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Title: Bedtime to the brain: How infants sleep habits intertwine with sleep neurophysiology

Authors

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1 **Abstract**

2 Adequate sleep is critical for development and facilitates the maturation of the
3 neurophysiological circuitries at the basis of cognitive and behavioral function. Observational
4 research has associated sleep problems in early life with worse later cognitive, psychosocial,
5 and somatic health outcomes. Yet, the extent to which day-to-day sleep habits in early life
6 relate to neurophysiology - acutely and long-term - remains to be explored. Here, we report
7 that sleep habits in 32 healthy 6-month-olds assessed with actimetry are linked to
8 fundamental aspects of their neurophysiology measured with high-density
9 electroencephalography (hdEEG). Our study reveals four key findings: First, daytime sleep
10 habits are linked to EEG slow wave activity (SWA). Second, habits of nighttime movement
11 and awakenings from sleep are connected with spindle density. Third, habitual sleep timing
12 is linked to neurophysiological connectivity quantified as Delta-coherence. And lastly, Delta-
13 coherence at age 6 months predicts nighttime sleep duration at age 12 months. These novel
14 findings widen our understanding that infants' sleep habits are closely intertwined with three
15 particular levels of neurophysiology: sleep pressure (determined by SWA), the maturation of
16 the thalamocortical system (spindles), and the maturation of cortical connectivity
17 (coherence). Our companion paper complements this insight in the perspective of later
18 developmental outcomes: early thalamocortical connectivity (spindle density) at age 6
19 months predicts later behavioural status at 12 and 24 months. The crucial next step is to
20 extend this concept to clinical groups to objectively characterize infants' sleep habits "at risk"
21 that foster later neurodevelopmental problems.

22

23 **Highlights**

24

- 25 ● Infant's habitual sleep behavior (actimetry) is linked with their sleep neurophysiology
26 (EEG)
- 27 ● Habits of daytime sleeping (naps) are related to slow wave activity
- 28 ● Infant's movements and awakenings at nighttime are linked to their sleep spindles
- 29 ● Sleep timing (infant's bedtimes) is associated with cortical connectivity in the EEG

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31 **Keywords:** EEG, development, infancy, slow wave activity, spindles, coherence, sensitive
32 period, sleep regulation, brain maturation

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1. Introduction

Adequate sleep is essential to human health, as it fosters optimal neuronal functioning and cognitive performance (Prince and Abel, 2013; Xie et al., 2013). Sufficient continuous sleep is furthermore crucial for neurodevelopment, as causally demonstrated in animal models (Frank et al., 2001; Shaffery et al., 2002) or correlatively reported in children (Simola et al., 2014). The behavioral state of sleep, allows for the maturation of neurophysiological circuitries, which are considered the basis for cognitive and behavioral functioning. Yet, whether day-to-day sleep habits determine the outcome of brain physiology has not been examined in early human infancy - the most vulnerable developmental period of the lifespan, which also shows the most variable sleep behavior (Iglowstein et al., 2003).

During infancy, sleep habits show the largest individual variability of the human lifetime (Iglowstein et al., 2003). Notably, in approximately 30% of infants, sleep is considered a burden (Lam et al., 2003). Observational research links early sleep behaviors to problematic later psychosocial, cognitive, and somatic outcomes (Gregory et al., 2009, 2005; Mindell et al., 2017; Simola et al., 2014). Thus, clinical reference values are essential for predicting or identifying possible sleep-related risks for subsequent mood disorders or cognitive performance issues later in life. Although neurophysiological features, *e.g.*, slow waves and spindles in the electroencephalogram (EEG), were proposed to link sleep behavior and brain functioning (Kurth et al., 2012), such systematic examination is still lacking. Particularly in the most vulnerable period for neuronal development - infancy - it remains entirely unexplored how sleep habits are intertwined with neurophysiological features.

In recent years, high-density (hd)EEG has evolved as a new powerful pediatric imaging method as it is non-invasive and provides good spatial and temporal resolution (Lustenberger and Huber, 2012). The increased use of hdEEG led to the discovery that topographical maps of sleep undergo maturation across childhood (Kurth et al., 2010). Analytical advances revealed specific sleep hdEEG features associated with aspects of neuronal function. Consequently, four features from non-rapid eye movement (NREM) sleep have proven to be of specific interest for infant research. The first core EEG feature is slow wave activity (SWA; EEG power between 0.75-4.25 Hz) which indicates the homeostatic regulation of sleep need, *i.e.*, increasing with the duration of prior wakefulness and decreasing during the time spent asleep (Achermann et al., 1993; Jenni et al., 2005). However, infant homeostatic sleep regulation remains understudied, and contradictory findings exist, *e.g.*, whether it reflects homeostatic across-night decline (Jenni et al., 2004;

1 Schechtman et al., 1994). The second core feature of infant sleep EEG is theta activity (EEG
2 power in 4.5 - 7.5 Hz), which declines in the course of the night and was therefore proposed
3 to potentially reflect the dissipation of sleep pressure (Jenni et al., 2004). However, which of
4 the two markers - SWA or theta activity - more reliably reflects sleep pressure build-up
5 across wakefulness in infants remains unknown. The third core EEG feature is spindles in
6 the sigma frequency range (11-16 Hz): waxing and waning oscillations generated by the
7 thalamocortical system that may serve a sleep-protective function by preventing waking up
8 from external perturbations during sleep (Andrillon and Kouider, 2020; Fernandez and Lüthi,
9 2020). Finally, the fourth core EEG feature in infancy is neuronal connectivity, as reflected in
10 EEG coherence. Coherence indicates cortical connectivity by quantifying the EEG
11 synchronicity between electrodes from different locations (Markovic et al., 2020; Tarokh et
12 al., 2010). Cortical connectivity assessed in sleep is a trait-like characteristic property that
13 emerges as a consequence of both internal (genetic, maturational) and external influences
14 (environmental). External influences were identified as the more substantial contributor
15 (Markovic et al., 2020), which triggers the question to what extent parents' actions, e.g.,
16 influencing infants' sleep timing, can modify cortical connectivity of infant sleep.
17 Importantly, these four core EEG features are also related to learning and plasticity
18 processes (Born and Feld, 2012; Cairney et al., 2018; Holz et al., 2012; Mölle et al., 2004;
19 Tarokh et al., 2014; Wilhelm et al., 2014). For example, SWA indicates episodic memory
20 processing in children's naps (Lokhandwala and Spencer, 2021) and increased spindle
21 content in naps related to successful learning in a generalization task (Friedrich et al., 2019).
22 Our companion paper demonstrates that sleep spindles in healthy infancy predict their later
23 developmental outcomes (Jaramillo et al., 2021). Yet, whether infants' sleep habits, *i.e.*,
24 napping behavior, bedtimes, and nighttime awakenings, connect to the four primary sleep
25 EEG features remains unexplored.

26

27 Adults' sleep habits are manifested in their neurophysiology, as shown by increased SWA in
28 long vs. short sleepers after sleep deprivation (Aeschbach et al., 1996) and more low sigma
29 power for early vs. late chronotypes (Mongrain et al., 2005). Effects of sleep habits on EEG
30 characteristics are also evident in adolescents; morning types, for example, exhibit reduced
31 spindles (Merikanto et al., 2017). Beyond its relationship with neurophysiology, sleep
32 duration and bedtimes in adolescence are linked to brain morphology (gray matter volume)
33 and behavioral performance (Urrila et al., 2017).

34 While the link between sleep habits and neurophysiology is entirely unexplored in infants
35 and young children, acute deviations from otherwise regular sleep schedules significantly
36 affect their neurophysiology. For example, habitually napping toddlers who miss a nap
37 demonstrate a substantial homeostatic response at nighttime, with the typical increased

1 power in SWA (Lassonde et al., 2016). Similarly, acute sleep deprivation in young children
2 raised sleep pressure and thus triggered a homeostatic response of increased SWA,
3 specifically affecting developing brain areas (Kurth et al., 2016). Therefore, it is conceivable
4 that chronically extending or restricting young children's sleep beyond their individual needs
5 is a potential risk for neurodevelopment and could affect emotional lability, impulsivity
6 (Gruber et al., 2012), and neurocognitive functioning (Molfese et al., 2013). In addition, it is
7 crucial to consider an infant's sleep in the complex context it is experiencing daily: while
8 some sleep habits are more "internally" determined in infants (e.g., fragmentation of sleep,
9 total sleep need (Franken et al., 2001)), other infant sleep habits depend on both internal
10 needs with external influences of the parents (e.g., sleep timing). Fortunately, an infant's
11 internal and external sleep habits can be summarized with five sleep composites (Schoch et
12 al., 2020). These five core domains can be used to capture the complexity and multi-
13 dimensionality of sleep behaviors in the first year of life. They include *Sleep Activity*,
14 reflecting movement and awakenings at night; *Sleep Timing*, summarizing the clock time of
15 bedtimes and sleep times; *Sleep Night*, characterizing nighttime sleep opportunity and
16 duration; *Sleep Day*, representing duration and number of daytime naps and their regularity;
17 and *Sleep Variability*, reflecting the variability of timing and nighttime sleep between the
18 recorded days.

19
20 In summary, adults' and adolescents' sleep habits are manifested in their neurophysiology,
21 with specific EEG features underlying this link. However, this examination is lacking in
22 infancy, the most vulnerable period of the human lifespan, which sets the foundation for
23 brain and behavioral development. We thus tested the hypothesis that infants' sleep habits
24 at age 6 months are closely linked to infants' neurophysiology at 6 months assessed with
25 hdEEG during sleep. To characterize this linkage, we investigated correlations between
26 infant's SWA, theta power, spindle density, and Delta-coherence with sleep habits, as
27 quantified from actigraphy (core composites *Sleep Day*, *Sleep Night*, *Sleep Timing*, *Sleep*
28 *Variability*, and *Sleep Activity*) (Schoch et al., 2020). We also evaluated the topographical
29 dimension of these associations across the scalp. Further, we tested whether infants' sleep
30 behaviors infer sleep neurophysiology or *vice versa*. Longitudinal recordings at ages 3, 6,
31 and 12 months provided the basis for examining the direction of predictive associations.

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34 **2. Methods**

35 **2.1 Participants**

36 We invited parents with healthy 6-month-old infants enrolled in a research project tracking
37 infant sleep (Schoch et al., 2021, 2020) to participate in an at-home EEG assessment. Of

1 152 families, 24 agreed to participate in the EEG recording. Additionally, we recruited 11
2 families for an hdEEG sleep assessment and sleep tracking at infant age 6 months. Of the
3 35 participants, 32 (n = 15 female) were included in the final analyses, as three were
4 excluded due to incomplete recordings (n = 2 inability to fall asleep, n = 1 too short sleep
5 period). Infants were healthy (i.e., absence of central nervous system disorders, acute
6 pediatric disorders, brain damage, chronic disease, family background of narcolepsy,
7 psychosis, or bipolar disorder), primarily breastfed (> 50% of feedings), and had no
8 antibiotics intake until age 3 months.
9 They had been delivered vaginally and at term with a birth weight above 2500 g. Parents
10 were required to have good knowledge of the German language. Ethical approval was
11 obtained from the *cantonal ethics committee* (BASEC 2016-00730), and study procedures
12 adhered to the declaration of Helsinki. Parents gave written informed consent after an
13 explanation of the study. Families received small gifts for their participation, including a 40
14 CHF voucher.

15

16 **2.2 Experimental design**

17 We used actigraphy at 3, 6, and 12 months in 22 infants or at 6 months only in 10 infants to
18 assess sleep habits. At each assessment, infant sleep habits were measured for
19 approximately 11 continuous days using ankle actigraphy (GENEactiv, Activinsights Ltd,
20 Kimbolton, UK) and parents filled in a concurrent 24-h-diary. Actigraphs were worn
21 continuously and only removed for bathing/swimming, which caregivers documented.

22

23 **2.3 hdEEG assessed at families' homes**

24 Neurophysiological markers were obtained at 6 months using sleep hdEEG. EEG
25 measurement was conducted at the families' home using a high-density sponge electrode
26 net and scheduled to each infant's habitual bedtime (124 electrodes, Electrical Geodesics
27 Sensor Net, Electrical Geodesics Inc., EGI, Eugene, OR). Nighttime sleep was measured for
28 a maximum of 2 hours. The net was soaked in electrolyte water (1 l) containing potassium
29 chloride (1%) and baby shampoo for 5 minutes before application. After applying the
30 electrode net, impedances were kept below 50 k Ω . EEG data were referenced to the vertex
31 during recording, sampled at 500 Hz with a bandpass filter (0.01, 200 Hz).

32

33 **2.4 Quantifying infant sleep habits**

34 According to our laboratory standards based on actigraphy analysis, sleep habits were
35 quantified as five infant sleep composites (Schoch et al., 2020). In brief, we computed sleep-
36 wake patterns at a 1-minute resolution using a 6-step modification (Schoch et al., 2019) of
37 the Sadeh algorithm (Sadeh et al., 1995), taking into account the sleep diaries. Using a

1 principal component analysis, we derived 5 sleep composites from 48 commonly-used sleep
2 variables based on sleep-wake patterns (PCA, (Schoch et al., 2020). The five sleep
3 composites are *Sleep Day*, *Sleep Night*, *Sleep Activity*, *Sleep Timing*, and *Sleep Variability*.
4 *Sleep Day* includes daytime nap duration, number, and regularity. *Sleep Night* includes
5 nighttime sleep opportunity and duration. *Sleep Activity* includes movements and
6 awakenings at night. *Sleep Timing* characterizes the clock time of bed- and sleep times.
7 *Sleep Variability* summarizes the variability of timing and duration of nighttime sleep between
8 the recorded days. In case of missing a single recording day, missing sleep variables that
9 were part of the PCA were imputed.

10

11 **2.5 hdEEG analysis**

12 EEG analysis was performed with Matlab (R2020b). First, EEG data was bandpass filtered
13 (0.5 - 50 Hz) and down-sampled to 128 Hz. Sleep stages were visually scored by two
14 independent raters according to the AASM Manual (Iber et al., 2007), using 20 s epochs and
15 discussing to reach consensus for final scoring. Artifacts were rejected by visualizing
16 frequency and power for both channels and time, using a semiautomatic approach (Huber et
17 al., 2000). Afterward, the EEG was re-referenced to average reference. The outermost
18 electrodes (Kurth et al., 2010) and additional channels (max. 10 %) with a low percentage of
19 good epochs were removed, resulting in recordings from 74 - 109 electrodes (M = 100.5, SD
20 = 7.5). Missing electrodes (excluded due to artifacts) were interpolated for topographical
21 analysis.

22 EEG Power was determined for each electrode in the slow wave activity (SWA, 0.75-4.25
23 Hz) and theta (4.5 - 7.5 Hz) frequency range, averaged across the first 25 - 30 minutes of
24 artifact-free NREM sleep (30 minutes unless less data was available n = 3).

25 In the same data, spindles were detected automatically using an approach similar to
26 (Ferrarelli et al., 2007; Gerstenberg et al., 2020; Lustenberger et al., 2015) as described in
27 the companion paper (Jaramillo et al., 2021). Fast spindle density (13.5 - 16 Hz) was
28 quantified as the average number of spindles detected per minute.

29 Coherence was calculated between all possible pairs of electrodes using Welch's method.
30 Coherence values range from 0 to 1 and indicate the level of correlation between two signals
31 at a specific frequency. Specifically, coherence was defined as $|P_{xy}(f)|^2 / (P_{xx}(f)P_{yy}(f))$
32 where $P_{xy}(f)$ is the cross-spectral density and $P_{xx}(f)$ and $P_{yy}(f)$ are the auto-spectral
33 density functions of the two signals x and y at frequency f (Bendat and Piersol, 2011). To
34 limit the number of electrode pairs, i.e., connections, we applied the data-driven clustering
35 method described by ten Caat et al. (2008) across the SWA, theta, and fast spindle
36 frequency ranges. However, as the results were similar and there was a high correlation
37 among coherence data of the three frequency ranges, we limited our analyses to the SWA

1 frequency range (correlation Delta-coherence and theta-coherence $r(29) = 0.81$, $p < 0.001$,
2 Delta-coherence and high sigma coherence $r(29) = 0.41$, $p = 0.02$). The clustering method
3 partitioned electrodes into spatially connected regions based on the coherence of each
4 electrode with its neighbors. Coherence between pairs of resulting regions was analyzed as
5 the average coherence across all connections with one electrode belonging to one region
6 and the other electrode belonging to the other region. Between-region connections
7 exceeding a predefined threshold for coherence (i.e., 0.5) were detected.

8

9 **2.6 Statistical analysis**

10 Statistical analysis was performed in R Studio (1.3.959 using R version 4.0.0) with the
11 following packages *mice* (Buuren and Groothuis-Oudshoorn, 2011), *dplyr* (Wickham et al.,
12 2015), *tidyr* (Wickham and Henry, 2019), and *magrittr* (Bache and Wickham, 2014). To
13 examine global effects, we averaged the four EEG features across all electrodes. We used
14 generalized linear models with the EEG features as the outcome and sleep habits at 6
15 months (5 sleep composites) as predictors while controlling for exact age, sex, and
16 breastfeeding status (yes/no, corrected model). We performed an uncorrected model with
17 only the sleep composite and age as predictors if a predictor reached $p < 0.1$ in the
18 corrected model. For power and spindles, we additionally examined localized effects for
19 each electrode based on one imputation with a partial Pearson correlation (factor age) for
20 each electrode and with statistical nonparametric mapping (SnPM) cluster correction. In
21 brief, the order of the two correlation variables was shuffled randomly, and a Pearson
22 correlation was calculated for each electrode. The maximal number of neighboring
23 electrodes with an r-value above the critical threshold was determined separately for positive
24 and negative r-values. 5000 permutations were performed to obtain a distribution of maximal
25 cluster sizes for positive and negative r-values, and the threshold was set for both
26 distributions to the 97.5th percentile. Next, we tested whether previous sleep habits predict
27 later EEG measures by predicting EEG measures at 6 months by sleep behavior at 3
28 months while controlling for sex and age at EEG recording. To examine the predictive effects
29 of EEG features for later sleep habits, we ran models using the four EEG features at 6
30 months as predictors for sleep habits at age 12 months while controlling for age at EEG
31 recording, sex, breastfeeding status, and sleep habits age 6 months. The significance level
32 was set to $p < 0.05$.

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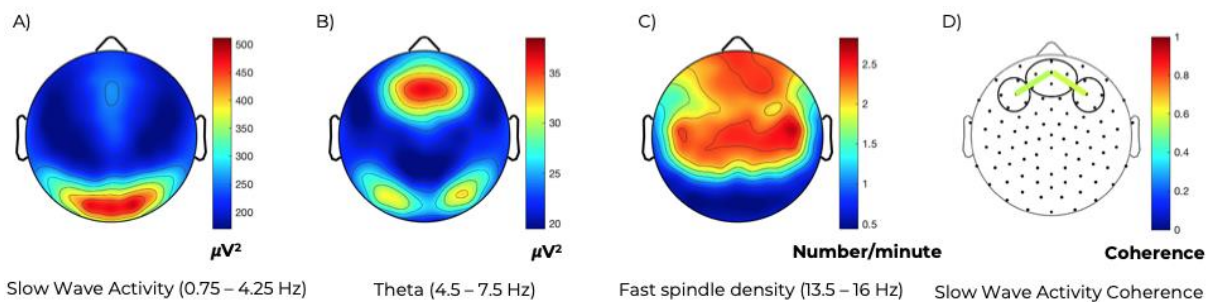
36 **3 Results**

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1 3.1 Localization of sleep in infants: Topographies of SWA, theta, spindle density, and 2 Delta-coherence

3 We mapped the four neurophysiological features at 6 months of age across the scalp and
4 visualized the topographical distribution of SWA, theta, and spindles (Fig 1). SWA was
5 observed in occipital regions and theta power in frontocentral areas and occipital areas.
6 Spindles showed the highest density in central and frontal areas. Between-region Delta-
7 coherence exceeded the predefined threshold of 0.5 between frontal and frontotemporal
8 regions.

9



10

11 **Fig 1.** Topographical distribution of the four EEG features across the first 30 minutes of
12 artifact-free NREM sleep at 6 months of age (N = 32). Maps A)-C) are based on 109
13 electrodes and represent averages across all participants. Values are color-coded and
14 scaled to maximum (red) and minimum (blue). A) Slow wave activity (SWA, 0.75 - 4.25 Hz)
15 is highest in the occipital area. B) Theta power (4.5 - 7.5 Hz) shows the highest presence in
16 frontocentral regions and increased power at occipital regions. C) Fast spindles (13.5 - 16
17 Hz) show the highest density in central and frontal regions. D) For Delta-coherence, two
18 between-region connections were detected bilaterally between prefrontal and frontotemporal
19 areas (Coherence left = 0.56, Coherence right = 0.58).

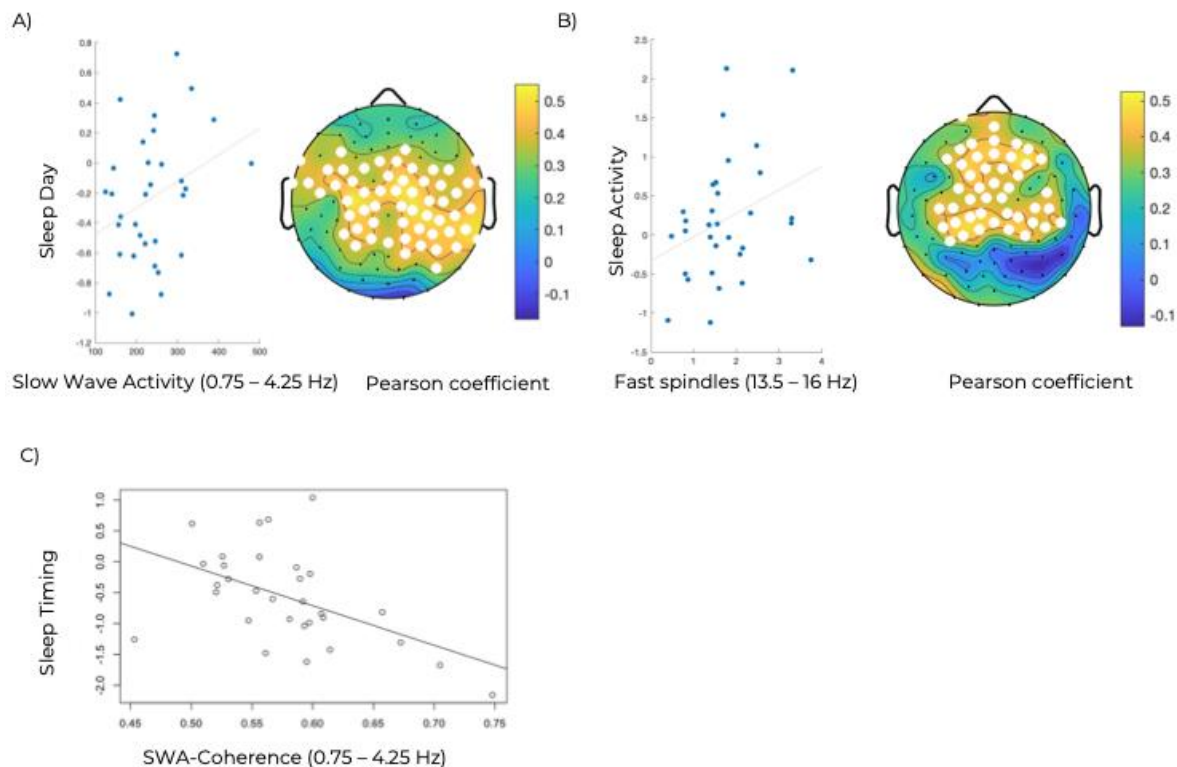
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21 3.2 Neurophysiological markers are associated with sleep habits at 6 months

22 Subsequently, we tested whether sleep habits and EEG features at age 6 months are
23 associated. Overall (averaged across all electrodes), daytime sleep habits (*Sleep Day*) were
24 associated with SWA (uncorrected $t(25.89) = 2.12$, $p = 0.04$, corrected $t(17.98) = 1.85$, $p =$
25 0.08), i.e., Infants who habitually slept more during the day showed more SWA. Electrode-
26 wise partial correlation between SWA and *Sleep Day* was significant in a large global cluster
27 of 58 electrodes when correcting for the age at the EEG assessment (Fig 2). No other sleep
28 composite was significantly associated with global SWA at 6 months (all $p > 0.1$,
29 Supplementary Table 1). None of the sleep composites were significantly linked to global
30 theta power (all $p > 0.09$, Fig 2A).

1 In contrast, global spindle density was positively associated with *Sleep Activity* (uncorrected
2 $t(26.33) = 2.41$, $p = 0.02$, corrected $t(19.26) = 2.27$, $p = 0.03$). Infants whose actimetry
3 revealed more activity and awakenings habitually from sleep showed increased spindle
4 density during the night of the EEG assessment. The electrode-wise partial correlation
5 between spindle density and *Sleep Activity* was significant in a large central cluster of 45
6 electrodes when correcting for the age at the EEG assessment ($p_{97.5}$ threshold = 26, Fig
7 2B). No other sleep composite was significantly associated with global spindle density (all p
8 > 0.1 , Supplementary Table 1).

9 Sleep habits were associated with Delta-coherence at 6 months: *Sleep Timing* was
10 negatively associated with Delta-coherence (uncorrected $t(26.01) = -3.11$, $p = 0.004$,
11 corrected $t(19.02) = -3.24$, $p = 0.004$, Fig 2C). Infants with earlier sleep timings showed
12 increased Delta-coherence. No other sleep composite was significantly associated with
13 Delta-coherence (all $p > 0.05$, Supplementary Table 1).



14

15

16 Fig 2. Associations between the 4 EEG features and sleep habits at 6 months with
17 illustrations on a scalp model (N = 32). A) Left: SWA averaged across all 109 electrodes
18 plotted against *Sleep Day* (reflecting daytime sleep habits). Right: Electrode-wise partial
19 correlation between SWA and *Sleep Day* at 6 months of age, corrected for age at EEG
20 assessment. Significant electrodes are indicated as white dots (statistical nonparametric
21 mapping cluster correction for multiple comparisons). B) Left: Fast spindle density averaged

1 across all 109 electrodes plotted against *Sleep Activity* (reflecting movements and
2 awakenings during sleep). Right: Electrode-wise partial correlation between spindle density
3 and *Sleep Activity*, corrected for age at EEG assessment. Significant electrodes are
4 indicated as white dots (statistical nonparametric mapping cluster correction for multiple
5 comparisons). C) Delta-coherence between prefrontal and frontotemporal areas plotted
6 against *Sleep Timing* (reflecting sleep- and bed-times).

7

8 **3.3 Sleep habits at 3 months do not predict sleep EEG features at 6 months**

9 Next, we explored if sleep behaviors influence long-term neurophysiology. None of the sleep
10 habits at age 3 months consistently predicted EEG features at 6 months (Supplementary
11 Table 2). We also explored if sleep neurophysiology at 6 months predicted infant sleep
12 habits at 12 months. Delta-coherence at 6 months significantly predicted Sleep Night at 12
13 months (uncorrected $t(16.27) = 2.73$, $p = 0.01$, corrected $t(10.84) = 1.84$, $p = 0.09$,
14 Supplementary Table 3). Thus, infants with higher Delta-coherence at 6 months had more
15 nighttime sleep at 12 months, indicating that more mature neurophysiology at 6 months
16 predicts more mature sleep behavior at 12 months. SWA, theta, and spindle density were
17 not predictive of later sleep habits.

18

19

20 **4. Discussion**

21

22 Our present work on nighttime hdEEG neurophysiology and behavioral sleep habits (as
23 measured by ankle actimetry and sleep diaries) in healthy 6-month-old infants reveals four
24 key findings. First, more pronounced daytime sleep habits are linked to increased SWA
25 across a sizable, globally distributed electrode cluster. Second, more nocturnal activity and
26 awakenings from night sleep are connected with more evident sleep spindles. Third, sleep
27 timing is associated with EEG coherence at age 6 months, and fourth, coherence at age 6
28 months predicts the duration of nighttime sleep at 12 months. These novel findings widen
29 our understanding that daytime sleep behavior, movement activity at night, and bedtimes of
30 infants are closely intertwined with sleep on the neurophysiological level, which implies that
31 the EEG may be used to monitor whether sleep habits are within norms. The concept that
32 observed sleep behavior is connected to measured sleep in the brain is evident on three
33 distinct levels: sleep pressure (reflecting SWA), the maturation of the thalamocortical system
34 (spindles), and maturation of cortical connectivity (coherence). Considering that sleep habits
35 in early life relate to later maturational outcomes (Spruyt et al., 2008; Timofeev et al., 2020),
36 our study introduces two novel findings: neurophysiology is intertwined with internal and

1 external factors, and infant sleep habits may affect brain development pathways in the long
2 term.

3

4 The first main result aligns with the concept that SWA is tightly linked to sleep-wake
5 regulation (Schechtman et al., 1994). Our findings contribute to the insight that infants with
6 increased daytime sleep pressure (*i.e.*, more pronounced napping) experience nearly
7 globally elevated SWA at night. This finding may seem counter-intuitive considering that
8 napping reduces sleep pressure (and thus SWA) in children (Lassonde et al., 2016) and
9 adults (Werth et al., 1996). However, it can be explained by the specific dynamics of sleep
10 pressure accumulation in infants, *i.e.*, infants with a fast build-up of sleep pressure might
11 generally experience increased sleep need, both during the day and at night.

12 Contrastingly, we found no link between infants' sleep habits and theta power. Interestingly,
13 the dissipation of sleep pressure across sleep in infancy has been suggested to be reflected
14 in theta instead of SWA (Jenni et al., 2004). However, a follow-up study analyzed the same
15 dataset and demonstrated an across-night decrease of the slope of slow waves (Fattinger et
16 al., 2014). Though we only report results concerning SWA, the slope (slope 55, corrected for
17 slow wave amplitude, as in Fattinger et al.) was highly correlated to SWA in our exploratory
18 analyses, potentially indicating that the slope reflects both the sleep pressure build-up as
19 well as its dissipation.

20 From a spatial dimension, SWA predominated over occipital regions at age 6 months, in line
21 with findings at age 3 months (Guyer et al., 2019) and at preschool age (Kurth et al., 2010).
22 Therefore, we conclude that the localization of SWA on the scalp remains stable across the
23 first years of life. Interestingly, the association between an infant's daytime sleep habits and
24 SWA is represented in a sizable near-global cluster across central and temporal scalp
25 regions and not in the region of maximal SWA.

26

27 As expected, spindle density was maximal over frontal and central scalp areas (D'Atri et al.,
28 2018). The association of spindles with nighttime movements and awakenings aligned with
29 the location of maximal spindle detection. To our knowledge, this is the first demonstration of
30 a link between infants' nighttime movements/awakenings (*i.e.*, *Sleep Activity*) with spindle
31 density. This discovery was initially surprising, considering that previous research with
32 human adults reported a "protective role" of spindles for sleep - thereby preventing
33 awakenings (Dang-Vu et al., 2010; Fernandez and Lüthi, 2020; Schabus et al., 2012).
34 However, we acknowledge that *Sleep Activity* computation is based on nighttime actimetric
35 movement. Infants' recorded nighttime movements may also entail myoclonic twitches,
36 which are the spontaneous movements typically observed in Rapid Eye Movement (REM)
37 sleep (Sokoloff et al., 2020). These twitches provide topographically precise activity to

1 integrate peripheral fiber innervation to the developing central nervous system, as
2 extensively studied in rats (Blumberg et al., 2013; Tiriach et al., 2015). Twitching is thus
3 assumed critical for the microcircuitry development of the sensorimotor cortex. Compelling
4 novel research in human infants discovered that twitches also occur in NREM sleep and in
5 synchrony with sleep spindles (Sokoloff et al., 2021). Thus, our data fundamentally extend
6 the known concept that spindles reflect thalamocortical network strength (Fernandez and
7 Lüthi, 2020) and propose a core linkage of spindles with sensorimotor microcircuitry
8 development in infants. In other words, thalamocortical connectivity underlying infants'
9 spindles may be enhanced through twitching activity in sleep. The concept that spindles are
10 valuable biomarkers for neurodevelopment is supported by the discovery in our companion
11 paper where we report that spindles at 6 months predict gross motor development at both 12
12 and 24 months of age (Jaramillo et al., 2021). Our findings highlight the importance of
13 characterizing neurophysiological dynamics across development, as their functions differ
14 according to developmental stage (Purcell et al., 2017).

15

16 The third novel finding was that habitual *Sleep Timing* of healthy 6-month-olds was
17 manifested in cortical connectivity (Delta-coherence), such that earlier bedtimes indicated
18 increased cortical connectivity. In a more global context of sleep-wake pattern maturation,
19 the general trend is that sleep increasingly consolidates towards the nighttime (Iglowstein et
20 al., 2003). Thus, earlier infant bedtimes generally signify a more mature pattern. Our novel
21 data confirm this on the neurophysiological level: more mature *Sleep Timing* aligns with
22 more mature cortical connectivity, *i.e.*, increased connectivity (Kurth et al., 2013; Tarokh et
23 al., 2010). Thus, the effective implementation of infants' bedtimes should be considered
24 based on the brain's maturational status.

25 The spatial dimension also supports this concept, as topographical coherence reached
26 significance only between frontal and frontotemporal areas. Knowing that preterm infants
27 maintain reduced connectivity in exactly frontal regions (Gozdas et al., 2018), our finding
28 suggests that frontal connectivity reflects neurophysiological maturational status.

29

30 Furthermore, cortical connectivity is determined by both internal (*i.e.*, demands of the infant's
31 sleep need) as well as external (*i.e.*, contextual demands of the parents) influences
32 (Markovic et al., 2020). Interestingly, among the five sleep composites (*Sleep Day*, *Sleep*
33 *Night*, *Sleep Timing*, *Sleep Activity*, and *Sleep Variability*), *Sleep Timing* is likely most
34 reflective of these two. We thus conclude that both sleep timing and cortical connectivity
35 indicate maturational status and represent the multidimensional nature-and-nurture
36 dynamics.

37

1 Overall, the main findings of this paper were observed in infants aged 6 months. In addition,
2 we found that Delta-coherence at 6 months predicted nighttime sleep duration at 12 months,
3 indicating that more mature neurophysiology at 6 months (Tarokh et al., 2010) predicts more
4 mature sleep habits at 12 months. This finding could be indicative that the maturing of
5 neurophysiology precedes the development of sleep habits. However, additional
6 associations between infants' EEG features at age 6 months with either their previous (at
7 age 3 months) or their later sleep habits (at age 12 months) could not be observed. A
8 potential explanation could be the high variability of sleep habits across the first year of life,
9 even within the same infant (Schoch et al., 2020).

10

11 Epidemiological research reports the connection between chronically “poor” sleep habits in
12 early life and problematic later psychosocial, cognitive, and somatic outcomes (Lam et al.,
13 2003; Simola et al., 2014). Surprisingly, so far, the underlying neurophysiological links have
14 not been investigated. We thus applied quantitative methodologies to address a fundamental
15 knowledge gap and demonstrated that three sleep EEG features relate to infants' sleep
16 habits. Interestingly, diverse aspects of sleep habits are associated with distinct features of
17 sleep neurophysiology, illustrating that further advances in our research field require a
18 comprehensive assessment of both - sleep habits and sleep neurophysiology. Furthermore,
19 our results introduce a new concept of the multi-dimensionality of sleep: While sleep habits
20 are known to be intertwined with sleep pressure, influenced by circadian and homeostatic
21 sleep regulators, we show for the first time that sleep habits also closely connect with
22 neuronal connectivity. Consequently, this work highlights the interesting novel translational
23 perspective that sleep habits, which can be modified (e.g., bedtimes), are connected to
24 neurophysiological maturation processes, which has been beyond our range of influence.
25 Therefore, aligning neurophysiological needs with the behavioral implementation in sleep-
26 wake structuring is essential, both for the infant's developmental outcome (Mindell et al.,
27 2017; Spruyt et al., 2008) as well as family dynamics and well-being in the long term (Lam et
28 al., 2003).

29

30 We assessed infant sleep habits comprehensively at 3, 6, and 12 months of age and
31 conducted a nighttime sleep neurophysiology assessment at the single time point at age 6
32 months. Repeated measures of sleep neurophysiology would be needed to establish the
33 stability of neurophysiological measures and extrapolate the reported findings to other age
34 groups. They would allow studying the directionality of the relationships by using, for
35 instance structural equation modeling. There are other aspects of the sleep EEG, which we
36 did not include in this study, because of strong correlations with the included variables such
37 as slow spindles, sigma power etc. Future studies will need to investigate potential

1 associations of these variables and sleep habits. Further, experimental alterations of sleep
2 habits (Werner et al., 2015) and sleep neurophysiology (Ngo et al., 2013) are required to
3 establish the directionality of their longitudinal associations.
4

5 In conclusion, we report that sleep habits are linked to multiple sleep neurophysiology
6 features in healthy infants. The next crucial step is to characterize which sleep habits
7 represent a risk profile for neurodevelopmental problems to identify infants who benefit most
8 from sleep interventions.
9

10

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18

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22

22

23 **CRedit roles**

24 **Sarah F. Schoch:** Conceptualization; Data curation; Formal analysis; Funding
25 acquisition; Investigation; Methodology; Project administration; Software; Validation;
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1 Funding acquisition; Investigation; Methodology; Software; Writing - original draft;
2 Writing - review & editing.

3

4 ***Data and code availability statements***

5 Data and code are available upon request to the authors, pending ethical approval,
6 and in alignment with consenting framework. R Analysis scripts are available on
7 OSF.

8

9

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Supplementary Table 1. Associations between sleep habits and EEG features at 6 months.

| | Corrected Model | | Uncorrected Model | |
|------------------|--------------------------------------|-------------|------------------------------------|-------------|
| | Estimate + SE [95 % CI] | P Value | Estimate + SE [95 % CI] | P Value |
| (Intercept) | -124.2 ± 181.66 [-503.78, 255.38] | 0.50 | -82.88 ± 159.98 [-411.18, 245.42] | 0.61 |
| Exact age | 55.11 ± 30.43 [-8.41, 118.62] | 0.09 | 57.28 ± 27.25 [1.36, 113.19] | 0.05 |
| Female sex | -18.64 ± 29.68 [-80.57, 43.28] | 0.54 | | |
| <i>Sleep Day</i> | <i>71.45 ± 38.66 [-9.78, 152.69]</i> | <i>0.08</i> | <i>69.76 ± 32.86 [2.2, 137.33]</i> | <i>0.04</i> |
| Sleep Night | 12.58 ± 15.26 [-19.32, 44.48] | 0.42 | | |
| Sleep Activity | 15.27 ± 20.74 [-28.18, 58.72] | 0.47 | | |

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|-------------------|--------------------------------|----------------|--------------------------------|----------------|
| Sleep Timing | 0.23 ± 19.83 [-41.16, 41.62] | 0.99 | | |
| Sleep Variability | -22.95 ± 20.15 [-65.02, 19.12] | 0.27 | | |
| Breastfeeding | 53.74 ± 51.79 [-57.65, 165.14] | 0.32 | | |
| Theta | Estimate + SE [95 % CI] | P Value | Estimate + SE [95 % CI] | P Value |
| (Intercept) | 17.65 ± 19.52 [-23.06, 58.36] | 0.38 | 20.67 ± 18.4 [-17.07, 58.41] | 0.27 |
| Exact age | 2.37 ± 3.28 [-4.46, 9.21] | 0.48 | 0.85 ± 3.09 [-5.49, 7.2] | 0.78 |
| Female sex | -6.38 ± 3.18 [-13.01, 0.24] | 0.06 | | |
| Sleep Day | 0.21 ± 3.99 [-8.1, 8.52] | 0.96 | | |
| Sleep Night | 0.3 ± 1.62 [-3.07, 3.67] | 0.85 | | |
| Sleep Activity | 0.12 ± 2.19 [-4.45, 4.69] | 0.96 | | |
| Sleep Timing | 3.74 ± 2.13 [-0.7, 8.18] | 0.09 | 2.31 ± 2.02 [-1.84, 6.47] | 0.26 |
| Sleep Variability | -3.13 ± 2.15 [-7.61, 1.36] | 0.16 | | |
| Breastfeeding | -4.14 ± 5.24 [-15.25, 6.97] | 0.44 | | |
| Spindles | Estimate + SE [95 % CI] | P Value | Estimate + SE [95 % CI] | P Value |

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|-----------------------|---------------------------------|-------------|--------------------------------|-------------|
| (Intercept) | 3.04 ± 1.85 [-0.84, 6.91] | 0.12 | 4.4 ± 1.8 [0.71, 8.09] | 0.02 |
| Exact age | -0.27 ± 0.31 [-0.91, 0.38] | 0.40 | -0.47 ± 0.31 [-1.09, 0.16] | 0.14 |
| Female sex | -0.55 ± 0.3 [-1.18, 0.08] | 0.08 | | |
| Sleep Day | 0.06 ± 0.4 [-0.77, 0.89] | 0.88 | | |
| Sleep Night | 0.02 ± 0.16 [-0.31, 0.34] | 0.92 | | |
| <i>Sleep Activity</i> | <i>0.47 ± 0.21 [0.04, 0.91]</i> | <i>0.03</i> | <i>0.47 ± 0.2 [0.07, 0.87]</i> | <i>0.02</i> |
| Sleep Timing | -0.35 ± 0.2 [-0.77, 0.08] | 0.11 | | |
| Sleep Variability | 0.22 ± 0.21 [-0.22, 0.66] | 0.31 | | |
| Breastfeeding | 0.41 ± 0.56 [-0.82, 1.65] | 0.48 | | |

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| Coherence | Estimate + SE [95 % CI] | P Value | Estimate + SE [95 % CI] | P Value |
|------------------|--------------------------------|----------------|--------------------------------|----------------|
| (Intercept) | 0.57 ± 0.13 [0.29, 0.84] | < 0.001 | 0.5 ± 0.12 [0.26, 0.75] | < 0.001 |
| Exact age | 0 ± 0.02 [-0.05, 0.04] | 0.82 | 0.01 ± 0.02 [-0.03, 0.05] | 0.66 |
| Female sex | 0.05 ± 0.02 [0.01, 0.1] | 0.02 | | |

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|---------------------|---|-------------|---------------------------------|-------|
| Sleep Day | 0 ± 0.03 [-0.06, 0.05] | 0.87 | | |
| Sleep Night | 0.02 ± 0.01 [0, 0.04] | 0.05 | 0.02 ± 0.01 [0, 0.04] | 0.12 |
| Sleep Activity | -0.01 ± 0.01 [-0.04, 0.02] | 0.44 | | |
| <i>Sleep Timing</i> | -0.04 ± 0.01 [-0.07, -0.02] | 0.004 | -0.04 ± 0.01 [-0.07, -0.01] | 0.004 |
| Sleep Variability | 0.01 ± 0.01 [-0.01, 0.04] | 0.29 | | |
| Breastfeeding | -0.01 ± 0.04 [-0.1, 0.08] | 0.81 | | |

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Supplementary Table 2. Associations between sleep habits at infants age 3 months and EEG Features at age 6 months.

| | Corrected Model | Uncorrected Model |
|--|-----------------|-------------------|
| | | |

| SWA | Estimate + SE [95 % CI] | P Value | Estimate + SE [95 % CI] | P Value |
|-------------------|------------------------------------|----------------|--------------------------------|----------------|
| (Intercept) | 423.05 ± 514.53 [-694.82, 1540.91] | 0.43 | | |
| Exact age | -44.51 ± 93.82 [-248.37, 159.35] | 0.64 | | |
| Female sex | 3.27 ± 32.48 [-67.32, 73.86] | 0.92 | | |
| Sleep Day | 44.11 ± 46.3 [-56.64, 144.86] | 0.36 | | |
| Sleep Night | 11.14 ± 17.53 [-26.99, 49.26] | 0.54 | | |
| Sleep Activity | 21.97 ± 21.06 [-23.83, 67.77] | 0.32 | | |
| Sleep Timing | 1.63 ± 25.89 [-54.66, 57.91] | 0.95 | | |
| Sleep Variability | -5.86 ± 20.72 [-50.9, 39.18] | 0.78 | | |
| Theta | Estimate + SE [95 % CI] | P Value | | |
| (Intercept) | 78.39 ± 69.89 [-73.48, 230.25] | 0.28 | | |
| Exact age | -9 ± 12.74 [-36.69, 18.69] | 0.49 | | |
| Female sex | -4.02 ± 4.41 [-13.61, 5.57] | 0.38 | | |
| Sleep Day | -3.29 ± 6.28 [-16.96, 10.38] | 0.61 | | |

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|---------------------|------------------------------------|----------------|--------------------------------|----------------|
| Sleep Night | 0.95 ± 2.38 [-4.24, 6.13] | 0.70 | | |
| Sleep Activity | 3.58 ± 2.86 [-2.65, 9.8] | 0.23 | | |
| Sleep Timing | 4.83 ± 3.54 [-2.89, 12.54] | 0.20 | | |
| Sleep Variability | -3.24 ± 2.82 [-9.37, 2.89] | 0.27 | | |
| Spindles | Estimate + SE [95 % CI] | P Value | Estimate + SE [95 % CI] | P Value |
| (Intercept) | -5.46 ± 5.55 [-17.51, 6.58] | 0.34 | -7.49 ± 4.91 [-17.83, 2.85] | 0.14 |
| Exact age | 1.21 ± 1.01 [-0.99, 3.41] | 0.25 | 1.65 ± 0.86 [-0.17, 3.47] | 0.07 |
| Female sex | -0.37 ± 0.35 [-1.13, 0.39] | 0.31 | | |
| Sleep Day | 0.73 ± 0.5 [-0.36, 1.83] | 0.17 | | |
| Sleep Night | 0 ± 0.19 [-0.41, 0.41] | 0.99 | | |
| Sleep Activity | -0.15 ± 0.23 [-0.64, 0.34] | 0.52 | | |
| <i>Sleep Timing</i> | <i>-0.66 ± 0.28 [-1.26, -0.05]</i> | <i>0.04</i> | <i>-0.42 ± 0.2 [-0.84, 0]</i> | <i>0.05</i> |
| Sleep Variability | 0.08 ± 0.22 [-0.41, 0.57] | 0.74 | | |
| Coherence | Estimate + SE [95 % CI] | P Value | Estimate + SE [95 % CI] | P Value |

| | | | | |
|-------------------|----------------------------|------|--|--|
| (Intercept) | -0.43 ± 0.41 [-1.34, 0.48] | 0.32 | | |
| Exact age | 0.19 ± 0.08 [0.02, 0.35] | 0.03 | | |
| Female sex | 0.02 ± 0.03 [-0.04, 0.08] | 0.46 | | |
| Sleep Day | -0.06 ± 0.04 [-0.14, 0.02] | 0.14 | | |
| Sleep Night | 0.01 ± 0.01 [-0.02, 0.04] | 0.69 | | |
| Sleep Activity | 0 ± 0.02 [-0.04, 0.04] | 0.85 | | |
| Sleep Timing | -0.01 ± 0.02 [-0.05, 0.04] | 0.70 | | |
| Sleep Variability | 0 ± 0.02 [-0.04, 0.03] | 0.92 | | |

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Supplementary Table 3. Associations between EEG features at infant age 6 months and sleep habits at age 12 months.

| | Corrected Model | | Uncorrected Model | |
|-------------|---------------------------|---------|-------------------------|---------|
| | Estimate + SE [95 % CI] | P Value | Estimate + SE [95 % CI] | P Value |
| (Intercept) | -4.6 ± 5.3 [-16.26, 7.07] | 0.40 | | |
| Exact Age | 0.96 ± 0.97 [-1.17, 3.09] | 0.34 | | |

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|--------------------|-----------------------------------|----------------|----------------------------------|----------------|
| Female sex | -0.33 ± 0.36 [-1.12, 0.46] | 0.37 | | |
| SWA | 0 ± 0 [-0.01, 0.01] | 0.92 | | |
| Theta | -0.01 ± 0.02 [-0.06, 0.03] | 0.59 | | |
| Spindles | -0.28 ± 0.23 [-0.78, 0.22] | 0.24 | | |
| Coherence | -1.39 ± 3.12 [-8.23, 5.45] | 0.66 | | |
| Sleep Day 6 Mo | 0.19 ± 0.5 [-0.92, 1.3] | 0.71 | | |
| Sleep Night | Estimate + SE [95 % CI] | P Value | Estimate + SE [95 % CI] | P Value |
| (Intercept) | 1.72 ± 5.98 [-11.51, 14.94] | 0.78 | 7.49 ± 5.62 [-4.43, 19.41] | 0.20 |
| Exact Age | -1.35 ± 1.21 [-4.02, 1.33] | 0.29 | -2.17 ± 1.06 [-4.41, 0.06] | 0.06 |
| Female sex | 0.64 ± 0.35 [-0.14, 1.41] | 0.10 | | |
| SWA | 0 ± 0 [-0.01, 0] | 0.70 | | |
| Theta | <i>0.06 ± 0.02 [0.02, 0.1]</i> | <i>0.01</i> | 0.03 ± 0.02 [-0.02, 0.08] | 0.2 |
| Spindles | <i>0.51 ± 0.21 [0.04, 0.99]</i> | <i>0.04</i> | 0.22 ± 0.27 [-0.35, 0.79] | 0.42 |
| Coherence | <i>6.88 ± 3.73 [-1.35, 15.11]</i> | <i>0.09</i> | <i>9.31 ± 3.41 [2.09, 16.53]</i> | <i>0.01</i> |
| Sleep Night 6 Mo | 0.25 ± 0.23 [-0.26, 0.76] | 0.31 | | |

| | Estimate + SE [95 % CI] | P Value | Estimate + SE [95 % CI] | P Value |
|-----------------------|--------------------------------|----------------|--------------------------------|----------------|
| Sleep Timing | | | | |
| (Intercept) | -0.85 ± 3.87 [-9.39, 7.68] | 0.83 | 0.87 ± 4.28 [-8.17, 9.91] | 0.84 |
| Exact Age | 0.26 ± 0.68 [-1.25, 1.77] | 0.71 | -0.08 ± 0.75 [-1.65, 1.49] | 0.92 |
| Female sex | -0.17 ± 0.25 [-0.71, 0.37] | 0.50 | | |
| SWA | 0 ± 0 [-0.01, 0] | 0.06 | 0 ± 0 [-0.01, 0] | 0.09 |
| Theta | -0.01 ± 0.01 [-0.05, 0.02] | 0.42 | | |
| Spindles | -0.01 ± 0.17 [-0.38, 0.36] | 0.94 | | |
| Coherence | 0.96 ± 3.17 [-6.13, 8.05] | 0.77 | | |
| Sleep Timing 6 Mo | 0.69 ± 0.27 [0.08, 1.3] | 0.03 | | |
| | Estimate + SE [95 % CI] | P Value | Estimate + SE [95 % CI] | P Value |
| Sleep Activity | | | | |
| (Intercept) | -11.6 ± 5.19 [-23.02, -0.18] | 0.05 | -10.3 ± 5.14 [-21.13, 0.53] | 0.06 |
| Exact Age | 2.75 ± 0.96 [0.65, 4.86] | 0.02 | 1.77 ± 0.92 [-0.17, 3.7] | 0.07 |
| Female sex | -0.14 ± 0.33 [-0.86, 0.58] | 0.68 | | |
| SWA | 0 ± 0 [-0.01, 0.01] | 0.92 | | |
| Theta | -0.03 ± 0.02 [-0.07, 0.01] | 0.16 | | |

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|--------------------------|---------------------------------|----------------|-----------------------------------|----------------|
| Spindles | $-0.71 \pm 0.25 [-1.27, -0.14]$ | 0.02 | $-0.33 \pm 0.22 [-0.78, 0.13]$ | 0.15 |
| Coherence | $-5.25 \pm 2.85 [-11.5, 0.99]$ | 0.09 | $-4.09 \pm 3.21 [-10.88, 2.71]$ | 0.22 |
| Sleep Activity 6 Mo | $0.58 \pm 0.27 [-0.03, 1.19]$ | 0.06 | | |
| Sleep Variability | Estimate + SE [95 % CI] | P Value | Estimate + SE [95 % CI] | P Value |
| (Intercept) | $-12.83 \pm 6.5 [-27.14, 1.48]$ | 0.07 | $-16.24 \pm 5.41 [-27.64, -4.83]$ | 0.01 |
| Exact Age | $2.51 \pm 1.2 [-0.12, 5.15]$ | 0.06 | $2.86 \pm 0.97 [0.82, 4.89]$ | 0.01 |
| Female sex | $-0.25 \pm 0.42 [-1.18, 0.67]$ | 0.56 | | |
| SWA | $0 \pm 0 [-0.01, 0.01]$ | 0.66 | | |
| Theta | $0 \pm 0.02 [-0.06, 0.05]$ | 0.95 | | |
| Spindles | $-0.56 \pm 0.28 [-1.16, 0.05]$ | 0.07 | $-0.34 \pm 0.23 [-0.83, 0.16]$ | 0.17 |
| Coherence | $-0.75 \pm 3.72 [-8.9, 7.41]$ | 0.84 | | |
| Sleep Variability 6 Mo | $0.37 \pm 0.26 [-0.2, 0.94]$ | 0.18 | | |

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