PL, Pandharipande P, Gehlbach BK, et al. Atypical sleep in ventilated patients: empirical electroencephalography findings and the path toward revised ICU sleep scoring criteria. *Crit Care Med* 2013;41:1958–67.
15. Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. *Sleep* 2000;23:1043–51.
16. Budhiraja R, Quan SF. Outcomes from the Tucson Children's Assessment of Sleep Apnea Study (TuCASA). *Sleep Med Clin* 2009;4:9–18.
17. Goodwin JL, Enright PL, Kaemingk KL, et al. Feasibility of using unattended polysomnography in children for research--report of the Tucson Children's Assessment of Sleep Apnea study (TuCASA). *Sleep* 2001;24:937–44.
18. Curley MA, Harris SK, Fraser KA, Johnson RA, Arnold JH. State Behavioral Scale: a sedation assessment instrument for infants and young children supported on mechanical ventilation. *Pediatr Crit Care Med* 2006;7:107–14.
19. Carno MA, Hoffman LA, Henker R, Carrillo J, Sanders MH. Sleep monitoring in children during neuromuscular blockade in the pediatric intensive care unit: a pilot study. *Pediatr Crit Care Med* 2004;5:224–9.
20. Al-Samsam RH, Cullen P. Sleep and adverse environmental factors in sedated mechanically ventilated pediatric intensive care patients. *Pediatr Crit Care Med* 2005;6:562–7.
21. Gehlbach BK, Chapotot F, Leproult R, et al. Temporal disorganization of circadian rhythmicity and sleep-wake regulation in mechanically ventilated patients receiving continuous intravenous sedation. *Sleep* 2012;35:1105–14.
22. Kamdar BB, Yang J, King LM, et al. Developing, implementing, and evaluating a multifaceted quality improvement intervention to promote sleep in an ICU. *Am J Med Qual* 2014;29:546–54.
23. Kamdar BB, Niessen T, Colantuoni E, et al. Delirium transitions in the medical ICU: exploring the role of sleep quality and other factors. *Crit Care Med* 2015;43:135–41.
24. Tong NK, Beran J, Kee SA, et al. Immunogenicity and safety of an adjuvanted hepatitis B vaccine in pre-hemodialysis and hemodialysis patients. *Kidney Int* 2005;68:2298–303.
25. Tarullo AR, Balsam PD, Fifer WP. Sleep and infant learning. *Infant Child Dev* 2011;20:35–46.
26. Campbell IG, Darchia N, Higgins LM, et al. Adolescent changes in homeostatic regulation of EEG activity in the delta and theta frequency bands during NREM sleep. *Sleep* 2011;34:83–91.
27. Darchia N, Campbell IG, Tan X, Feinberg I. Kinetics of NREM delta EEG power density across NREM periods depend on age and on delta-band designation. *Sleep* 2007;30:71–9.
28. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* 2006;104:21–6.
29. Bourne RS, Mills GH. Sleep disruption in critically ill patients--pharmacological considerations. *Anaesthesia* 2004;59:374–84.
30. Hu RF, Jiang XY, Zeng YM, Chen XY, Zhang YH. Effects of earplugs and eye masks on nocturnal sleep, melatonin and cortisol in a simulated intensive care unit environment. *Crit Care* 2010;14.
31. Richardson A, Allsop M, Coghill E, Turnock C. Earplugs and eye masks: do they improve critical care patients' sleep? *Nurs Crit Care* 2007;12:278–86.
32. Scotto CJ, McClusky C, Spillan S, Kimmel J. Earplugs improve patients' subjective experience of sleep in critical care. *Nurs Crit Care* 2009;14:180–84.

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## DISCLOSURE STATEMENT

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