2021 43rd Annual International Conference of the
IEEE Engineering in Medicine & Biology Society (EMBC)
Oct 31 - Nov 4, 2021. Virtual Conference

Scalp EEG markers of normal infant development using visual and computational approaches

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Abstract— **The infant brain is rapidly developing, and these changes are reflected in scalp electroencephalography (EEG) features, including power spectrum and sleep spindle characteristics. These biomarkers not only mirror infant development, but they are also altered by conditions such as epilepsy, autism, developmental delay, and trisomy 21. Prior studies of early development were generally limited by small cohort sizes, lack of a specific focus on infancy (0-2 years), and exclusive use of visual marking for sleep spindles. Therefore, we measured the EEG power spectrum and sleep spindles in 240 infants ranging from 0-24 months. To rigorously assess these metrics, we used both clinical visual assessment and computational techniques, including automated sleep spindle detection. We found that the peak frequency and power of the posterior dominant rhythm (PDR) increased with age, and a corresponding peak occurred in the EEG power spectra. Based on both clinical and computational measures, spindle duration decreased with age, and spindle synchrony increased with age. Our novel metric of spindle asymmetry suggested that peak spindle asymmetry occurs at 6-9 months of age.**

Clinical Relevance— **Here we provide a robust characterization of the development of EEG brain rhythms during infancy. This can be used as a basis of comparison for studies of infant neurological disease, including epilepsy, autism, developmental delay, and trisomy 21.**

I. Introduction

The rapid development of the human brain between birth and two years of age is associated with marked changes in the scalp electroencephalogram (EEG). A common metric used to characterize the EEG is the power of band-specific oscillations. Generally speaking, in healthy infants, lower frequency power (<6Hz) decreases while higher frequency power (>6Hz) increases during this time period [1][2]. Moreover, a 3-4 Hz posteriorly dominant rhythm (PDR) appears around 3 months of age, which then gradually increases in frequency to 5-7 Hz by 12 months. The normal ontogeny of such EEG patterns can be altered by disease. For instance, reduced power in the frontal EEG derivations of a 3-month-old may indicate increased risk of autism or expressive language delay later in life [3]. Likewise, developmentally delayed children exhibit lower mean frequencies, greater delta power, and lower theta and alpha power than normal controls [4]. Further, a type of epilepsy called infantile spasms is associated with diffusely increased power in all frequency bands [5].

Sleep spindles are another salient EEG feature that evolves during normal infant development. Sleep spindles are short bursts of 10-16 Hz electrical activity lasting up to several seconds that occur primarily during stage 2 sleep [6][7]. In healthy infants, spindles can first be appreciated at 2 months of age. Spindle duration peaks around 5-12 months, then decreases until around two years of age [7][8]. Spindles initially appear mostly asynchronous, occurring independently in the left and right frontocentral head regions and with equal abundance. The degree of synchrony of spindles increases gradually until 18-24 months of age, at which time they should be universally synchronous. This synchronization is believed to reflect the ongoing myelination of the brain. Functionally, spindles have been linked to memory consolidation in adults [9][10], and various spindle characteristics are correlated with cognitive performance in children, including memory, sensorimotor function, and planning ability [11]. As with EEG band power, spindles can be an important marker of disease. For instance, infants with trisomy 21 exhibit delayed evolution of sleep spindles as well as spindles that are less abundant than those of normal infants [12]. Additionally, adults with high-functioning autism have less abundant sleep spindles than healthy adults [13]. Furthermore, the spindles of adults with cortical malformations can appear persistently asymmetric (i.e. only occurring in one hemisphere) compared to the symmetry of healthy adult spindles [14].

While EEG band power and sleep spindles are powerful metrics for normal development and studying disease, previous studies in infants are limited. Many studies investigate small cohorts [15][16][17], while others study broad age spans, ranging from infancy to adolescence [1][8]. Further, most studies of young children rely on visual interpretation/analysis alone, which suffers from modest interrater reliability. Beyond being very time consuming, visual spindle analysis requires a consensus of 2-3 experts for substantial reliability and four or more experts for near-perfect reliability [18]. While automated detection of sleep spindles is increasingly common, to our knowledge, the only use in an infant cohort was a single magnetoencephalogram study of seven infants [15].

To thoroughly study the evolution of infant EEG while addressing the limitations of prior studies, we collected EEG data from a large cohort of healthy infants (n=240), subdividing them into eight age-based subgroups. To quantify the EEG ontogeny associated with normal infant development,

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we paired visual and computational analyses to assess changes in EEG band power and sleep spindles, and we present a novel measure of spindle symmetry.

II. Methods

A. EEG recordings and Dataset

This study was approved by the Institutional Review Board of the Children's Hospital of Orange County (CHOC). We retrospectively identified 240 healthy subjects less than 2 years old who had routine EEGs performed between 2012 and 2018. This cohort was divided into 8 subgroups, with 30 subjects each, based on corrected age (0-3 months, 3-6 months, etc., corrected for prematurity) (Table 1). Children with known neurological disease or abnormal EEG findings were excluded. Routine EEGs were recorded using a Nihon Kohden EEG acquisition system, with 19 scalp electrodes following the 10-20 international standard electrode placement. Data were recorded at or downsampled to 200Hz, and recording duration was 37 ± 7.5 minutes (mean ± standard deviation). A registered polysomnographic technologist (CG) staged the data as wakefulness, stage 1, stage 2, and stage 3 sleep for infants 3-24 months old, or wakefulness, quiet sleep, and active sleep for infants 0-3 months old in accordance with the American Academy of Sleep Medicine (AASM) guidelines.

Artifactual EEG segments containing photic stimulation and impedance checks were marked via visual inspection and removed. Automated amplitude-based artifact detection was also implemented [19]. Briefly, after applying a broadband bandpass filter (1.5-40Hz Butterworth), time segments with an amplitude exceeding four times the standard deviation above the mean channel amplitude were defined as artifact and removed.

B. Clinical Analysis

For each subject, a clinical evaluation of PDR, sleep spindle duration, and sleep spindle synchrony was performed by board-certified pediatric neurologists (CS, TY) under the supervision of a board-certified pediatric epileptologist (DS). Reviewers were blinded to age. Degree of spindle synchrony was defined as the percentage of all sleep spindles that occurred simultaneously in both the left and right hemispheres, based on amplitude symmetry. The entire EEG record was viewed, and a single value of each metric was determined for each subject.

TABLE I. Participant Demographics

Group	Age, mean (SD)	Female *n* (%)	Stage 2 Sleep *n (%)*
0-3 m.	1.54 (0.94)	12 (40.00)	15 (50.00)
3-6 m.	4.67 (0.93)	16 (53.33)	23 (76.67)
6-9 m.	7.41 (0.83)	19 (63.33)	27 (90.00)
9-12 m.	10.24 (0.74)	19 (63.33)	23 (76.67)
12-15 m.	13.57 (0.87)	17 (56.67)	20 (66.67)
15-18 m.	16.33 (0.97)	15 (50.00)	25 (83.33)
18-21 m.	19.01 (0.73)	17 (56.67)	21 (70.00)
21-24 m.	22.54 (0.92)	16 (53.33)	22 (73.33)

C. Computational Analysis

We extracted segments of EEG during wakefulness and stage 2 sleep for computational analysis. All subjects had periods of wakefulness recorded, while 187 subjects demonstrated stage 2 sleep (Table 1). Wakefulness was selected because the PDR is most prominent during quiet wakefulness, and stage 2 sleep was chosen due to its association with sleep spindles. For the computational analysis, note that the subjects in the 0-3 month age group do not exhibit standard non-REM sleep stages (instead their sleep is scored as quiet or active). Moreover, sleep spindles do not fully emerge until roughly 1-2 months corrected age [7]. However, for this age group we analyzed quiet sleep due to the similarity in structure to stage 2 sleep [1].

Power analysis. For each electrode and each brain state (wakefulness and stage 2 sleep), power was calculated as the squared magnitude of the discrete Fourier transform in 5-second windows, divided by the number of samples, and averaged across all windows. The mean power for each age group was calculated across subjects, and then the relative power was defined as the power in 1 Hz frequency bins divided by the power of the 3–6 month age group.

Sleep spindle analysis. Stage 2 sleep was used for the sleep spindle analysis. A wavelet-based automatic sleep spindle detection algorithm was applied, in which time segments were classified as a sleep spindle if the power in the extended sigma band (10-16Hz) crossed two amplitude thresholds [20][21]. Sleep spindles were visually detected for two subjects from each age group under the supervision of a board-certified pediatric epileptologist (DS); these events were used as a ground truth to validate the performance of the automatic detector and select the parameters that provided the highest specificity. The algorithm contained two parameters that could be tuned to capture infant sleep spindles. The maximum allowable individual spindle duration was set to 10 seconds to capture long infant spindles [22]. The amplitude threshold was tested across three different multiplier values; we ultimately chose the highest threshold value for all subjects, as we wanted to maximize the specificity of the detection. When comparing automatically detected spindles to visually marked spindles, the precision was 79.7% ± 17.5% (mean ± standard deviation) across all groups.

After detecting spindles for each subject, we calculated duration and amplitude symmetry for each spindle to match the visual assessment of spindle duration and synchrony, respectively. Sleep spindle duration was defined as the difference between each spindle's start and end time. An average spindle duration was computed for each subject. To approximate spindle synchrony, we measured amplitude asymmetry between the left and right hemispheres using channels C3 and C4, respectively. For each spindle, the amplitude envelope in the extended sigma band was determined for channels C3 and C4 using a Hilbert transform. Spindle amplitude asymmetry for each individual spindle was then defined as the ratio of the mean extended sigma amplitude in C3 to the mean extended sigma amplitude in C4, then normalized by subtracting one and taking the absolute value. An asymmetry value of zero indicated that the spindle amplitude was equal in C3 and C4, while a positive value

indicated that the spindle amplitude was asymmetric, i.e. higher in one hemisphere than the other. All individual spindle asymmetry values were averaged for each subject.

D. Statistics

Differences across age groups were evaluated using a one-way Kruskal Wallis test (Levene's test for homogeneity of variance on all measures were $p < 0.05$), with Dunn's test to account for multiple comparisons. Chi-square test statistic was used to test the variation in the five visual asynchrony percentage levels across the eight age groups. Ranked (Spearman) correlation was performed between both the clinical and computational measures of sleep spindle duration and synchrony/asymmetry.

III. Results

A. The peak frequency and power of the posterior dominant rhythm increase with age

Clinical evaluation of the EEG indicated a significant increase in the peak frequency of the PDR with age (Fig. 1A), from 3.8 Hz at 0-3 months to 7.5 Hz at 21-24 months old. Statistically, the PDR was significantly higher for every group in the second year compared to every age group in the first year of development (all $p<0.05$). The rate of increase in the PDR with age slowed around 15 months, with no significant differences between the 15-18, 18-21, and 21-24 month age groups.

Computational analysis of the EEG showed a similar trend, with the relative EEG power spectrum exhibiting a corresponding peak between 5 Hz and 10 Hz during wakefulness (Fig. 1B, left). EEG power above 5 Hz increased with age during wakefulness until 18 months, at which we noted a decline in beta band power relative to the 15-18 month age group. In the 21-24 month age group, both alpha and beta band power decreased relative to the 18-21 month age group. Similarly, during stage 2 sleep, EEG power above 5 Hz increased with age, with the largest increases occurring in the beta frequency band, relative to the 3-6 month age group (Fig. 1B, right). We also noted a peak in stage 2 EEG power in the 10-15 Hz range, which increased in power with age, likely reflecting the presence of sleep spindles.

B. Sleep spindle duration decreases in the first year

Based on visual assessment of sleep spindles, we found a significant decrease in spindle duration between subjects in the first and second year of infancy (Fig. 2A, $p<0.001$). The first six months of infancy were characterized by long spindles (median duration 3.5 seconds) with high variance across subjects. During the first year, spindle duration decreased, with the median value reaching one second at 12-15 months. In the second year of infancy, the median duration of visually marked spindles was one second for each age group, with less variability in duration across subjects.

The spindle durations calculated using automated sleep spindle detection mirrored the clinical results (Fig. 2B). Spindles in the 3-6 month and 6-9 month age groups had median durations of 3.0 seconds, and 2.1 seconds, respectively, significantly longer than those in age groups greater than 12 months (all $p<0.01$). Spindle duration steadily

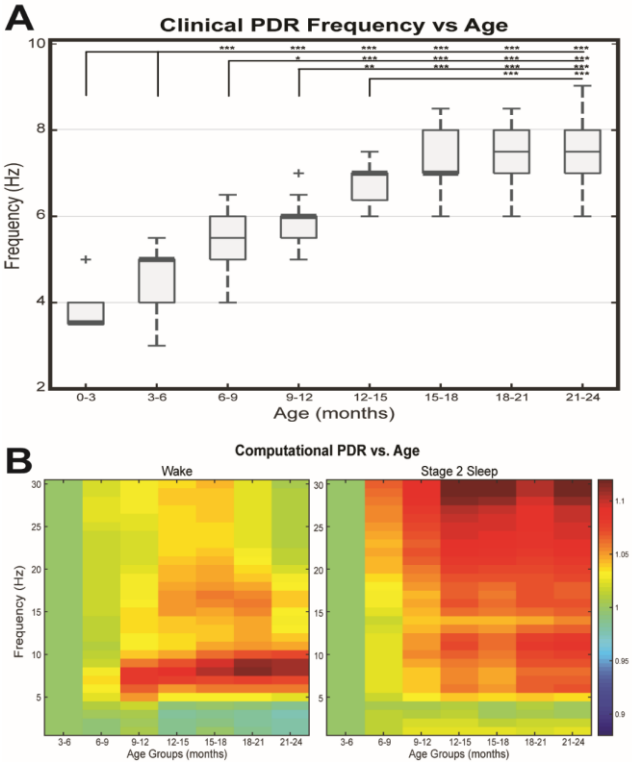

Figure 1. A) Clinical assessment of PDR vs. age. B) Average EEG power in channels O1/O2 for each age group, measured relative to 3-6 months. Results are shown for wakefulness (left) and stage 2 sleep (right).

decreased until 12-15 months of age (median duration 1.4 seconds). We found no significant changes in spindle duration between groups in the second year (all $p>0.9$).

C. Sleep spindle symmetry increases with age

Visual assessment of sleep spindle asynchrony was measured as the percentage of sleep spindles in the EEG record that were not synchronous, evaluated in increments of 25% (Fig. 2C). A synchronous sleep spindle was defined as one which was visually apparent in both the left and right hemispheres, with approximately symmetric amplitude. The variance of this measure was high, with a range greater than or equal to 50% in every age group except 21-24 months. However, there was a trend of decreasing asynchrony with age, with (1) subjects less than 3 months old having significantly higher asynchrony than those older than 9 months, (2) subjects less than 9 months old having higher asynchrony than subjects older than 18 months, and (3) subjects less than 18 months old having significantly higher asynchrony than those older than 21 months (Fig. 2C, all $p<0.05$).

The computational metric for spindle asymmetry exhibited lower variance within age groups than the clinical measure, and it thus provided a more detailed picture of the

changes during infancy (Fig. 2D). The computational spindle asymmetry initially increased, peaking at 6-9 months. After this peak, the spindle asymmetry steadily decreased with age until 12-15 months. Spindle asymmetry was significantly higher for subjects 6-12 months old, compared to subjects 12-21 months old (all $p < 0.05$). No significant differences were noted between the 12-15, 15-18, 18-21, and 21-24 month age groups (all $p > 0.67$), and low values indicated high levels of symmetry during the second year.

IV. Discussion and Conclusion

Peak power and the posterior dominant rhythm. Visual analysis demonstrated a clear increase in the PDR from 3 Hz to 7 Hz between birth and 18 months of age, consistent with established knowledge [23]. However, from 18 to 24 months of age, no further significant increase in the PDR was noted, despite prior reports that the PDR should gradually increase to ~8 Hz at 24 months of age [23]. We suspect this is due to our small subgroup sample size; 30 subjects is likely insufficient to detect the smaller increases expected at 18-24 months of age. In the computational analysis, we noted that the EEG peak frequency was consistently higher than the PDR, while both increased similarly with age. We suspect that the peak frequency analysis is capturing slightly different information than the visual analysis of the PDR. For example, when clinicians are interpreting the PDR, periods of isolated eye closure/quiet wakefulness are chosen, but the computational analysis incorporated all wakefulness data. Further, the EEG power is presented relative to values seen at 3-6 months of age, which may shift the relative peak frequency to higher values.

Automated sleep spindle detection. Automated sleep spindle detection was previously applied to healthy infants using MEG data [15]; however, we are the first to do so using infant scalp EEG. Given our large dataset, we opted for automated sleep spindle detection with high specificity to minimize false positive detections [20][21]. We chose this algorithm because it demonstrated the highest level of specificity when compared to five other sleep spindle detectors [24]. This algorithm was also successfully used to study normal longitudinal EEG changes in children 2 to 5 years of age [25] and thalamocortical dysfunction in children with epileptiform discharges [26].

Sleep spindle duration. Using an automated algorithm to detect spindles, we showed that infant sleep spindles reach their maximum duration in the 3-6 month age range, then subsequently shorten until around 12-15 months, after which their duration remains stable through 2 years of age (Fig. 2B). This pattern was significantly correlated with visual estimation of spindle duration (Fig. 2A; $\rho = 0.54$, $p < 0.05$), and it was also consistent with previous studies utilizing visual spindle marking [7][8]. During the first year of life, average spindle duration was 2.3 +/- 0.95 seconds, whereas in the second year of life, average duration shortened to 1.6 seconds, and the standard deviation decreased to +/-0.44 seconds, demonstrating increased spindle duration stability from 1-2 years of age.

Sleep spindle synchrony and symmetry: When sleep spindles first appear around 2 months of age, they occur in a predominantly asynchronous fashion. This is believed to be due to the neonatal brain lacking sufficient interhemispheric myelination to support synchronous activity between the left and right thalamocortical relay circuits. As myelination progresses throughout the first few years of life, spindles become proportionally more synchronous until reaching full synchrony around 18-24 months of age.

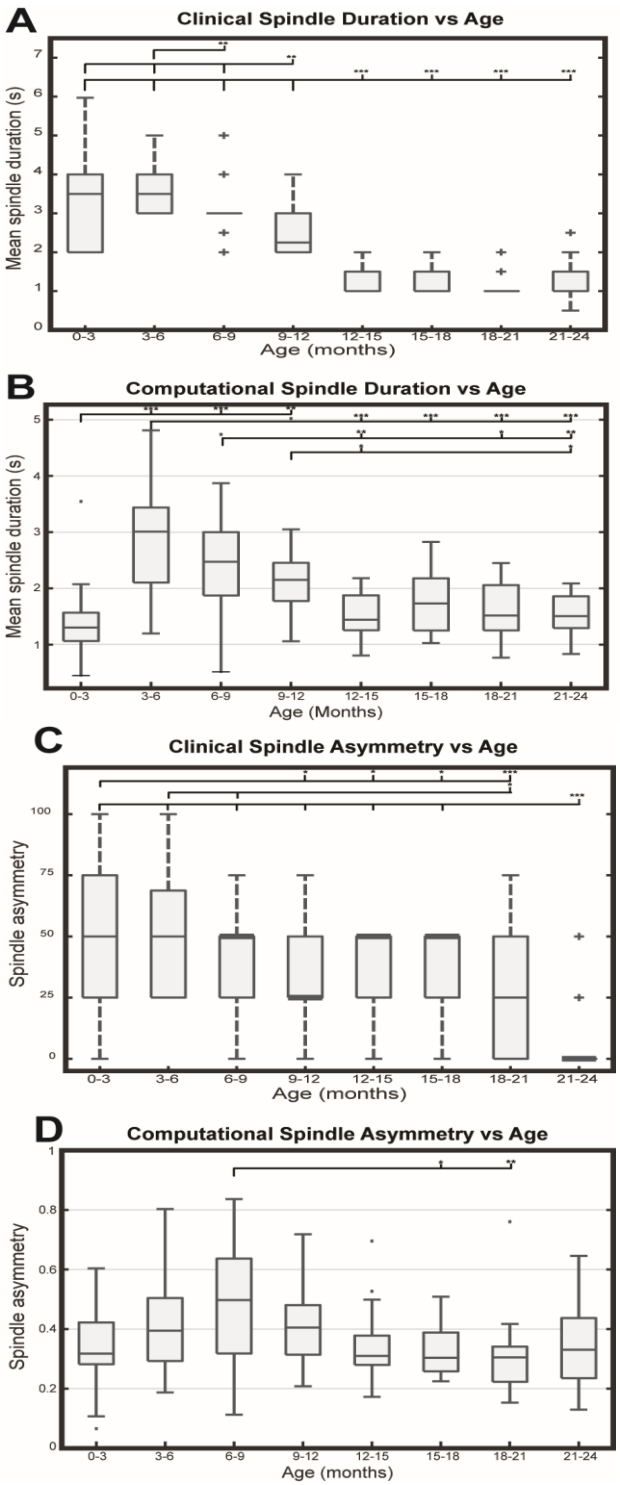

Figure 2. A) Visual assessment of sleep spindle duration vs. age. B) Average spindle duration for each subject vs. age, using automated detection. C) Visual assessment of sleep spindle asymmetry vs. age. D) Mean computational spindle asymmetry for each subject vs. age. For all subfigures, * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

While clinically marked spindles demonstrated a trend of decreasing asynchrony with age (Fig. 2C), the significance of this trend was undoubtedly complicated by a high variance in the measurement, particularly in the first six months of infancy (51 +/- 25%). Our computational analysis of spindle asymmetry showed significant changes during the first year of life, with spindles initially increasing in asymmetry between 3-6 and 6-9 months of age, then decreasing until 12-15 months of age, after which asymmetry remained consistent through 2 years of age. Visual estimation of asynchrony at 21-24 months of age found the vast majority of subjects to have complete spindle synchrony by that time, whereas computationally measured asymmetry remained distinct from the asymmetry value of zero (which denotes complete symmetry). While both visual and computational sleep spindle asymmetry appeared to decrease with age, the two metrics were not found to be significantly correlated (ρ = 0.11, p=0.13), which may be due to the wide variance in visually marked symmetry, as previously described. The ordinal asynchrony values (0%, 25%, 50%, 75%, or 100%) were tested across each age group to test independence (χ^2 = 112.5, $p < 0.05$).

One limitation of our study is that certain neurophysiological characteristics, including elements of sleep spindles, exhibit high interindividual variability [7]. Although we attempted to mitigate this by analyzing entire routine EEG studies and collecting data from 240 children, each 3-month age range we studied consisted of only 30 subjects. Moreover, some subjects did not exhibit substantial durations of non-REM sleep and others lacked a posterior dominant rhythm for analysis.

Overall, this work provides a rigorous characterization of healthy EEG ontogeny in young children. This results in both a description of normal brain development and a basis of comparison for the study of neurological diseases such as such as autism, trisomy 21, and epilepsy [5][12][13][26]. Peak power, the PDR, and sleep spindle duration and symmetry all exhibit consistent evolution with age that can be accurately and objectively measured with robust, widely available computational methods. As these techniques become more integrated into clinical practice, they will become standardized tools to enhance EEG interpretation and augment its clinical utility.

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