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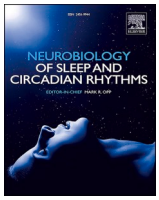

Lack of association between behavioral development and simplified topographical markers of the sleep EEG in infancy

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ABSTRACT

The sleep EEG mirrors neuronal connectivity, especially during development when the brain undergoes substantial rewiring. As children grow, the slow-wave activity (SWA; 0.75–4.25 Hz) spatial distribution in their sleep EEG changes along a posterior-to-anterior gradient. Topographical SWA markers have been linked to critical neurobehavioral functions, such as motor skills, in school-aged children. However, the relationship between topographical markers in infancy and later behavioral outcomes is still unclear. This study aims to explore reliable indicators of neurodevelopment in infants by analyzing their sleep EEG patterns. Thirty-one 6-month-old infants (15 female) underwent high-density EEG recordings during nighttime sleep. We defined markers based on the topographical distribution of SWA and theta activity, including central/occipital and frontal/occipital ratios and an index derived from local EEG power variability. Linear models were applied to test whether markers relate to concurrent, later, or retrospective behavioral scores, assessed by the parent-reported Ages & Stages Questionnaire at ages 3, 6, 12, and 24 months. Results indicate that the topographical markers of the sleep EEG power in infants were not significantly linked to behavioral development at any age. Further research, such as longitudinal sleep EEG in newborns, is needed to better understand the relationship between these markers and behavioral development and assess their predictive value for individual differences.

1. Introduction

Electroencephalography (EEG) during sleep is a non-invasive technique that allows observing neuronal activity in a state of low external interference. Using high-density (hd) electrode arrays with a multitude of channels, EEG provides a high temporo-spatial resolution and is ideal for vulnerable populations like young children due to its non-invasiveness. EEG during sleep offers a unique window into the connection between sleep with cognitive and psychological outcomes (Gregory et al., 2009; Mindell et al., 2017). Sleep EEG topography, in particular, allows the study of region-specific neurodevelopment in early childhood (Page et al., 2018; Satomaa et al., 2020), which has yet to be fully understood in infancy.

Time spent in the behavioral stage of sleep is a crucial part of a child's development, and the neurophysiological activity captured with the sleep EEG can provide valuable insights into the child's brain connectivity. Previous research has shown a correlation between EEG patterns and behavioral and cognitive outcomes in healthy children (Buchmann et al., 2011; Ednick et al., 2009; Reynaud et al., 2018) and infants (Jaramillo et al., 2021; Schoch et al., 2021). The non-rapid-eye-movement (NREM) sleep EEG, and therein specifically the oscillatory activity of slow wave activity (SWA, spectral power in the 1–4.5 Hz frequency range), undergoes drastic changes across childhood and the period of brain development, for example, with a shift in the

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predominant location of SWA from posterior to anterior regions of the scalp (Kurth et al., 2010). This shift in SWA topography mirrors the development of cortical anatomy (Shaw et al., 2008) and can be easily understood through a simplified frontal/occipital ratio of SWA (LeBourgeois et al., 2019).

Gray matter thickness also follows a spatial gradient similar to SWA (Deoni et al., 2016; Shaw et al., 2008; Sowell et al., 2004; Thompson et al., 2001). Interestingly, the maturation of SWA along the posterior-anterior gradient of the scalp relates to behavioral-maturational changes in the cortex and is predictive of changes in brain function. For example, the maturation of motor skills (4.4–25.9 years) follows the SWA change with an estimated delay of 3.7 years (Kurth et al., 2012). SWA maps relate not only to gray (Buchmann et al., 2011; Kurth et al., 2017) but also to white matter (LeBourgeois et al., 2019) and can be altered in functional neurological disorders. For example, school-age children and adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD) have been found to have a 20% reduction in SWA across the entire brain (Furrer et al., 2019) and show furthermore region-specific alterations compared to healthy controls (Ringli et al., 2013). This aligns with previous neuroimaging results showing reduced gray matter in children with ADHD (Casey et al., 1997; Mostofsky et al., 2002), and the reversibility of these changes through stimulant medication (Rubia et al., 2021).

The sleep EEG topography is linked to myelination in preschool- and school-age children. This relationship was investigated using the mcDESPOT (multi-compartmental model-based DESPOT) protocol (Deoni et al., 2008), a magnetic resonance imaging (MRI) technique that models proton density to distinguish tissue properties and estimates brain myelin content. In healthy children aged 2–8 years, the simplification of sleep SWA maps by using a frontal/occipital (f/o) ratio was found to predict whole-brain myelin outcomes 3.5 years later (LeBourgeois et al., 2019). This discovery provided a specific EEG marker for brain myelin. But also further sleep-EEG markers for cortical morphology have been tested, for example, a central/occipital (c/o) ratio approach was used to identify preterm-born infants, who are generally at heightened risk for neurodevelopmental impairments (Guyer et al., 2019). The c/o ratio unraveled significant neurophysiological differences between term- and preterm-born infant cohorts at age 3 months, that predominated in the theta frequency range (4.5–7.5 Hz). However, it remains to be determined which behavioral functionality this ratio relates to and to what extent it serves as a predictive marker. Such markers could reflect the maturation of neuronal structures and the maturation of connections that are related to the establishment of homeostatic and circadian sleep regulators, such that the maturation of these neuronal substrates could contribute to the gradual increase of sleep consolidation across infancy and early childhood (Jenni et al., 2004).

Once established, non-invasive neurophysiological markers can critically support diagnosis and thereby promote intervention strategies addressing the problem that many neurodevelopmental disorders go undiagnosed until school-age (Bachmann et al., 2017; Brett et al., 2016; Sheldrick et al., 2017).This study aimed to evaluate simple and reliable indicators of neurodevelopmental growth by analyzing topographical sleep EEG patterns and behavioral outcomes in healthy infants. Specifically, we hypothesized that an increased c/o ratio of theta power and an increased f/o ratio of SWA correspond to advanced behavioral-developmental status. Additionally, we captured the specific scalp regions showing the greatest interindividual differences with a data-driven variability index in SWA and theta power.

2. Methods

2.1. Participants

This study included 35 healthy 6-month-old infants in a larger longitudinal investigation of primarily actimetric sleep-wake assessments (Schoch et al., 2022). Two participants did not fall asleep, leaving 33 participants with EEG data. Participants obtained an at-home hdEEG (124 electrodes) sleep assessment, and parent-rated surveys about infants' behavior were completed at 3 (N = 21), 6 (N = 31), 12 (N = 22), and 24 (N = 27) months of age. Inclusion criteria were vaginal birth, birth at term (37–43 weeks of gestation), primarily breastfeeding until 3 months, birth weight above 2500g, and families being native German speakers or having a high level of knowledge of the language. In addition, participants had to be in good general health and neither received any medications affecting the sleep-wake cycle nor antibiotics before the assessment started. Participants were excluded for diagnosis of central nervous system disorders, brain damage, chronic diseases, or family history of sleep or mental disorders. The study procedures were approved by the cantonal ethics committee (BASEC 2016-00730) and adhered to the Declaration of Helsinki. The parents of the infants provided written consent for their participation in the study after being fully informed of the study procedures.

2.2. Study design

2.2.1. Behavioral development

To assess the infants' developmental status, the primary caregiver completed a translated version of the age-appropriate Ages and Stages Questionnaire (ASQ) (Squires et al., 1995) at all time points. The ASQ is a validated method for quantifying behavioral development (Gollenberg et al., 2010), consisting of 5 subdomains (Communication, Gross Motor, Fine Motor, Problem Solving, and Personal Social) and of a Collective Score that encompasses all subdomains. In addition to the Collective Score, this study focused on the Gross Motor and Personal Social subdomains, as developmental delay in the first year of life is most frequent within the Gross Motor area, resulting from EEG and MRI-based research (Valla et al., 2015). A close association between Personal Social development and infants' sleep habits was revealed in our previous study with over 150 infants (Schoch et al., 2022). This is consistent with the intertwined role of early sleep in social-emotional development (Kaley et al., 2012; Mindell et al., 2017; Williams et al., 2016). Specifically, the Gross Motor subdomain assessed how infants use their muscles for activities such as rolling, sitting, walking, and running and how their legs and arms are incorporated in various situations, and the Personal Social subdomain captured infants' interactions with others and self-help skills. For example, at 6 months, the Gross Motor subdomain entails, "Does your baby roll from back to belly without putting its arms under itself?", while the Personal Social subdomain at 12 months entails, "Does your baby play with a doll or stuffed animal by hugging it?". ASQ scores did not reveal any outliers, neither at 3, 6, nor at 12 months (Fig. S1).

2.2.2. Sleep EEG assessment at-home

The hdEEG sleep recording was performed at the infants' homes and scheduled to their habitual evening bedtimes. A 124-electrodes sponge net was used (Electrical Geodesics Sensor Net, Electrical Geodesics Inc., EGI, Eugene, OR), which was soaked in a solution of electrolyte for 3–5 min, that was composed of potassium chloride (10 mL), baby shampoo (1 mL) and warm tap water (1L). The net size was matched with head circumference, and the net was carefully positioned on the infant's head and adjusted to vertex and mastoids. Impedances were kept below 50 kΩ, and the recording was performed on a Mac computer with software from Electrical Geodesics Inc. (EGI, Eugene, OR) with a sampling rate of 500 Hz and a band-pass filter of 0.01–200 Hz. The recording was referenced to the vertex (Cz) and lasted up to 2 h.

2.2.3. Sleep EEG preprocessing

The EEG data was first down-sampled to 128 Hz and filtered using a band pass filter (0.5–50 Hz). Sleep stages were assigned in 20-s epochs by two independent scorers using the American Academy of Sleep Medicine (AASM) Manual with pediatric adjustments (Iber, 2007). Disagreement between scores was resolved through discussion. Artifacts

were semi-automatically identified and visually verified using EEG frequency and power information (Huber et al., 2000). Poor-quality channels likely influenced by muscle artifacts were excluded from the analysis. One recording was excluded due to over 50% missing electrodes in the central area (37 excluded electrodes after noise correction). One participant with only 13.7 min of NREM was excluded. EEG power was calculated for the remaining participants (n = 31) and electrodes (on average 101 electrodes per infant). In the SWA (0.75–4.25 Hz) and theta (4.5–7.5 Hz) frequency range for the first 30 min of artifact-free NREM sleep (comprising stages N2 and N3). For three participants included, artifact-free NREM sleep was only 28, 26, and 25 min.

2.2.4. Sleep EEG analysis

We employed a three-pronged analytical approach, including markers of sleep EEG topography based on literature (i, ii) and a data-driven topography marker (iii) based on SWA and theta power. The first literature-based marker (i) was inspired by research on term- and preterm-born 3-month-olds and included three primary regions of interest (occipital, central, frontal) (Guyer et al., 2019). We used theta power in line with this study and also considered SWA, which reflects brain maturation and behavior (Huber et al., 2004, 2006; Kurth et al., 2010; Wilhelm et al., 2014). We captured EEG power in three clusters: occipital, central, and frontal (Fig. 1A and B), and thereof calculated each subject's central/occipital (c/o) and frontal/occipital (f/o) ratios. The c/o ratio was obtained by averaging the power in SWA and theta frequencies at central and occipital clusters, respectively. (i.e., SWA-c/o-GRatio, Theta-c/o-GRatio). The f/o ratio was calculated similarly by averaging the power in SWA and theta frequencies at frontal and occipital clusters for each subject: SWA-f/o-GRatio, Theta-f/o-GRatio.

The second literature-based marker (ii) was derived from research on the maturation of SWA topography in healthy children and adolescents ages 2–20 years (Kurth et al., 2010). This maturation was found to follow a gradient from the occipital to frontal regions and is believed to be linked to the development of brain myelin (LeBourgeois et al., 2019). To apply this marker in our analysis, we identified electrode clusters with occipital and frontal electrodes (Fig. 1C) and calculated a f/o ratio by averaging the power in SWA and theta frequencies for each subject (SWA-f/o-GRatio, Theta-f/o-GRatio).

The third approach was data-driven, and (iii) was designed to identify the scalp regions with the largest variability between subjects within the current dataset. This approach illuminated locations where inter-individual differences in infant EEG power were maximal. We first computed the standard deviation (SD) of SWA and theta power across subjects for each electrode. We then sorted the electrodes based on the SD and defined the 10% of electrodes with the highest SD as a cluster of interest (Fig. 1D). The mean within each cluster provided the Local Variability Index (LVI), which was calculated for both SWA and theta power (SWA-LVI, Theta-LVI). Based on the primary investigation of this paper to assess the association between topographical sleep patterns and brain maturation, the LVI would specifically unravel individual differences within the cohort that would probably relate to individual behavioral developmental status. Individual EEG data for SWA and theta frequency ranges, normalized to the average across the subjects' EEG power map did not reveal any outliers (Fig. S2).

2.3. Statistical analysis

An ANOVA was performed to test for power differences among selected electrodes for 5 frequency ranges as defined previously (Kurth et al., 2010): SWA 1–4.5 Hz, theta 4.75–7.75 Hz, alpha 8–9.75 Hz, sigma 10–15 Hz, and beta 20–25 Hz. General linear models were used to conduct three analyses: First, to investigate the associations for the four EEG markers (f/o-GRatio, c/o-GRatio, c/o-KRatio, and LVI) measured at 6 months in the two frequencies (SWA, theta) with the concurrent behavior measured at 6 months. Second, to examine the predictive power of the EEG markers measured at 6 months at both frequencies, for later behavioral outcomes measured at 12 and 24 months. Third, to determine whether behavioral status would be the driver, behavioral measures at 3 months were evaluated on their prediction of EEG markers at 6 months. For all models, three infant behavioral variables were included (Composite, Gross Motor, Personal Social).

For each general linear model, we controlled for sex and exact age at EEG recording and set the significance level to $p < 0.05$. p-values were corrected for multiple testing using the false discovery rate method (Benjamini and Hochberg, 1995). We used R Studio (R version 4.0.0), the packages mice, dplyr, tidyr, and magrittr (Bache and Wickham, 2014; Wickham et al., 2015; Wickham and Henry, 2019), and Matlab R2020a.

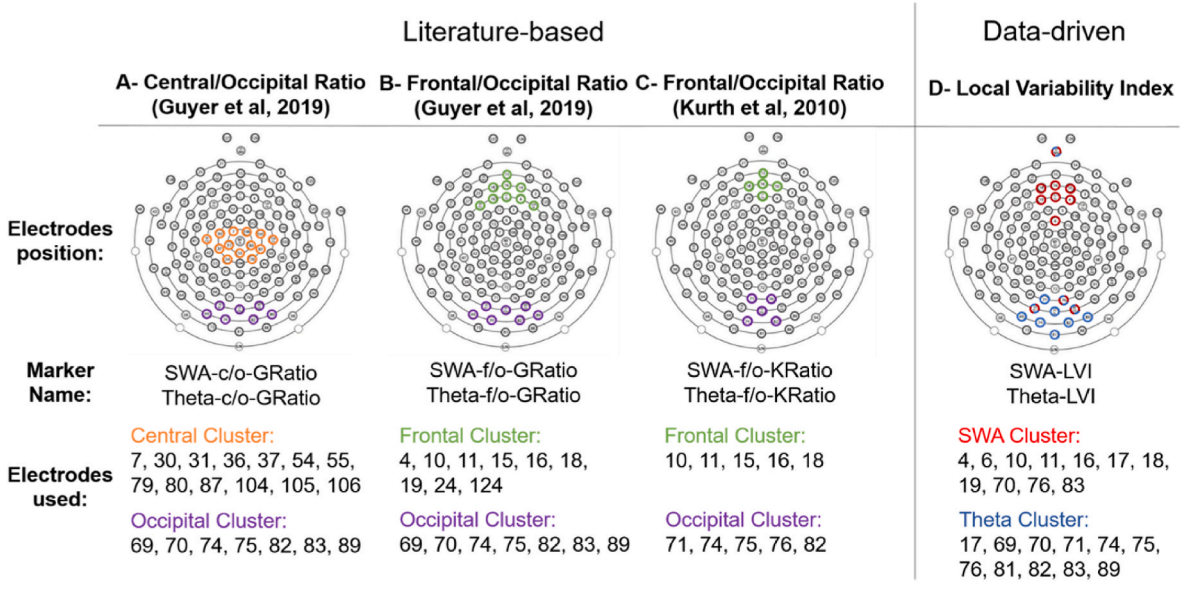

Fig. 1. Electrode clusters used to calculate topographical markers. Literature-based markers: a) central and occipital cluster for SWA-c/o-GRatio and Theta-c/o-GRatio, b) frontal and occipital cluster for SWA-f/o-GRatio, Theta-f/o-GRatio, and c) frontal and occipital cluster for SWA-f/o-KRatio, Theta-f/o-KRatio. Data-driven markers: d) SWA and Theta cluster for SWA-LVI and Theta-LVI.

3. Results

First, we investigated the EEG power spectrum of selected electrodes (along the posterior-anterior axis) over the right and left hemispheres, which revealed a typical age-specific pattern. ANOVA was performed for 5 classical frequency ranges: SWA 1–4.5 Hz, theta 4.75–7.75 Hz, alpha 8–9.75 Hz, sigma 10–15 Hz, and beta 20–25 Hz, which revealed a significant effect of electrode location in the right hemisphere in the SWA band ($p < 0.005$, $f = 18$) and no significant effect in the other frequency bands ($p \geq 0.17$; Fig. 2). In the left hemisphere, a location effect was found for the beta frequency band ($p = 0.03$; $f = 2.4$). Interestingly, no other location effect reached significance among the electrodes of the left hemisphere ($p \geq 0.11$).

3.1. Association between topographical EEG markers and infants' concurrent behavioral status

Next, we examined the relationship between infant sleep EEG markers at age 6 months and their behavioral scores at the same age. Neither significant associations with overall behavior (Composite) nor with Gross Motor nor with Personal scores were detected for any of the ratios (p-values≥0.31; Table 1). Thus, results do not support the application of GRatio, KRatio, or LVI as markers for concurrent behavioral status in healthy infants at 6 months of age, as captured with the ASQ survey.

3.2. Association between topographical EEG markers and infants' future behavioral status

We then examined whether the topographical sleep EEG markers at 6 months of age predict later behavioral outcomes at 12 and 24 months of age. The results showed that the GRatios, KRatios, and LVI were not significant predictors of overall behavior, as measured by the Composite score at 12 or 24 months (SWA-c/o-GRatio, Theta-c/o-GRatio, SWA-f/o-GRatio, Theta-f/o-GRatio: range of p-values 0.61–0.91; Table 2). These results indicate that the selected topographical sleep EEG markers assessed in healthy infants at 6 months do not predict later behavioral outcomes, as captured by the parent-reported ASQ, at either 12 or 24 months. Therefore, our hypothesis that GRatios, KRatios, or LVI could serve as simple predictors of behavioral outcomes at 12 and 24 months is not supported.

3.3. Association between infant behavioral status and successive topographical EEG markers

Finally, we explored the relationship between behavioral status and topographical-maturational EEG markers and vice versa. Specifically, we investigated whether infant behavioral scores at age 3 months predict EEG markers at 6 months. Findings show no correlation between overall behavior (Composite), Gross Motor, or Personal Social scores at 3 months with the GRatios, KRatios, or LVI (Table 3).

In sum, results show no significant concurrent, predictive, or retrospective relationships between parent-reported Composite, Gross Motor, or Personal Social skills and the simplified topographical EEG markers, as investigated in healthy infants age 6 months.

4. Discussion

This study aimed to determine the applicability of a straightforward, easy-to-use infant sleep EEG maturation indicator as a behavioral correlate. This investigation was based on the assumption that brain activity during the first hour of nighttime sleep of healthy infants is related to behavioral scores and developmental outcomes, for which we used a simple measure based on previous research in children and adolescents. However, the results of the current study did not support the hypothesis, such that none of the markers evaluated - the central/occipital ratio or the frontal/occipital ratios, or the local variability index in SWA or theta frequencies - reliably indicated concurrent, predictive, or retrospective infant developmental behavioral scores in a sample of healthy, full-term infants.

We calculated three topographical ratios (central/occipital and two frontal/occipital) and evaluated their relationship with parent-rated behavioral developmental status. We targeted SWA and theta power, that have been previously linked to neurostructural and behavioral maturation (Kurth et al., 2010), and showed high inter-individual variability in 3-month-old infants (Guyer et al., 2019), respectively. However, our results did not align with the conclusions of previous studies on 3-month-old preterm/term-born infants and older children. This difference may arise from the age differences between study populations. In the current study, EEG was evaluated at 6 months of age, and behavior was measured at 3, 6, 12, and 24 months, while in (Guyer et al., 2019), measures took place at 3 months, and in (Kurth et al., 2010), and (LeBourgeois et al., 2019), assessments were done between 2.4-19.4 years and 2.4–8.0 years, respectively. This suggests that findings regarding EEG topographical markers may not be directly transferable

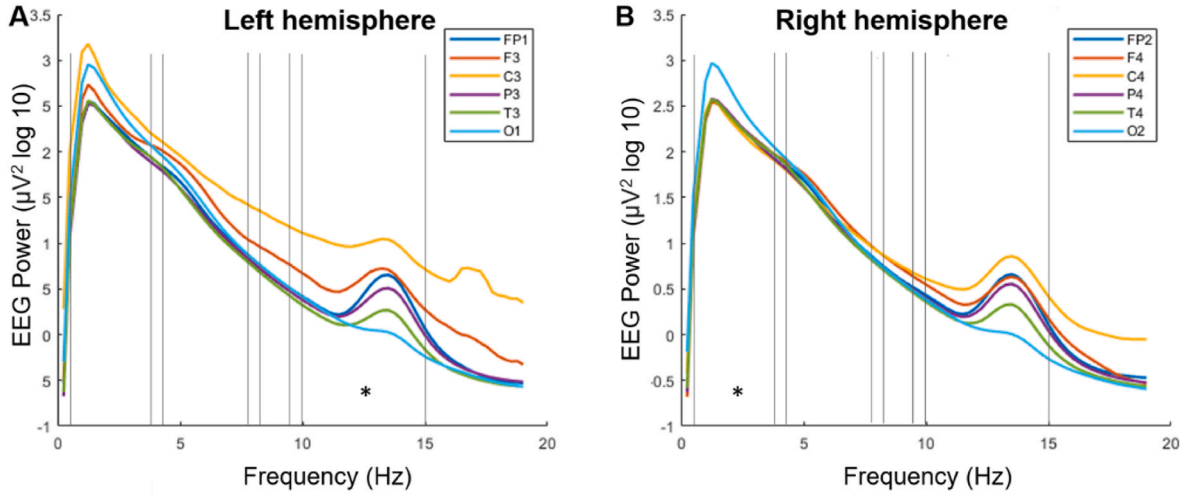

Fig. 2. Power spectrum of A) electrodes on the left hemisphere and B) electrodes on the right hemisphere of the scalp in 31 healthy infants, including the first 30 min of artifact-free NREM nighttime sleep (n = 31 for all channels). For a visual representation, lines were smoothed through the moving average adjustment, including five data points. Asterisks represent significant ANOVA in the corresponding averaged frequency ranges with $p < 0.05$.

Table 1
Relationship between maturational sleep EEG markers and concurrent behavioral status in 31 healthy infants aged 6 months. Statistics are based on linear mixed models with b as an unstandardized beta coefficient and the False Discovery Rate-corrected p-values addressing multiple comparisons.

Behavioral scores (ASQ)	c/o-GRatio						f/o-GRatio					
	Composite		Gross Motor		Personal Social		Composite		Gross Motor		Personal Social	
	b	p	b	p	b	p	b	p	b	p	b	p
SWA	1.01	0.31	−1.10	0.81	0.34	0.44	0.43	0.58	0.78	0.51	−0.19	0.95
Theta	−0.1	0.93	−0.64	0.56	0.82	0.72	0.23	0.81	0.56	0.31	−0.85	0.66
Behavioral scores (ASQ)	f/o-KRatio						LVI					
	Composite		Gross Motor		Personal Social		Composite		Gross Motor		Personal Social	
	b	p	b	p	b	p	b	p	b	p	b	p
SWA	0.43	0.66	0.71	0.48	−0.32	0.77	−0.40	0.70	−1.39	0.17	0.95	0.35
Theta	0.29	0.77	0.95	0.37	−0.67	0.58	0.37	0.71	−0.61	0.56	1.84	0.91

Table 2
Topographical sleep EEG markers in healthy infants as predictors of behavioral status at A) age 12 (n = 22) and B) 24 months (n = 27). Statistics are based on linear mixed models with b as an unstandardized beta coefficient and the False Discovery Rate-corrected p-values addressing multiple comparisons.

A)

Behavioral scores (ASQ)	EEG markers at 6 mo as predictors of behavioral outcome at 12 mo											
	c/o-GRatio						f/o-GRatio					
	Composite		Gross Motor		Personal Social		Composite		Gross Motor		Personal Social	
	b	p	b	p	b	p	b	p	b	p	b	p
SWA	0.46	0.64	−0.84	0.65	−0.46	0.60	0.12	0.89	0.17	0.95	−0.51	0.59
Theta	0.11	0.91	−0.35	0.77	−0.67	0.69	−0.50	0.61	0.39	0.64	−0.46	0.95
Behavioral scores (ASQ)	f/o-KRatio						LVI					
	Composite		Gross Motor		Personal Social		Composite		Gross Motor		Personal Social	
	b	p	b	p	b	p	b	p	b	p	b	p
SWA	0.10	0.92	0.20	0.85	0.42	0.68	−0.28	0.86	0.70	0.45	−0.20	0.89
Theta	−0.37	0.78	−0.37	0.81	0.13	0.89	−0.76	0.48	−1.7	0.11	−0.18	0.95

B)

Behavioral scores (ASQ)	EEG markers at 6mo as predictors of behavioral outcomes at 24 mo											
	c/o-GRatio						f/o-GRatio					
	Composite		Gross Motor		Personal Social		Composite		Gross Motor		Personal Social	
	b	p	b	p	b	p	b	p	b	p	b	p
SWA	0.71	0.48	−1.28	0.80	−0.40	0.72	0.61	0.54	−0.58	0.64	1.50	0.16
Theta	0.8	0.42	−0.57	0.62	0.15	0.88	0.16	0.86	−0.81	0.52	0.58	0.80
Behavioral scores (ASQ)	f/o-KRatio						LVI					
	Composite		Gross Motor		Personal Social		Composite		Gross Motor		Personal Social	
	b	p	b	p	b	p	b	p	b	p	b	p
SWA	0.66	0.54	−1.01	0.33	1.20	0.25	−0.38	0.73	0.60	0.56	−1.47	0.19
Theta	0.19	0.84	−1.36	0.22	−0.10	0.94	0.58	0.56	0.12	0.90	0.03	0.97

Table 3
Maturational sleep EEG markers in infants age 6 months in relation to behavioral status at age 3 months (n = 21). Statistics are based on linear mixed models with b as an unstandardized beta coefficient and the False Discovery Rate-corrected p-values addressing multiple comparisons.

Behavioral scores (ASQ)	c/o-GRatio						f/o-GRatio					
	Composite		Gross Motor		Personal Social		Composite		Gross Motor		Personal Social	
	b	p	b	p	b	p	b	p	b	p	b	p
SWA	0.76	0.45	0.40	0.68	0.60	0.52	−0.39	0.70	0.76	0.45	−0.38	0.76
Theta	0.77	0.46	0.61	0.54	−0.37	0.66	−0.74	0.47	0.53	0.71	−0.50	0.66
Behavioral scores (ASQ)	f/o-KRatio						LVI					
	Composite		Gross Motor		Personal Social		Composite		Gross Motor		Personal Social	
	b	p	b	p	b	p	b	p	b	p	b	p
SWA	−0.48	0.70	0.66	0.51	−0.62	0.58	0.17	0.86	−0.77	0.46	0.75	0.46
Theta	−0.88	0.40	0.15	0.88	−0.76	0.47	0.66	0.52	0.27	0.79	1.53	0.15

across age groups, and thus, the topographical distribution of these markers would need to be verified at different ages to ensure their validity and reliability for moving forward toward a generalized use.

Another potential explanation for the lack of association may be that the current study population of healthy full-term infants is highly homogeneous compared to other studies investigating the relationship between EEG power and developmental status. Relatedly, the low sample size is a limitation and could also explain the lack of association in this study. Thus, the EEG markers used in this study may not be sensitive enough to detect any correlation. Yet, if a correlation is not present in a smaller population like the current one, these specific topographical associations may be overall negligible in healthy infants. In contrast, previous studies with populations of preterm-born or autistic children, typically more heterogeneous regarding age and health, have found links between EEG power and behavioral scores with sample sizes as small as n = 30 (Page et al., 2018). Notably, the current study sample was well-controlled, with strict inclusion criteria and a very narrow age range of 5.8 months (SD ± 0.17).

A further possible reason for the lack of association between EEG power topography and infant developmental status could be the simplified behavioral testing used in this study (Squires et al., 1995). Although the parent-reported metric of the ASQ has been shown to have valid correlations with the BAYLEY Scales of Infant Development II in children aged 24 months (Gollenberg et al., 2010), its evaluation focused on identifying developmental delays, with an overall sensitivity of 100% and specificity of 87% at 24 months for severe delays. This framework may not be sufficient to capture individual variability in behavior among our comparably homogeneous, healthy and carefully screened cohort of 6-month-olds. Other studies have used different measures, such as infant motor performance (Campbell, 2021) or the Bayley Scales of Infant Development-II (Balasundaram and Avulakunta, 2022) in relationship to MRI (Butera et al., 2022) or EEG (van 't Westende et al., 2022). These studies have yet included older or broader age ranges with a more comprehensive range of tests. Therefore, while the ASQ may be appropriate for the developmental screening of high-risk populations in the clinical context (Singh et al., 2017), it may not have enough sensitivity for use in a healthy, homogenous infant cohort. Thus, the simplified markers proposed in this study may be too specific and not general enough to reflect the differences in the population and the behavioral outcome measures used.

Our results reveal that the chosen topographical markers are not suited to predict acute or later measures of parent-rated infant behavior in a healthy cohort. In contrast, in a separate analysis, we identified spindle density as a potential early marker for infant behavioral developmental outcomes (Jaramillo et al., 2023). These findings suggested that fast spindle density (or spindle frequency) can be used as an early EEG biomarker in the context of thalamocortical maturation and potentially for early diagnosis in relation to deviations thereof. Thus, the selection of the EEG marker is fundamental for specificity in predicting behavioral ratings, especially in homogenous cohorts of healthy infants. Future adaptations may explore effects across the full night data. The current limitation to 30 min early-night data was based on reasons of compliance with at-home recordings and comparability with existing pediatric hdEEG research (Guyer et al., 2019; Kurth et al., 2010; LeBourgeois et al., 2019). Exploring the stability of effects across the night would be an interesting avenue to investigate. However, considering an overarching objective of developing a simplified marker for infancy that is practical and efficient for diagnostics, it is important to note that utilizing across-night EEG data may not result in a feasible and applicable tool in real-world settings.

Beyond neuro-maturational dynamics, the sleep EEG is shaped by various factors, with the most significant being sleep history (Borbély, 1982), experience-dependent plasticity (Huber et al., 2004, 2006; Wilhelm et al., 2014), contextual stress (Jones et al., 2021), genetics and their interactions with the immediate environment (Adamczyk et al., 2015; Reineberg et al., 2018). For instance, a twin study with adolescents showed that environmental impact could account for 66% (compared to 19% for genetic) of the variance in EEG coherence (Markovic et al., 2021). Although infants have had a shorter exposure to the environment, the family environment still contributes to variability that can be reflected in brain connectivity and, therefore, in the sleep EEG (Markovic et al., 2023). Indeed, beyond the sleep EEG, behavior can also be influenced by the immediate environment. For instance, sleeping arrangements and co-sleeping can relate to developmental outcomes such as attachment (Mileva-Seitz et al., 2016) or self-regulation, which is related to prefrontal functioning (Goldberg, 2001).

Other important factors affecting the lack of correlation between behavior and EEG in our infant cohort might include sleep habits, which are linked to neurophysiological connectivity (Schoch et al., 2021). The current study did not consider daytime sleep, which might have affected the homeostatic dynamics of SWA or theta, which could underlie locally-biased variations in EEG, which have been shown to undergo dynamics in relation to children's age (Kurth et al., 2016; Lassonde et al., 2016; Schoch et al., 2021).

Our findings indicate that simplified topographical sleep EEG markers in the SWA and theta range in healthy 6-month-olds are no direct indicators of behavioral development at 6, 12, or 24 months, contrary to previous observations in older or clinical populations. The interplay between developmental and sleep-related processes is highly complex and requires further elucidation. Future studies with larger sample sizes, clinical groups, and longitudinal sleep EEG data would help generate clarity and extract clinically-relevant markers. Further, expanding the sample's age range would allow us to better understand the stability of individual traits versus dynamic and transitional states.

Credit author statement

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Sarah F. Schoch: Conceptualization, Methodology, Investigation, Data Curation, Supervision, Project administration.

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Declaration of competing interest

None. R.H. is a partner of Tosoo AG, a company developing wearables for sleep electrophysiology monitoring and stimulation. M.K. is cofounder and board member of the company Deep Breath Intelligence (DBI) which provides services in the field of breath analysis. In the last two years M.K. received advisory fees from Bayer, Novartis, and GSK.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbscr.2023.100098.

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