

Social, motor, and cognitive development through the lens of sleep network dynamics in infants and toddlers between 12 and 30 months of age

Journal Article**Author(s):**

Page, Jessica; Lustenberger, Caroline; Fröhlich, Flavio

Publication date:

2018-04

Permanent link:

<https://doi.org/10.3929/ethz-b-000283464>

Rights / license:

[In Copyright - Non-Commercial Use Permitted](#)

Originally published in:

Sleep 41(4), <https://doi.org/10.1093/sleep/zsy024>

Funding acknowledgement:

171525 - Improving sleep quality for healthy aging with wearables (SNF)



ORIGINAL ARTICLE

Social, motor, and cognitive development through the lens of sleep network dynamics in infants and toddlers between 12 and 30 months of age

Jessica Page^{1,2,†}, Caroline Lustenberger^{1,3,†} and Flavio Fröhlich^{1,2,4,5,6,7,*}

¹Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, ²Carolina Center for Neurostimulation, University of North Carolina at Chapel Hill, Chapel Hill, NC, ³Institute of Robotics and Intelligent Systems, Mobile Health Systems Lab, ETH Zurich, 8092 Zurich, Switzerland, ⁴Department of Cell Biology and Physiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, ⁵Neuroscience Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, ⁶Department of Neurology, University of North Carolina at Chapel Hill, Chapel Hill, NC and ⁷Department of Biomedical Engineering, University of North Carolina at Chapel Hill, Chapel Hill, NC

*Corresponding author. Flavio Fröhlich, 115 Mason Farm Rd., NRB 4109F, Chapel Hill, NC 27599. Email: flavio_frohlich@med.unc.edu.

†Shared first authorship

Abstract

Widespread change in behavior and the underlying brain network substrate is a hallmark of early development. Sleep plays a fundamental role in this process. Both slow waves and spindles are key features of nonrapid eye movement sleep (NREM) that exhibit pronounced developmental trajectories from infancy to adulthood. Yet, these prominent features of NREM sleep are poorly understood in infants and toddlers in the age range of 12 to 30 months. Moreover, it is unknown how network dynamics of NREM sleep are associated with outcomes of early development. Addressing this gap in our understanding of sleep during development will enable the subsequent study of pathological changes in neurodevelopmental disorders. The aim of the current study was to characterize the sleep topography with high-density electroencephalography in this age group. We found that δ , θ , and β oscillations and sleep spindles exhibited clear developmental changes. Low δ and high θ oscillations correlated with motor, language, and social skills, independent of age. These findings suggest an important role of network dynamics of NREM sleep in cortical maturation and the associated development of skills during this important developmental period.

Statement of Significance

The beginning years of life are marked by vast developmental change and within this important period is the transition from infancy to toddlerhood. Sleep serves as a means to better understand the interplay between development and the underlying neuronal networks. The sleep topography undergoes pronounced change, which is reflected in the sleep characteristics during rapid eye movement and nonrapid eye movement (NREM) sleep. Specifically, features of NREM sleep such as sleep spindles and slow waves are well documented in children and adults, and are associated with learning and memory. What remains unclear is the extent to which these associations are evident in infancy and toddlerhood. Moreover, only a few studies examine toddlerhood, and no study has yet to characterize the sleep network dynamics in the age range that covers the transition from infancy to toddlerhood (12–30 months). To address this gap, this paper seeks to characterize the sleep network dynamics and identify associations with cognitive performance. The data provided here aim to serve as a reference for future investigation of sleep network dynamics in children at risk for neurodevelopmental disorders that clinically emerge in the examined age range.

Key words: development; infants; toddlers; NREM; sleep spindles; slow waves; fine motor; social; language; θ

Submitted: 26 July, 2017; Revised: 15 December, 2017

© Sleep Research Society 2018. Published by Oxford University Press on behalf of the Sleep Research Society. All rights reserved. For permissions, please e-mail journals.permissions@oup.com.

Introduction

The rapid maturation of basic sensory, cognitive and social functions, and their underlying network-level substrate in early childhood builds the foundation for the subsequent development of more complex functions [1]. Cortical maturation is reflected in changes of the sleep electroencephalogram (EEG), specifically within nonrapid eye movement (NREM) sleep [2–8]. Dominant brain oscillations during NREM sleep, slow wave activity (SWA) and sleep spindles, have been associated with performance on measures of cognitive performance, “IQ” [9–14], learning efficiency [15, 16], memory consolidation [17–22], and motor skill development [5, 23, 24]. Thus, demarcating normative features of sleep in young children represents an important foundation for understanding brain maturation and may ultimately serve as a marker of brain development.

A prominent feature of NREM sleep that changes with age is slow waves that are related to the slow oscillations. Slow oscillations arise from the low-frequency oscillation (1 Hz) in the membrane potential of cortical neurons and with synchronization across many neurons are depicted as slow waves in the surface EEG [25–27]. Slow waves can be quantified by calculating SWA (EEG power in the δ range < 4.5 Hz) which represents a well-established marker of sleep homeostasis and sleep depth [28]. SWA further likely reflects synaptic density because more and stronger synapses benefit synchronization [29, 30]. SWA changes dramatically during development, peaking before puberty and gradually declining after that. These maturation dynamics follow the trajectory of cortical development, such as the formation and pruning of synapses [31, 32]. Kurth et al. showed in a cross-sectional study that the topography of slow waves changes from young childhood to young adulthood through a regional shift of SWA along the postero–anterior axis [4]. Thus, slow waves peak regionally over occipital regions in 2- to 5-years-old children but show a clear maximum over frontal regions in adults. These findings were further verified in a longitudinal study [23]. The underlying shift from more posterior to frontal regions may reflect the development of more sophisticated cognitive processes that children develop with age [5].

Sleep spindles also reflect maturational and regional differences during NREM sleep. Sleep spindles (10–16 Hz) represent thalamocortical derived activity [33] consisting of a waxing and waning of the EEG lasting between 0.5 and 2 s [34]. Sleep spindles are observed in infants as young as 1–2 months [35]. Slow (11–13 Hz) and fast spindles (13–16 Hz) are formed at around 24 months [36]. Slower frequencies are located over frontal regions and are more pronounced during slow wave sleep, whereas faster frequencies are located over centroparietal regions and are more prominent during stage 2 sleep [24, 33, 37].

Multiple changes occur in σ activity (covering the spectral power in the spindle frequency range) and spindle characteristics across development [33, 38]. Overall, spindles become faster from infancy to adolescents [33, 38–41], but there seems to be a significant decrease in spindle frequency in 2- to 5-years-old [42]. In addition, clear changes in power, duration, amplitude, and density of sleep spindles are seen with development. However, the directions and the amount of change depend on the age window assessed and the electrodes measured because clear topographical differences exist [4, 33, 38, 41, 43]. For instance, it was shown that from 4 to 24 years of age over frontal regions of slow σ activity gradually decreases, whereas power in faster

σ bands showed little change over centro–parietal regions [41, 44]. There are also remarkable changes in sleep spindle characteristics in the first few months of life [39, 45–48]. Alterations of sleep spindle characteristics are thought to be a reflection of the maturation of the thalamocortical system [33].

Sleep has been widely examined across the lifespan. However, thus far, no studies have examined associations of cognitive performance or other measures of behavioral performance with spindles or other NREM oscillations in children younger than 30 months of age. There is further a gap in the literature regarding the topographical investigation of brain activity during sleep in infants and toddlers, 12–30 months of age (but see Ref. [2]). This is a critical period marked by accelerated rates of brain development, such as the establishment of primary sensory, cognitive, and social functions. Here, we performed high-density EEG in typically developing children in this age group. For the first time, we provide a detailed topographical description of the main features of NREM sleep as a function of age and show how these features correlate with behavioral function after controlling for age.

Methods

Participants

Participants were 30 (14 males, 16 females) healthy infants and toddlers (mean age = 20 months, $SD = 5.19$, range = 12–30). All participants were screened with either the First Year Inventory (FYI) or the M-CHAT-R/F (Modified Checklist for Autism in Toddlers, Revised with Follow-Up) to ensure that participants were free of a developmental disability (DD) and risk of an autism spectrum disorder (ASD). Exclusion criteria were a reported history or presence of sleep problems, epilepsy, neurological/metabolic/genetic disorders, developmental disability, family history of an ASD, and severe visual, hearing, or motor impairments that would impede participation. We used a phone interview with a parent to identify participants described as good sleepers (sleep between 8 and 14 hr) at night, habitual nappers (nap a minimum 5 days per week), and free of medication (affecting sleep/daytime alertness/the circadian system). All participants were of healthy weight and height for age (i.e. 5th–85th percentile BMI) and born full-term. Two participants that did not sleep during the lab visit and one participant with an excessive rocking artifact in the EEG signal were excluded from analysis. We here present the data from the remaining 27 participants. Participant and maternal demographics are shown in Table 1. Since many analyses focus on two age groups determined by the median split of the age, demographics are demarcated as such. All experimental procedures were explained to parents before they provided written consent as approved by the Institutional Review Board at the University of North Carolina at Chapel Hill. Parents were compensated with cash for their participation in the study. All participants completed a home visit and a lab visit (nap).

Home visit

During the home visit, participants completed the *Mullen Early Scales of Learning* (MSEL) [49], and the *Vineland Adaptive Behavior Scales—2nd Edition* (VABS-2) [50]. The MSEL is a standardized norm-referenced tool designed to measure cognitive functioning from birth to 68 months of age. We use the Fine-Motor

Table 1. Participant and maternal demographics split by age

	Participants (n = 27)	
	<20 months n (%)	>20 months n (%)
Gender		
Female	8 (29.6)	7 (26.0)
Male	6 (22.2)	6 (22.2)
Race/ethnicity		
White	10 (37.8)	11 (40.7)
Black/African American	2 (7.4)	1 (3.7)
Asian/Pacific Islander	0 (0.0)	1 (3.7)
Other/Multiracial	1 (3.7)	0 (0.0)
Hispanic/Latino	0 (0.0)	1 (3.7)
Marital status		
Married	12 (44.45)	12 (44.45)
Never married	2 (7.4)	0 (0.0)
Widowed	0 (0.0)	1 (3.7)
Household income		
Less than \$25,000	3 (11.1)	1 (3.7)
\$25,000 to \$49,999	2 (7.4)	5 (18.5)
\$50,000 to \$74,999	2 (7.4)	4 (14.9)
\$75,000 to \$99,999	2 (7.4)	2 (7.4)
Greater than \$100,000	5 (18.5)	1 (3.7)
Maternal education		
Some college/vocational	2 (7.4)	0 (0.0)
4-year degree	4 (14.9)	7 (26.0)
Graduate/professional	8 (29.6)	6 (22.2)

<20 months—younger than 20 months.

>20 months—older than 20 months.

Standard Score and Visual Reception Standard Score from the MSEL as predictor variables in our EEG analysis. The VABS-2 is a standardized norm-referenced tool designed to measure daily functioning in individuals from birth to 90 years of age. The three predictor variables used from the VABS-2 for the analyses were the Communication Domain Standard Score (subscales: Receptive Communication, Expressive Communication), Motor Domain Standard Score (Subscales: Fine and Gross Motor), and the Socialization Domain Standard Score (subscales: Interpersonal Relationships, Play and Leisure Time, and Coping Skills.) Performance on the MSEL and VABS is shown in [Table 2](#).

Before the lab visit, all families completed questionnaires about their child's feeding, sleeping behaviors, and a brief demographic questionnaire. Parents were asked to complete a sleep diary and record all napping and sleeping for 7 days and return all questionnaires on the day of the lab visit.

Lab visit

Infants arrived at the lab 30 min before their typical naptime. This allowed time for the child to become acclimated with the setting. All infants were recorded with a 128-channel high density electrode net (Electrical Geodesic, Inc., Portland, OR). The net was placed on the infant before they fell asleep. Infants either slept in a bed, in a pack-n-play, or a car seat. Infant sleep behavior was videotaped and monitored. The average nap duration was 77.4 ± 4.2 SEM min.

EEG: recording and analysis

EEG signals were collected using Cz as the reference electrode. The signals were bandpassed filtered (0.1 to 200 Hz) and digitized

Table 2. Distribution of performance

	Younger group (n = 14)		Older group (n = 13)		P
	Mean	(SD)	Mean	(SD)	
MSEL	98.36	9.09	105.54	12.19	0.099*
MSEL VP	48.21	7.76	48.69	8.10	0.877
MSEL FM	54.43	6.55	49.46	9.29	0.125
MSEL RL	42.93	7.09	52.15	9.97	0.011**
MSEL EL	50.07	7.29	60.31	11.71	0.014**
VABS	94.43	11.62	102.31	9.60	0.066*
VABS Social	95.00	5.36	101.08	8.81	0.045**

Significant p value < 0.05**, trend level p value < 0.1*.

MSEL = Mullen Scales of Early Learning Composite; VP = Visual Perception; FM = Fine Motor; RL = Receptive Language; EL = Expressive Language; VABS = Vineland Adaptive Behavior Scales—Second Edition composite; VABS Social = Social (Domain Subscales: Interpersonal Relationships, Play and Leisure Time, and Coping Skills) standard score.

at 1000 Hz. Signals were offline resampled to 250 Hz, preprocessed using the PREP pipeline [51] including line-noise removal and robust average referencing (including bad channel removal), and additional band-pass filtering (0.5 to 40 Hz). Artifacts were rejected based upon visual scoring and semiautomatic artifact removal as published previously [4, 18].

Sleep EEG was scored visually for sleep stages (20 s epochs F4A1, C4A1, O2A1) in accordance with the American Academy of Sleep Medicine (AASM) [52] by two expert scorers and discrepancies were resolved by mutual agreement. We focused our scoring and analysis on NREM sleep (average 51.6 ± 3.3 SEM min). Only N2 and N3 were included in the NREM spectral analysis because (1) the missing electrooculography (EOG) and electromyography (EMG) made it difficult to separate between N1 and REM sleep, and (2) N1 represents more of a transition state between wake and NREM sleep and does not include sleep spindles or slow wave features. Spectral analysis was performed for all channels using the fast Fourier transform (Hanning window, 20 s epochs, average of five 4 s windows). The 20 s spectral power values were then averaged for all artifact-free NREM episodes. Since our narrow age group did not show overall frequency-unspecific/regional-unspecific difference in spectral values, we focused on absolute power values. This is in contrast to, e.g. the work of Kurth et al., that used normalized power values. However, for wider age ranges (e.g. 2–240 years of age), such a normalization is important because regional/frequency-specific differences are masked otherwise [4]. In our dataset, clear regional differences are still preserved by focusing on absolute power values.

Automatic spindle detection

To quantify specific sleep spindle characteristics, we performed an automatic sleep spindle detection using an established algorithm [53] with optimized settings as described in Ref. 54. The approach is described in detail in these publications. In short, we bandpass filtered the signal between 10 and 17 Hz. Thereafter, we detected sleep spindles from the filtered signal for each EEG channel separately based on upper threshold (six times the mean of filtered signal) and lower threshold (two times the mean of filtered signal) amplitude criteria. These threshold values have been used in a previous study defining age-related changes in spindle

characteristics in 2- to 5-years-old children [42]. Moreover, Warby and colleagues found an optimal detection performance for the used algorithm at six times the mean after the upper threshold value was modified from the original publication. For each spindle across all derivations, we calculated frequency, amplitude, duration, and density.

Statistical analysis

Statistical analyses were conducted in RStudio version 1.0.136 (RStudio, Inc., Boston, MA) and Matlab 2016 (Mathworks, Natick, MA). A median split of age was used to create two groups, older and younger than 20 months. We used unpaired t-tests to compare differences between the two groups (>20 and <20 months). EEG data (spectral calculations and spindle characteristics) from the two age groups were compared using electrode-wise unpaired t-tests. Correlations were performed using Pearson correlation (Table 3). To control for multiple comparisons across electrodes for both t-test and correlation analyses, we performed nonparametric statistical mapping (SnPM) with suprathreshold cluster analysis [55] as previously described and applied in high-density EEG studies [56–59]. Clusters of significant electrodes that were at least equal or above the 95th percentile on either side (minimal and maximal clusters) were considered significant and marked in the topographical plots.

Results

Performance on the MSEL and VABS

Table 2 shows means, SD, and *p* values for the older and younger groups on the MSEL for Visual Perception, Fine Motor, Expressive and Receptive Language and the VABS Socialization standard score. As expected, both receptive, expressive language and IQ show significant differences between the younger and older groups. In our sample, expressive and receptive language are highly associated with IQ and as one would expect during this distinct time period, the older group will have more exposure and thus more experience with language.

Developmental changes in spectral features of NREM sleep

We found an increase in SWA with significant positive correlations of power in the low δ (0.5–2 Hz), high θ (5.25–7 Hz), and β (20–25 Hz) frequency bands with age (Figure 1A). Negative correlations were found for high-spindle frequencies (13.25–15 Hz). Investigation of the averaged spectrogram for the two age groups revealed that the θ peak became slightly faster and more pronounced with age (Figure 1B). However, on an individual level, this could not be quantified because not all participants showed a clear distinct peak (Supplementary Figure 1). To further examine the age-dependent development of these spectral features, we computed the corresponding topographic maps after performing a median-split of the data by age (Figure 1C). There was also a clear developmental change in the spindle frequency range that was characterized by a decrease in power in the posterior regions. This decrease in posterior regions might reflect a shift from a single spindle peak in the younger children (around 14 Hz) to a double peak (around 12 and 16 Hz) with a trough around 14

Table 3. Correlations with age

Correlation	Measure	R	P
Age at HV	MSEL Composite	0.29	0.14
	MSEL Visual	0.16	0.42
	MSEL FM	−0.35	0.07*
	MSEL EL	0.47	0.01**
	MSEL RL	0.47	0.01**
	VABS Composite	0.33	0.09*
	VABS Communication SS	0.49	0.01**
	VABS Daily Living SS	0.12	0.55
	VABS Social Domain SS	0.37	0.06*
	VABS Motor Domain SS	0.2	0.39

Significant *p* value < 0.05**, trend level *p* value < 0.1* (statistics are not corrected for multiple comparisons).

MSEL = Mullen Scales of Early Learning Composite; Visual = Visual Perception; FM = Fine Motor; EL = Expressive Language; RL = Receptive Language; VABS = Vineland Adaptive Behavior Scales–Second Edition composite; VABS Communication = Communication domain standard score; VABS Daily Living = Daily Living domain standard score; VABS Social Domain = Social domain standard score; VABS Motor Domain = Motor domain standard score.

Hz in older children. Indeed, visual inspection of parietal spectra for each participant showed that only a few out of the 14 in the younger age group had a clear double peak, whereas the majority of the participants in the older group exhibited a double peak (Supplementary Figure 2). However, since not all participants showed a clear distinct peak in the spectral density plots, a statistical quantification was not possible. To better understand which spindle characteristics changed with age, we performed an automatic spindle detection (Figure 2). Similar to the spectral changes in the spindle frequency range of Figure 1C, spindle density and spindle duration significantly decreased in posterior regions. Furthermore, mean spindle frequency decreased in the same region. Thus, spindle power reduction might be specifically explained by a decrease in number and duration of sleep spindles in this age range. Considering other frequency bands in Figure 1C, the δ power topography showed a frontal increase and a clear occipital maximum for both age groups. Power globally increased with age; this effect was most pronounced and reached significance over frontal regions. For power in the θ band, there was a significant increase for frontal locations and for a right temporal cluster with age. However, the latter failed to reach statistical significance. β -Activity also significantly decreased with age, mainly over posterior temporal regions. However, the cluster sizes of significant electrodes did not remain significant after nonparametric suprathreshold cluster analysis.

It is important to note that the possible circadian influence, e.g. different naptimes, may have confounded age-related effects. All parents of the infants reported their child as taking one nap per day, though one can imagine that naptimes were slightly different between the age groups, with the younger infants typically having an earlier nap. However, even after controlling for naptime and the number of hours awake in comparing the groups, similar effects were found (Supplementary Figure 4). Naptime relative to 12 pm for the younger infants had a mean of 45 min (min. = −60, max. = 130), whereas naptime relative to 12 pm in older infants had a mean of 109 min (min. = 74, max. = 165, comparison *p* < 0.01). Thus, significant naptime differences could have conflated the age-related effects though after controlling for naptime (Supplementary Figure 4) this did not explain any age group differences in the data.

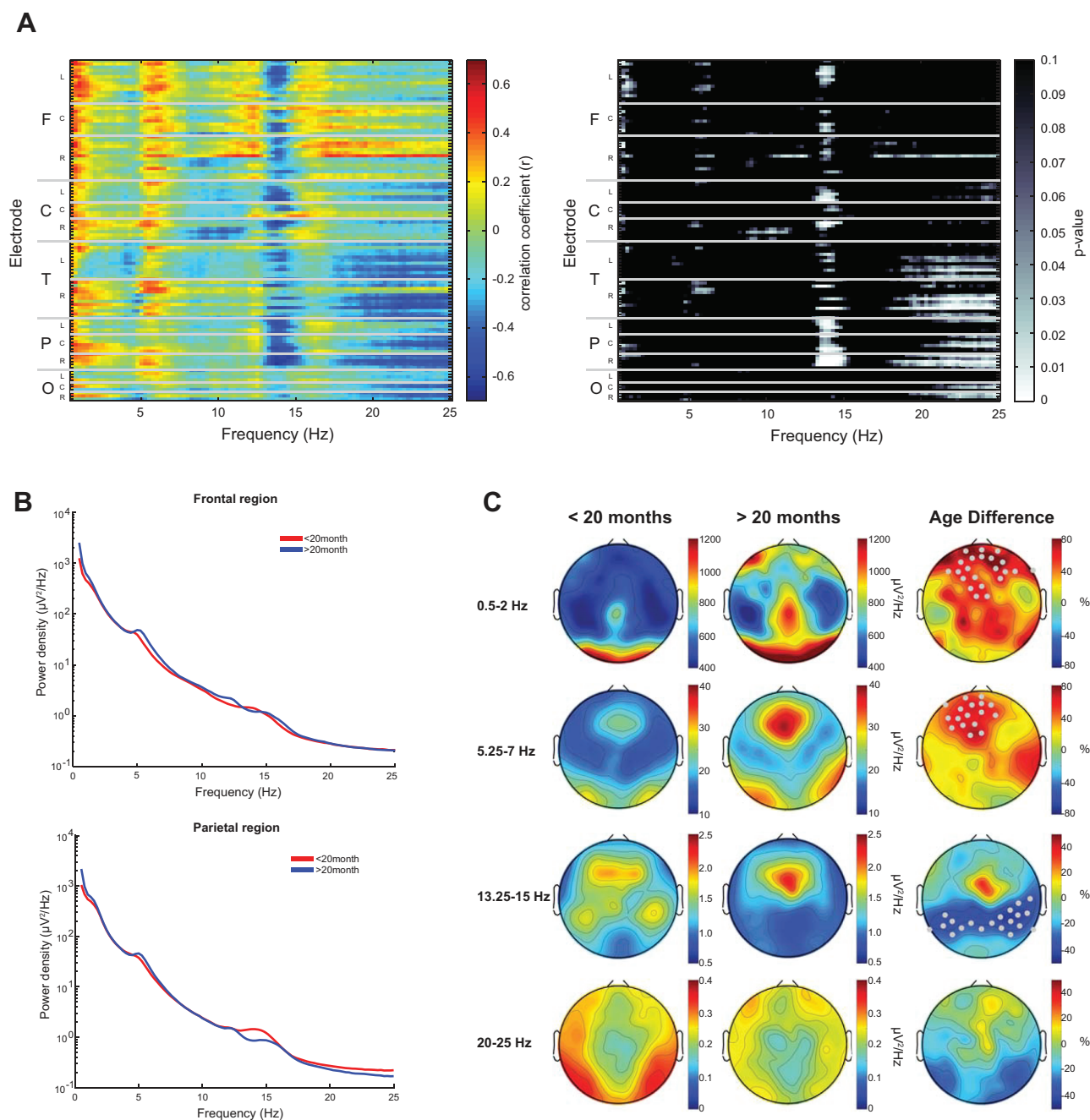


Figure 1. Spectral power during NREM sleep changes with age. (A) Correlation heat map of NREM spectral power values during NREM sleep and age. Left: Pearson correlation coefficients are depicted with warm and cold colors for positive and negative correlations, respectively. Right: p -values. (B) Spectral density plot for frontal and parietal electrode sites separated by median-split age group. Younger infants (<20 months) are shown in red and older infants (>20 months) are shown in blue. (C) Topographical illustration of distinct frequency bands that showed clear correlations with age (shown in (A)). Values are plotted on the planar projection of the hemispheric scalp model. Electrodes that showed a significant difference between age groups (unpaired t -test) after nonparametric statistical mapping (SnPM) and suprathreshold cluster analysis are marked with grey dots in the difference plot (older–younger).

NREM oscillations predict motor, language, and social skills, independent of age

The age range of 12–30 months is hallmarked by the development and maturation of motor, language, and social skills. We next investigated whether the frequency bands that we found to change with age were also related to skill development (Supplementary Figure 3 further shows the relationship of all frequency bins and channels with skill development). Several skills that we assessed with standardized scales were correlated

or tended to correlate with age, and therefore, we computed partial correlations controlled for age (Figure 3). Fine motor skills (measured by the MSEL, Table 3) were positively associated with low δ (0.5–2 Hz), high θ (5.25–7 Hz) activity at frontal and posterior electrode sites, and β (20–25 Hz) at parietal sites. Expressive language skills (measured by the MSEL) showed significant negative correlations over frontal and occipito-temporal regions in the δ band. Both Visual Perception and Receptive Language (measured by the MSEL) did not show any significant

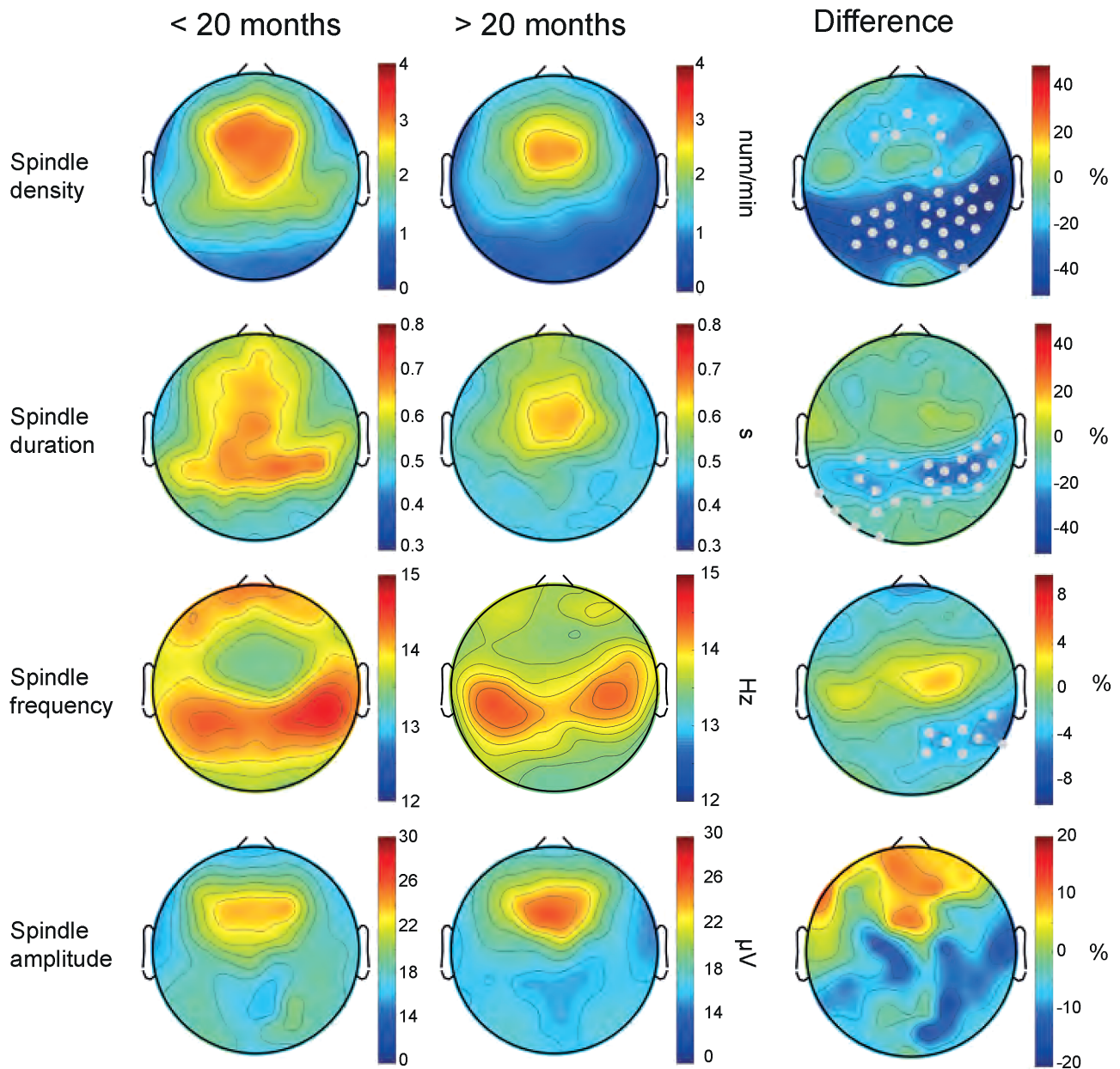


Figure 2. Topographical illustration of distinct frequency bands that showed clear correlations with age (shown in Figure 1A). Values are plotted on the planar projection of the hemispheric scalp model. Electrodes that showed a significant difference between age groups (unpaired *t*-test) after nonparametric statistical mapping (SnPM) and suprathreshold cluster analysis are marked with grey dots in the difference plot (older-younger).

correlations. The VABS standard score (indicative for social skill development) was negatively associated with power values in all observed frequency bands. Significant electrodes were widespread. Finally, we investigated whether maternal education level was predictive for spectral power values in infants and toddlers sleep. Indeed, higher maternal education levels were positively predictive for spindle and β power (Figure 3).

Discussion

The beginning years of life are the most sensitive periods for postnatal brain development [60, 61]. Within this critical period of development is the transition from infancy to toddlerhood

in which children exhibit vast behavioral changes. The present study aimed to investigate this time period by examining the sleep EEG in infants or toddlers between 12 and 30 months of age. The main findings show a pronounced change in power in the low δ , high θ , sleep-spindle, and β range during NREM sleep. We found that the density, duration, and frequency of sleep spindles changed with age in this group. However, most cognitive domains did not show any correlation with power in the spindle-frequency band when controlling for age. In contrast, other frequency bands, including the δ and θ bands, were correlated with language, fine-motor, and social communication. Collectively, low δ and high θ show a moderate change with age but are specifically predictive for skill maturation, whereas spindle activity seems to be mainly predictive for age.

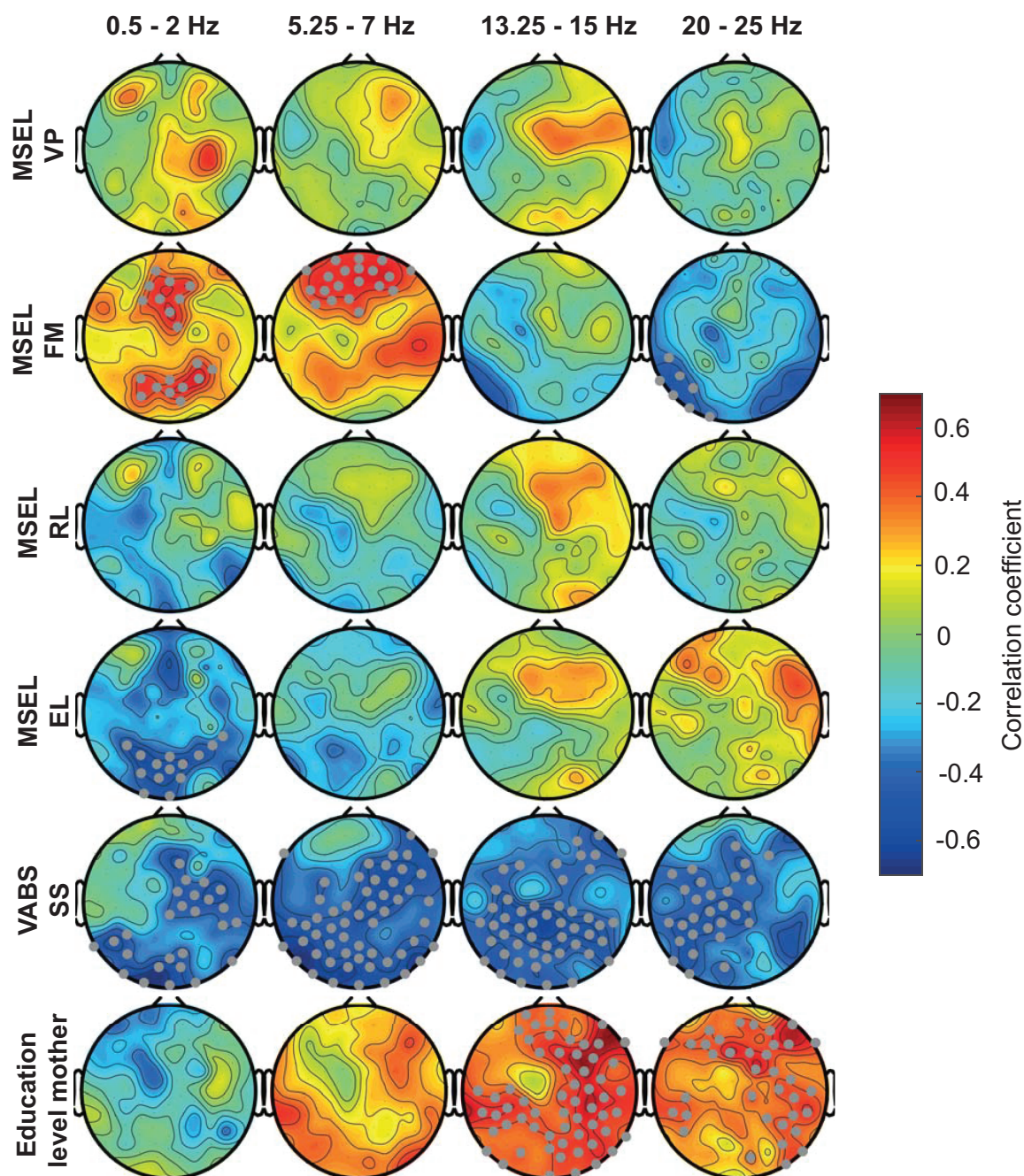


Figure 3. Topographical representation of Pearson correlation coefficients between different bands of spectral power, cognitive tasks (corrected for age), and maternal education level. Electrodes that showed significant correlations after permutation statistical correction (SnPM) marked with grey dots. Mullen Scales of Early Learning with subdomains (MSEL: Visual Perception, Fine Motor, Receptive Language, and Expressive Language). Vineland Adaptive Behavior Scale (VABS: Communication, Daily Living Skills, Socialization, and Motor Skills) standard score.

We found a split of the spindle spectral peak into a slower and faster peak with age in our sample. This finding expands previous research showing sleep spindle activity changes with maturation [33, 38, 42, 48]. We found a decrease in the spindle power specifically around 13–15 Hz for posterior regions. Overall, this decrease in power is mainly explained by a decrease in specific sleep spindle characteristics, spindle density, and duration, between the younger and older age groups. Furthermore, our results suggest a slight shift from a single spindle peak in the younger group in our sample (around 14 Hz) to a frontal double

peak (around 12 and 16 Hz) in the older group. One possible reason for the observed double peak could be changing anatomical and physiological properties of the thalamo–cortical system, the source of sleep spindles [33, 62]. The emergence of a double spindle peak is reported around 24 months [36]; however, in our data, the double peak emerged at around 20 months of age.

We further found that the δ power topography displayed a clear occipital maximum for both age groups with power globally increasing with age and becoming more pronounced over frontal regions. SWA, which represents δ power band during

NREM sleep, has been shown to regionally mature from toddlerhood to adulthood from posterior to anterior brain regions closely mirroring cortical maturation, specifically grey matter [4, 23, 63, 64]. In children between 2 and 5 years, the most pronounced δ activity is over occipital regions, which is in line with our findings [4]. Furthermore, it was shown that absolute δ power increases globally before puberty and thereafter consistently decreases with age. Here, we found a significant increase in a short age window of 18 months.

The θ band also shows a significant increase for frontal EEG locations. The θ peak became slightly faster when focusing on the averaged spectral density plot and was more pronounced in the older participants than the younger group. On an individual level, a θ peak shift is not possible to quantify since individual plots demonstrate that not all participants had a clear θ peak. Our findings support and expand earlier research showing an increase in power in the low-frequency range during the first year of life [2, 39, 65]. Furthermore, θ is present in older toddlers [4], though θ was not a focal point of investigation in previous studies with similar age groups [2, 4]. This oversight may be because θ is not a dominant feature in adult NREM sleep and the distinct θ peak in the spectrum of NREM sleep decreases around puberty [4, 66]. Of note, even though θ was observable as an overall peak in the averaged spectral density plot and most of the individual participants, not all participants had a clear distinct peak in this frequency range (Supplementary Figures 1). Future studies are needed to investigate this finding in further detail.

Due to the rapid development of behavioral skills in the age range studied here, we further examined how NREM sleep oscillations predict motor, language, and social skills, independent of age. Our findings suggest that oscillations such as low δ and θ activity reflect functional roles in sleep [39]. Fine motor skills were positively associated with low δ and high θ activity at frontal and posterior electrode sites. Although no previous studies report specific findings with regards to fine motor skills and its relationship to NREM sleep in the age group studied here, Kurth et al. and Lustenberger et al. find maturation of simple motor and complex motor skills are predicted by the topographical distribution of SWA in older children [5, 23].

Research examining sleep across the lifespan found clear associations with cognition, specifically "IQ." A child's IQ or rather developmental profile is a measure of multiple constructs often taking into account constructs such as language and motor development [49]. As children develop language, typically at differing rates in this time period, expressive and receptive languages are informative domains of a child's skillset. Interestingly, we found that expressive language skills were negatively correlated with δ activity over occipito-temporal regions. Similarly, the socialization domain (determined by the VABS standard score) was negatively associated with power values in all observed frequency bands. Why opposite correlation patterns between NREM sleep EEG oscillations and different skills were found is difficult to answer. Interestingly, lower-order proficiencies that develop earlier (e.g. motor skill learning) showed clear positive correlations with δ and θ activity, whereas more sophisticated skills that develop later (e.g. language, social skills) showed predominantly negative correlations. The development of language and social skills is seen as robust processes [61] that mediate other skillsets such as play [67, 68] and, furthermore, is strongly associated with

later academic achievement [69]. Thus, NREM sleep oscillations might depict these different time courses of skill development.

One interesting finding was that maternal education was associated with higher frequencies. Specifically, maternal education positively predicted power values for the higher frequency ranges, spindle band, and δ band. Additionally, maternal education was not significantly related to age ($r = -0.14, p = 0.5$). It is important to note that the level of maternal education in the current sample ranged from having some college credits to having a graduate or advanced professional degree. Maternal education has been examined in young infants from high and low SES backgrounds during resting state EEG [70]. Although no differences were found in their sample to date, no research has yet to examine the effects of maternal or paternal education on NREM sleep and this may be an interesting avenue to further consider to better understanding development and sleep. Thus, it would have been interesting to see whether this correlation would persist if lower levels of maternal education were present in the sample.

Limitations

Like any scientific study, our work has limitations. First, we solely examined NREM sleep and not REM sleep due to technical limitations. Specifically, we did not record the EMG and only had high-quality EOG data from some of the participants. Without EMG and EOG, it was challenging to identify REM sleep with certainty. Second, sleep was recorded during a midday nap, and some infants had only NREM sleep. Thus, overnight recordings might be better suited to obtain a more complete picture of sleep network dynamics that includes the structure of transitions between NREM and REM sleep. Third, given that this was a nap study and we wanted families to feel comfortable, we asked families to arrive during their child's typical naptime. Thus, it is necessary to consider circadian influence, of different nap times, that may have confounded age-related effects. However, even after controlling for nap time, age-related effects still persisted in our data set. Finally, we used a cross-sectional instead of a longitudinal design due to practical resource considerations. Given the strong interpersonal variance in human EEG data, a longitudinal design will shed a more refined light on the developmental maturation of NREM sleep in young children.

Conclusion

The transition between infancy and toddlerhood is a critical period in development. In this age range, there are pronounced changes in many developmental domains including language and social skills. The aim of the present study was to characterize the topography of sleep in this important and relatively understudied age range. Our findings show that NREM sleep oscillations depict the rapid transition of cortical maturation and skill development that occurs in this age range. These findings suggest that NREM sleep oscillations might be used as a normative trajectory in development. Our study provides a baseline as the first step towards detection of maturation delays in at-risk populations (e.g. children at-risk for an ASD) for which a developmental disorder is suspected.

Supplementary Material

Supplementary material is available at SLEEP online.

Acknowledgments

The authors would like to thank April Benasich and Sue Peters for their guidance and support with the infant EEG measurement. We would also like to thank Michael Murias for his guidance and feedback with EEG measurement. Finally, we thank Jhana Parikh for helping with data acquisition.

Funding

Research reported in this publication was partially supported by the National Institute of Mental Health under Award Number R01MH101547 (to F.F.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This work was also partially supported by UNC Psychiatry, UNC School of Medicine (to F.F.), North Carolina Translational NC TraCS 2KR721505 (J.P. and C.L.), and the Swiss National Science Foundation (to C.L., grant P300PA_164693, P3P3PA_171525).

Notes

Conflicts of interest statement. F.F. is the lead inventor of noninvasive brain stimulation technology for which UNC has filed multiple patents. F.F. is the founder, CSO, and majority owner of Pulvinar Neuro LLC.

References

- Tierney AL, et al. Brain development and the role of experience in the early years. *Zero Three*. 2009;**30**(2):9–13.
- Novelli L, et al. Mapping changes in cortical activity during sleep in the first 4 years of life. *J Sleep Res*. 2016;**25**(4):381–389.
- Buchmann A, et al. EEG sleep slow-wave activity as a mirror of cortical maturation. *Cereb Cortex*. 2011;**21**(3):607–615.
- Kurth S, et al. Mapping of cortical activity in the first two decades of life: a high-density sleep electroencephalogram study. *J Neurosci*. 2010;**30**(40):13211–13219.
- Kurth S, et al. Mapping the electrophysiological marker of sleep depth reveals skill maturation in children and adolescents. *Neuroimage*. 2012;**63**(2):959–965.
- Campbell IG, et al. Longitudinal trajectories of non-rapid eye movement delta and theta EEG as indicators of adolescent brain maturation. *Proc Natl Acad Sci*. 2009;**106**(13):5177–5180.
- Ringli M, et al. Developmental aspects of sleep slow waves: linking sleep, brain maturation and behavior. *Prog Brain Res*. 2011;**193**:63–82.
- Huber R, et al. Sleep, synaptic connectivity, and hippocampal memory during early development. *Trends Cogn Sci*. 2014;**18**(3):141–152.
- Doucette MR, et al. Topography of slow sigma power during sleep is associated with processing speed in preschool children. *Brain Sci*. 2015;**5**(4):494–508.
- Tessier S, et al. Intelligence measures and stage 2 sleep in typically-developing and autistic children. *Int J Psychophysiol*. 2015;**97**(1):58–65.
- Geiger A, et al. The sleep EEG as a marker of intellectual ability in school age children. *Sleep*. 2011;**34**(2):181–189.
- Fogel SM, et al. The function of the sleep spindle: a physiological index of intelligence and a mechanism for sleep-dependent memory consolidation. *Neurosci Biobehav Rev*. 2011;**35**(5):1154–1165.
- Bódizs R, et al. Sleep spindling and fluid intelligence across adolescent development: sex matters. *Front Hum Neurosci*. 2014;**8**:952.
- Gruber R, et al. The association between sleep spindles and IQ in healthy school-age children. *Int J Psychophysiol*. 2013;**89**(2):229–240.
- Lustenberger C, et al. Triangular relationship between sleep spindle activity, general cognitive ability and the efficiency of declarative learning. *PLoS One*. 2012;**7**(11):e49561.
- Hoedlmoser K, et al. Slow sleep spindle activity, declarative memory, and general cognitive abilities in children. *Sleep*. 2014;**37**(9):1501–1512.
- Rasch B, et al. About sleep's role in memory. *Physiol Rev*. 2013;**93**(2):681–766.
- Lustenberger C, et al. The multidimensional aspects of sleep spindles and their relationship to word-pair memory consolidation. *Sleep*. 2015;**38**(7):1093–1103.
- Marshall L, et al. Boosting slow oscillations during sleep potentiates memory. *Nature*. 2006;**444**(7119):610–613.
- Lustenberger C, et al. Feedback-controlled transcranial alternating current stimulation reveals a functional role of sleep spindles in motor memory consolidation. *Curr Biol*. 2016;**26**(16):2127–2136.
- Kurziel L, et al. Sleep spindles in midday naps enhance learning in preschool children. *Proc Natl Acad Sci*. 2013;**110**(43):17267–17272.
- Ngo HV, et al. Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. *Neuron*. 2013;**78**(3):545–553.
- Lustenberger C, et al. Developmental trajectories of EEG sleep slow wave activity as a marker for motor skill development during adolescence: a pilot study. *Dev Psychobiol*. 2017;**59**(1):5–14.
- Astill RG, et al. Sleep spindle and slow wave frequency reflect motor skill performance in primary school-age children. *Front Hum Neurosci*. 2014;**8**:910.
- Amzica F, et al. Electrophysiological correlates of sleep delta waves. *Electroencephalogr Clin Neurophysiol*. 1998;**107**(2):69–83.
- Contreras D, et al. Cellular basis of EEG slow rhythms: a study of dynamic corticothalamic relationships. *J Neurosci*. 1995;**15**(1 Pt 2):604–622.
- Steriade M, et al. A novel slow (< 1 Hz) oscillation of neocortical neurons in vivo: depolarizing and hyperpolarizing components. *J Neurosci*. 1993;**13**(8):3252–3265.
- Achermann P, et al. Sleep homeostasis and models of sleep regulation. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 5th ed. Philadelphia: Elsevier Saunders; 2011:405–417.
- Esser SK, et al. Sleep homeostasis and cortical synchronization: I. modeling the effects of synaptic strength on sleep slow waves. *Sleep*. 2007;**30**(12):1617–1630.
- Vyazovskiy VV, et al. Cortical firing and sleep homeostasis. *Neuron*. 2009;**63**(6):865–878.
- Huttenlocher PR. Synaptic density in human frontal cortex - developmental changes and effects of aging. *Brain Res*. 1979;**163**(2):195–205.

32. Huttenlocher PR, et al. Regional differences in synaptogenesis in human cerebral cortex. *J Comp Neurol*. 1997;**387**(2):167–178.
33. De Gennaro L., & Ferrara M. Sleep Spindles: An Overview. *Sleep Medicine Reviews*. 2003;**7**:423–440.
34. Gibbs FA, et al. *Atlas of Electroencephalography*. 1941.
35. Ellingson RJ. Development of sleep spindle bursts during the first year of life. *Sleep*. 1982;**5**(1):39–46.
36. Jankel WR, et al. Sleep spindles. *J Clin Neurophysiol*. 1985;**2**(1):1–35.
37. Andrillon T, et al. Sleep spindles in humans: insights from intracranial EEG and unit recordings. *J Neurosci*. 2011;**31**(49):17821–17834.
38. Clawson BC, et al. Form and function of sleep spindles across the lifespan. *Neural Plast*. 2016;**2016**:6936381.
39. Jenni OG, et al. Development of the nocturnal sleep electroencephalogram in human infants. *Am J Physiol Regul Integr Comp Physiol*. 2004;**286**(3):R528–R538.
40. Tarokh L, et al. Developmental changes in the human sleep EEG during early adolescence. *Sleep*. 2010;**33**(6):801–809.
41. Shinomiya S, et al. Development of sleep spindles in young children and adolescents. *Clin Electroencephalogr*. 1999;**30**(2):39–43.
42. McClain JJ, et al. Developmental changes in sleep spindle characteristics and sigma power across early childhood. *Neural Plast*. 2016;**2016**:3670951.
43. Chu CJ, et al. The maturation of cortical sleep rhythms and networks over early development. *Clin Neurophysiol*. 2014;**125**(7):1360–1370.
44. Nagata K, et al. [Developmental characteristics of frontal spindle and centro-parietal spindle]. *No To Hattatsu*. 1996;**28**(5):409–417.
45. Hughes JR. Development of sleep spindles in the first year of life. *Clin Electroencephalogr*. 1996;**27**(3):107–115.
46. Tanguay PE, et al. Evolution of sleep spindles in childhood. *Electroencephalogr Clin Neurophysiol*. 1975;**38**(2):175–181.
47. Louis J, et al. Ontogenesis of nocturnal organization of sleep spindles: a longitudinal study during the first 6 months of life. *Electroencephalogr Clin Neurophysiol*. 1992;**83**(5):289–296.
48. Scholle S, et al. Sleep spindle evolution from infancy to adolescence. *Clin Neurophysiol*. 2007;**118**(7):1525–1531.
49. Mullen EM. *Mullen scales of early learning*. Circle Pines, MN: AGS Circle Pines; 1995.
50. Sparrow SS, et al. *Vineland-II Adaptive Behavior Scales*. AGS Publishing: Crowley, TX; 2005.
51. Bigdely-Shamlo N, et al. The PREP pipeline: standardized preprocessing for large-scale EEG analysis. *Front Neuroinform*. 2015;**9**:16.
52. Iber C, et al. The scoring of cardiac events during sleep. *J Clin Sleep Med*. 2007;**3**(2):147–154.
53. Ferrarelli F, et al. Reduced sleep spindle activity in schizophrenia patients. *Am J Psychiatry*. 2007;**164**(3):483–492.
54. Warby SC, et al. Sleep-spindle detection: crowdsourcing and evaluating performance of experts, non-experts and automated methods. *Nat Methods*. 2014;**11**(4):385–392.
55. Nichols TE, et al. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp*. 2002;**15**(1):1–25.
56. Huber R, et al. Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. *Nat Neurosci*. 2006;**9**(9):1169–1176.
57. Lustenberger C, et al. Inter-individual and intra-individual variation of the effects of pulsed RF EMF exposure on the human sleep EEG. *Bioelectromagnetics*. 2015;**36**(3):169–177.
58. Plante DT, et al. Effects of partial sleep deprivation on slow waves during non-rapid eye movement sleep: A high density EEG investigation. *Clin Neurophysiol*. 2016;**127**(2):1436–1444.
59. Maric A, et al. Intra-individual increase of homeostatic sleep pressure across acute and chronic sleep loss: A high-density EEG study. *Sleep*. 2017. **40**(9). doi:10.1093/sleep/zsx122
60. Gilmore JH, et al. Longitudinal development of cortical and subcortical gray matter from birth to 2 years. *Cereb Cortex*. 2012;**22**(11):2478–2485.
61. Shonkoff JP. In: Shonkoff JP, Phillips DA, eds. *From Neurons to Neighborhoods: The Science of Early Childhood Development*. Oxford University Press: Washington (DC); 2000.
62. Lüthi A. Sleep spindles: where they come from, what they do. *Neuroscientist*. 2014;**20**(3):243–256.
63. Buchmann A, et al. EEG sleep slow-wave activity as a mirror of cortical maturation. *Cereb Cortex*. 2011;**21**(3):607–615.
64. Feinberg I, et al. Sleep EEG changes during adolescence: an index of a fundamental brain reorganization. *Brain Cogn*. 2010;**72**(1):56–65.
65. Sankupellay M, et al. Characteristics of sleep EEG power spectra in healthy infants in the first two years of life. *Clin Neurophysiol*. 2011;**122**(2):236–243.
66. Campbell IG, et al. Longitudinal trajectories of non-rapid eye movement delta and theta EEG as indicators of adolescent brain maturation. *Proc Natl Acad Sci U S A*. 2009;**106**(13):5177–5180.
67. Lifter K, et al. Object knowledge and the emergence of language. *Infant Behav Dev*. 1989;**12**(4):395–423.
68. Pierce-Jordan S, et al. Interaction of social and play behaviors in preschoolers with and without pervasive developmental disorder. *Top. Early Child. Special Educ*. 2005;**25**(1):34–47.
69. Walker D, et al. Prediction of school outcomes based on early language production and socioeconomic factors. *Child Dev*. 1994;**65**(2 Spec No):606–621.
70. Tomalski P, et al. Socioeconomic status and functional brain development - associations in early infancy. *Dev Sci*. 2013;**16**(5):676–687.