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Original Article

Original Article

Sleep state-dependent development of resting-state functional connectivity during the preterm period

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Abstract

Study Objectives: The brains of preterm infants exhibit altered functional connectivity (FC) networks, but the potential variation in sleep states and the impact of breathing patterns on FC networks are unclear. This study explores the evolution of resting-state FC from preterm to term, focusing on breathing patterns and distinguishing between active sleep (AS) and quiet sleep (QS).

Methods: We recruited 63 preterm infants and 44 healthy-term infants and performed simultaneous electroencephalography and functional near-infrared spectroscopy. FC was calculated using oxy- and deoxyhemoglobin signals across eight channels. First, FC was compared between periodic breathing (PB) and non-PB segments. Then sleep state-dependent FC development was explored. FC was compared between AS and QS segments and between preterm infants at term and term-born infants in each sleep state. Finally, associations between FC at term, clinical characteristics, and neurodevelopmental outcomes in late infancy were assessed in preterm infants.

Results: In total, 148 records from preterm infants and 44 from term-born infants were analyzed. PB inflated FC values. After excluding PB segments, FC was found to be elevated during AS compared to QS, particularly in connections involving occipital regions. Preterm infants had significantly higher FC in both sleep states compared to term-born infants. Furthermore, stronger FC in specific connections during AS at term was associated with unfavorable neurodevelopment in preterm infants.

Conclusions: Sleep states play a critical role in FC development and preterm infants show observable changes in FC.

Key words: preterm infant; electroencephalography; near-infrared spectroscopy; functional connectivity; sleep state; outcome; periodic breathing

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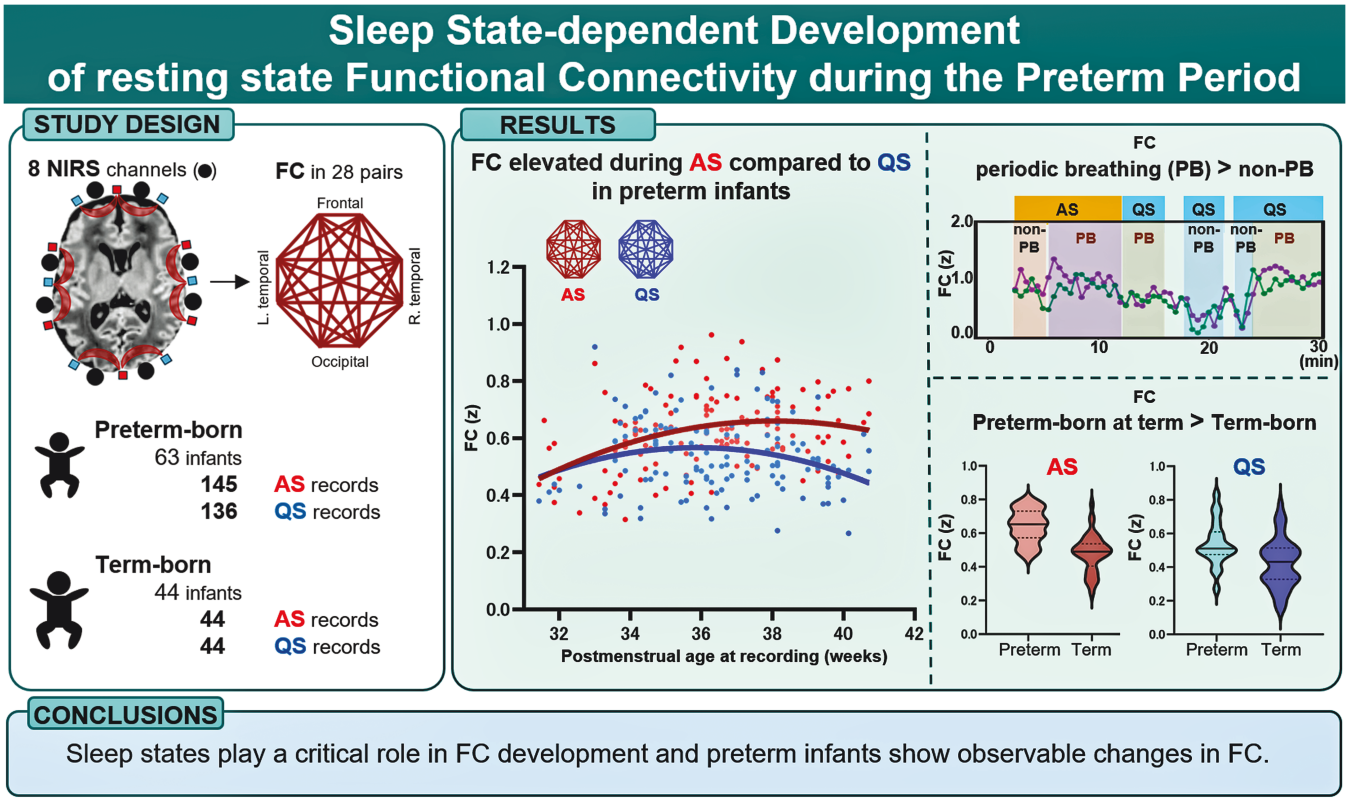
Graphical Abstract



Statement of Significance

Preterm infants often face neurodevelopmental challenges later in life. To address this, recent studies have focused on functional connectivity (FC) networks of the brain in such infants. However, few such studies have focused on sleep states or breathing patterns, which could affect FC analyses, as in studies of adults. In this study, we revealed the distinct resting-state FC development between preterm and term periods in active sleep and quiet sleep, as well as the effect of periodic breathing on FC analyses, using simultaneous electroencephalography and functional near-infrared spectroscopy. Our findings suggest that distinguishing sleep states and breathing patterns in FC analyses provides deep insights into preterm brain development.

Preterm birth impacts critical processes of brain development [1, 2], increasing the vulnerability to brain injury and altering the developmental trajectory [3]. Despite advances in perinatal care, preterm infants continue to be at elevated risk for long-term neurodevelopmental challenges, including intellectual disability and autism spectrum disorder [4–7]. This has prompted in vivo investigations using techniques such as resting-state functional magnetic resonance imaging (fMRI) to assess functional connectivity (FC) [8].

FC refers to temporal correlations among neurophysiological signals recorded in different brain areas [9]. In an adult fMRI study, low-frequency (<0.1 Hz) fluctuations driven by spontaneous blood oxygenation level-dependent (BOLD) signals had strong temporal correlations within specific brain networks in the resting state [10]. To date, many fMRI studies have been conducted on both preterm and term-born infants [11–18], as well as on fetuses [19, 20]. These studies suggest that immature resting-state FC networks can be identified from as early as 26 weeks postmenstrual age (PMA) in preterm infants; some primary cortical networks, such as the somatosensory, motor, visual, and auditory networks, are functionally synchronized and exhibit adult-like topologies by term-equivalent age; and preterm-born infants generally show weaker FC network strength at term-equivalent age compared to term-born infants.

However, it remains unknown whether FC networks develop differently during the preterm period depending on the sleep state, and how these networks differ. In adults, FC networks detected by fMRI vary according to vigilance state [21–23], highlighting the importance of considering this factor when evaluating FC [22]. In addition, the latest studies on neonates, employing functional near-infrared spectroscopy (fNIRS) or electroencephalography (EEG), indicate potential differences in FC networks between active sleep (AS) and quiet sleep (QS) [24–26]. To date, no fMRI studies have distinguished between sleep states in neonates.

When analyzing FC during early human development, another important factor to consider is the potential influence of specific breathing patterns. A recent fMRI study on healthy young adults revealed that two distinct breathing patterns, deep breaths, and bursts, significantly affected BOLD signals across the brain, leading to increased global FC [27]. In particular, bursts, characterized

by a serial, rhythmic set of breathing depth tapers, had a significant impact on global FC. A similar pattern, known as periodic breathing (PB), occurs in neonates and involves repetitive short cycles of respiratory pauses and breathing. PB is common in both preterm and term-born infants [28, 29] and has traditionally been considered a benign breathing pattern resulting from the immaturity of respiratory control [30]. Although the cycle duration of PB in infants is shorter than that of bursts in young adults, and the physiological mechanisms may differ, PB has the potential to inflate FC in neonates.

We studied the characteristics of sleep state-dependent FC between the preterm and term periods, taking into account the potential confounding effects of PB on FC analyses. First, we clarified the effect of PB on FC analyses. Then we explored sleep state-dependent FC development between the preterm and term periods after excluding PB segments, given their potential to distort FC analyses. Next, we investigated differences in FC networks between AS and QS, as well as between preterm-at-term and term-born infants within the same sleep state. Finally, we examined associations between FC and clinical characteristics and neurodevelopmental outcomes in preterm infants. For this comprehensive analysis, simultaneous EEG and fNIRS (EEG-fNIRS) recordings were obtained in preterm and term-born infants. Given the challenges of performing fMRI over a sufficiently extended time to distinguish sleep states in neonates, particularly during the preterm period [31], and considering the comparability of fNIRS oxy- and deoxy-hemoglobin (Hb) signals with BOLD fMRI signals in resting-state networks [32, 33], our approach involved the application of multichannel fNIRS combined with EEG. We hypothesized that PB has a significant influence on FC analyses and that FC networks differ between AS and QS in the preterm period even after adjusting for the effects of PB. We anticipate that accurate analysis of sleep state-dependent FC development will provide novel insights into the neuropathology of the preterm brain and accurate prognostic information that is pertinent to neurodevelopmental outcomes. Specifically, we posit that there may be a correlation between strong FC and favorable outcomes.

Methods

Ethical statement

The study was approved by the Ethics Committee of Nagoya University Hospital (approval no. 2019–0506 and 2021–0298). Written informed consent was obtained from the parents of all included infants.

Participants

We recruited 63 preterm infants admitted to the neonatal intensive care unit (NICU) at Nagoya University Hospital between April 2020 and August 2022, and 44 healthy term-born infants born at Nagoya University Hospital between October 2021 and June 2023. No statistical methods were employed to predetermine the sample size because this is the first study to assess the impact of PB and sleep states on FC analyses. However, our sample is comparable to or larger than those of previous studies using NIRS data [24, 25, 34–36]. Infants were recorded at least once by 41 weeks PMA. All preterm participants met the following criteria: gestational age (GA) at birth younger than 35.0 weeks, no major congenital malformations, and not intubated at the time of recording (infants with respiratory supports such as nasal continuous positive airway pressure, a high-flow nasal cannula, or nasal oxygen therapy were included). In addition, all term-born participants met the following criteria: GA at birth, 37.0–41.0 weeks, birth weight above the 10th percentile for GA at birth, 5 minutes Apgar score ≥8, no major congenital malformations, no clinical symptoms at the time of recording, no major problems at the 1-month check-up (passed metabolic and hearing screening tests), and mother free from hypertensive disorders of pregnancy, gestational diabetes mellitus requiring insulin injections, and severe psychiatric illness. An additional preterm infant and two term-born infants meeting the inclusion criteria were examined, but they were subsequently excluded from the analyses because NIRS data were not available due to body movements or measurement issues.

Procedure

In preterm infants, the experiment was conducted in the NICU, the growing care unit, or the EEG room at Nagoya University Hospital depending on the participant's general condition. Each infant underwent repeated recordings, with an interval of at least 10 days, until discharge to home or another hospital. After discharge, neurodevelopment was assessed at 10 months of corrected age, as described below. In term-born infants, the experiment was conducted in the EEG room at Nagoya University Hospital. Each infant was recorded once between days 1 and 9 after birth.

EEG-fNIRS recordings

EEG-fNIRS recordings were performed after infants fell asleep naturally. Each infant was placed in the supine position and held by one investigator throughout the recording. The recording continued until both AS and QS periods were captured. The EEG and NIRS data were obtained separately and synchronized using external electrical signals.

EEG (EEG-1200; Nihon Kohden, Tokyo, Japan) was recorded using at least eight electrodes (Fp1, Fp2, C3, C4, O1, O2, T3, and T4) placed according to the international 10–20 system, with a 0.002 s time resolution. In addition to the EEG, an electrooculogram, abdominal respiratory movements, a chin electromyogram, an electrocardiogram, and a video were recorded simultaneously to evaluate vigilance states and PB (Supplementary Figure S1).

An eight-channel NIRS device (ETG-100; Hitachi Medical Corporation, Tokyo, Japan) was placed around the infant's head, covering the frontal, left and right temporal, and occipital areas, with a headband made to fit the infant's head circumference (Figure 1A). Six sources and six detectors in a single row were plugged into the headband. A pair of adjacent sources and detectors made up a single measurement channel, and there were eight channels in total. In accordance with previous studies [24, 25, 34, 36–38], the distance between the source and the detector was set at 2 cm. The ring of the NIRS channels was set just above the Fp1, T3, O1, O2, T4, and Fp2 EEG electrodes. The NIRS instrument generated two wavelengths of near-infrared light (780 and 830 nm) and measured the time courses of the relative changes in oxy- and deoxy-Hb with a time resolution of 0.1 seconds.

Definition and detection of periodic breathing

PB is generally defined as three or more episodes of central apnea lasting >3 seconds, separated by ≤20 seconds of normal breathing, based on the definition provided by the American Academy of Sleep Medicine [39]. In this study, we developed an automated algorithm to detect PB using the envelope data of abdominal respiratory movement, filtered within the frequency range of 0.3–2.0 Hz. PB apnea was identified when the mean amplitude within a

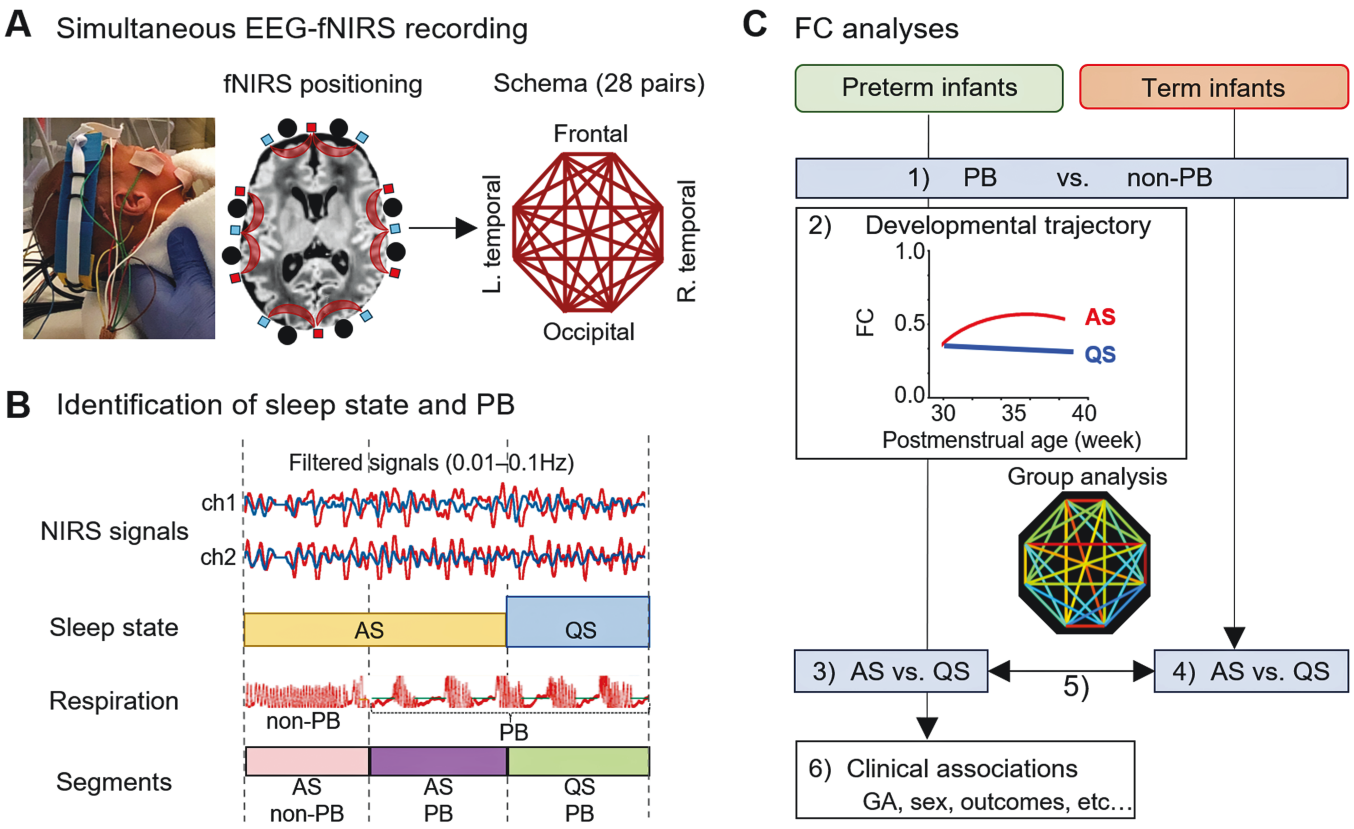


Figure 1. Overview of the study. (A) Simultaneous electroencephalography (EEG) and functional near-infrared spectroscopy (fNIRS) recording were performed. An eight-channel NIRS device was positioned around the infant's head, as illustrated in MRI data acquired at 34 weeks postmenstrual age. The source and the detector locations are indicated by distinct colored squares, with each color representing a different type. Circles on shaded curves represent NIRS channels. Functional connectivity (FC) in each connection pair is represented as the schema. (B) FC was calculated based on filtered oxyhemoglobin and deoxy-hemoglobin data. Active sleep (AS) and quiet sleep (QS) states were determined every 30 seconds using EEG, electrooculogram, and respiratory data. Periodic breathing (PB) and non-PB segments were evaluated separately. Four groups were distinguished: AS non-PB, AS PB, QS non-PB, and QS PB. (C) The analyses performed were as follows: comparison of FC between non-PB and PB segments in AS and QS (with only non-PB segments used in subsequent analyses); analysis of the FC trajectory in preterm infants in both AS and QS; comparison of FC between AS and QS in preterm infants at term; comparison of FC between AS and QS in term-born infants; comparison of FC between preterm infants at term and term-born infants in both AS and QS; and exploration of the associations between FC at term and clinical characteristics, such as gestational age (GA), sex, and developmental outcomes, in preterm infants.

sliding window of 3 seconds was <0.35 times the mean amplitude within the nearest 6-minute reference window. The algorithm classified segments as PB if they contained three or more episodes of repeated apneic intervals lasting 3–20 seconds, separated by breathing intervals of 3–20 seconds. Respiratory data were also reviewed manually to confirm PB detected by the algorithm according to the standard definition [39]. Additional details on the selection of PB and non-PB segments for analysis are in Supplementary Materials. During the manual review, episodes of apnea of prematurity, defined as apnea accompanied by bradycardia [40], were also identified.

Classification of vigilance states

Vigilance states were classified by two child neurologists (A.S. and H.K.) according to the criteria of the American Clinical Neurophysiology Society [41], as well as other reports referring to the characteristics of vigilance states in preterm and term infants [42–44]. The vigilance states were categorized into six groups (AS, QS, transitional sleep, indeterminate sleep, awake, and unclassifiable due to artifacts or data defects) every 30 seconds based on EEG patterns, rapid eye movements (REMs), respiratory patterns, and eye-opening/closing (Supplementary Figure S2). The classification was conducted using EEG polygraph data including EEG, electrooculograms, abdominal respiratory movements, and video recordings. Although PB is not a typical regular breathing pattern for QS, segments were classified as QS if all other parameters matched, except for PB-related respiratory patterns, in line with the previous reports [28, 45]. Data segments during AS and QS lasting ≥2 minutes were selected for analysis.

NIRS data preprocessing

NIRS data with motion artifacts (where the difference in the summed oxy- and deoxy-Hb signals was >0.15 mM·mm between four successive samples and the following four successive samples) or measurement errors (no signal change over eight consecutive samples) were excluded in each channel. Then, if five or more channels fulfilled the exclusion criteria, all data were excluded at the time points in samples for subsequent analyses. In addition, all data of a given channel were excluded if the signals had excessive noise (mean difference in the absolute value of the summed oxy-Hb and deoxy-Hb signals between two consecutive samples >0.2 mM·mm) or <30% of the NIRS data were from a single segment. In cases with artifacts or other vigilance states, the baseline signal after the exclusion of the affected data were corrected using the mean values of 10 samples from pre- and post-exclusion segments. Finally, the data were corrected based

on the mean of the first and final set of 10 samples. The oxy- and deoxy-Hb signals were filtered into the 0.01–0.1 Hz frequency band to eliminate physiological noise, such as the heartbeat and high- or low-frequency noise, as reported previously [35, 38].

FC parameters

For each record, FC was computed separately for PB in AS, non-PB in AS, PB in QS, and non-PB in QS segments using oxy-Hb and deoxy-Hb signals obtained from NIRS data provided the total duration of segments was ≥3 minutes (Figure 1B). Non-PB segments did not include any instances of either PB or apnea of prematurity. In cases where the amount of NIRS data was insufficient in three or more channels, FC parameters in other channels within the same segment were also considered insufficient. Pearson's correlation coefficients (r) were calculated using the time-course data for all 28 connections. The r values were converted into z scores using Fisher's z transformation, and the average z score for all 28 connections was calculated as the average FC (aveFC). To evaluate the developmental trajectories of FC, the mean FC value was calculated for connections displaying similar trajectories.

Neurodevelopmental assessment of preterm infants

The developmental quotients (DQs) of preterm infants were evaluated by a child neurologist blinded to the FC data at 10 months of corrected age. The Kyoto Scale of Psychological Development (KSPD) [46], which is a main tool used in the follow-up of preterm infants in Japan [47, 48], was used to this end. The KSPD assesses the postural–motor (fine and gross motor functions), cognitive–adaptive (non-verbal reasoning and visuospatial perception), and language–social (interpersonal relationships, socialization, and verbal abilities) domains. Notably, KSPD scores correlate strongly with those on the Bayley Scales of Infant and Toddler Development, third edition (Bayley-**III**). More specifically, strong correlations have been reported between the KSPD postural–motor DQ and the motor score on the Bayley-**III**, and between the KSPD cognitive–adaptive DQ and the cognitive score on the Bayley-**III** [47]. Only the postural–motor and cognitive–adaptive DQs were analyzed in this study because of the difficulty of assessing language–social ability in infants.

Statistical analysis

The overall study design is presented in Figure 1C. The clinical data of infants are shown as median (range) because most variables had a nonparametric distribution. In the analyses of preterm infants recorded at term, the datasets closest to 40.0 weeks PMA including both AS and QS were selected in cases with multiple recordings between 37.0 and 41.0 weeks PMA. To compare FC between PB and non-PB segments, as well as between AS and QS segments, a paired t-test was employed. A two-sample t-test, Welch's test, and the Mann–Whitney U test were used to compare values between preterm infants at term and term-born infants; a parametric distribution was assumed for the head circumference and FC data, whereas a nonparametric distribution was assumed for PMA at the time of recording. To evaluate linear associations, Pearson's or Spearman's rank correlation was performed depending on the data distribution; a parametric distribution was assumed for the cognitive–adaptive DQ at 10 months of corrected age, whereas a nonparametric distribution was assumed for postural–motor DQ. To assess FC trajectories as a function of PMA at the time of recording, we performed linear or nonlinear regression analyses depending on the data distribution. False discovery rate (FDR) adjustment was employed in the analyses of developmental trajectories and comparison of FC in each connection to reduce the false positive rate [49, 50]. In addition, we conducted multiple regression analyses of the aveFC for oxy-Hb signals at term and various clinical characteristics, and of the DQs and clinical factors in preterm infants at term. Two-tailed p-values <.05 were considered statistically significant. All statistical analyses were performed using SPSS software (version 29.0; IBM Japan Ltd., Tokyo, Japan).

Results

We collected 151 records from 63 preterm infants and 44 records from 44 healthy term-born infants. Each preterm infant had one to four recordings. Six preterm records for AS and 15 for QS were excluded from the analysis due to insufficient data. There were no records of term-born infants for whom AS and QS data were unacceptable for analysis. Consequently, we analyzed 148 records (145 AS, 136 QS) for 63 preterm infants and 44 records (44 AS, 44 QS) for 44 term-born infants. From the EEG polygraphs, the median (range) total, AS, and QS durations of the records were 68.5 (36.5–111.0), 32.0 (6.0–67.0), and 21.3 (4.5–50.5) minutes, respectively, for preterm infants, and 73.8 (47.5–96.0), 37.8 (15.0–67.5), and 23.5 (8.5–47.0) minutes for term-born infants.

Table 1 summarizes the clinical characteristics of the preterm infants. In preterm infants, the median (range) GA at birth was 31.6 (24.6–34.9) weeks and 31 (49%) were female. EEG-fNIRS recordings were performed between 31.4 and 40.7 weeks of PMA. In term-born infants, the median (range) GA at birth was 38.9 (37.6–40.6) weeks, and 22 (50%) were female.

PB analysis.

PB was frequently seen in infants (Figure 2, A and B). Among all AS (n = 145) and QS (n = 136) records obtained from preterm infants, PB was detected in 97 (67%) and 54 (40%), respectively. Records containing PB were broadly distributed between 31 and 40 weeks of PMA, as illustrated in Figure 2A. Figure 2C illustrates the aveFC, based on a representative time-course dataset and calculated using FC data from all 28 connections. Notably, the aveFC during PB segments was higher than that during non-PB segments in both sleep states. To further investigate, we compared the aveFC between non-PB and PB segments within the same records, separately for AS and QS. It was significantly higher in PB segments than in non-PB segments for both sleep states (n = 49, t = −3.7, p < .001 in AS and n = 18, t = −3.3, p = .004 in QS for oxy-Hb [Figure 2D]; and n = 49, t = −5.5, p < .001 in AS and n = 18, t = −6.1, p < .001 in QS for deoxy-Hb [Supplementary Figure S3]). Furthermore, hemodynamic changes during PB were associated with the mean duration of PB apnea (detailed in Supplementary Results and Figure S4). These findings indicate enhanced synchronicity among eight channels of NIRS during PB.

Consequently, we conducted further FC analyses using data from non-PB segments only. Two AS and four QS preterm records contained only PB segments and were thus excluded from the analysis. Therefore, non-PB segments from 143 records obtained during AS and 132 records obtained during QS were analyzed for preterm infants. Conversely, none of the records obtained during AS or QS for term-born infants consisted solely of PB segments; hence, non-PB segments from 44 records obtained during AS and QS were evaluated for term-born infants.

Sleep state-dependent FC development in preterm infants.

Initially, we calculated FC using oxy-Hb data and compared the developmental trajectories of FC between the preterm and term periods (Figure 3). AveFC for oxy-Hb exhibited changes corresponding to PMA at the time of recording; quadratic curves for both AS and QS are shown in Figure 3. In AS, aveFC increased up to 38.1 weeks PMA, exceeding the values observed in QS, and then decreased slightly or remained unchanged. In QS, aveFC declined from 35.9 weeks PMA. Therefore, the difference in FC between AS and QS significantly increased as a function of PMA (Supplementary Figure S5).

Next, the 28 connections were categorized into seven types based on brain region and FC trajectory (Figure 3). In both AS and QS, the absolute FC values were generally higher for both inter-hemispheric homologous connections and intra-hemispheric temporal connections compared to frontal–occipital, frontal–temporal, and temporal–occipital connections. The FC in inter-hemispheric homologous connections and intra-hemispheric temporal connections exhibited a positive association with PMA at the time of recording in AS. Although there was a trend toward an increase in the strength of the connections in QS, the increases were not statistically significant except for the frontal–frontal connection. In AS, the FC in frontal–occipital connections showed an increase up to 37.1 weeks PMA, followed by a slight decrease, whereas a decreasing trend was observed in QS. FC values for frontal–temporal connections tended to remain consistent between 31 and 41 weeks PMA in both AS and QS. Finally, in AS, the FC values for temporal–occipital connections increased up to 38.1 weeks PMA and remained consistent thereafter, whereas they tended to decrease slightly in QS. Consequently, the difference in FC between AS and QS increased over time in frontal–occipital and temporal–occipital connections, although the difference was only significant in temporal–occipital connections after FDR adjustment (Supplementary Figure S5).

The developmental trajectories of FC were similar between deoxy-Hb and oxy-Hb (Supplementary Figure S6).

Table 1. Clinical Characteristics of Preterm Infants

	(*N* = 63)
Gestational age at birth, weeks	31.6 (24.6–34.9)
Birth weight, g	1424 (343–2406)
Females	31 (49%)
Small for gestational age	12 (19%)
Days of intubation	6 (0–74)
Respiratory support[a] at 28 days after birth	31 (49%)
Caffeine treatment for apnea of prematurity	33 (52%)
Intraventricular hemorrhage grade III or IV	1 (2%)
Cystic periventricular leukomalacia	2 (3%)
Number of repeated EEG-fNIRS recordings	
1	18 (29%)
2	14 (22%)
3	22 (35%)
4	9 (14%)
DQ at 10 months of corrected age[b]	(*N* = 43)
Postural–motor	96 (37–127)
Cognitive–adaptive	96 (61–113)

Data are presented as median (range) or number (%).
[a]Mechanical ventilation, nasal continuous positive airway pressure, high-flow nasal cannula, or nasal oxygen therapy.
[b]One infant was excluded from the cognitive–adaptive DQ analysis because her score was below the minimum required for DQ calculation.
DQ, developmental quotient; EEG, electroencephalography; fNIRS, functional near-infrared spectroscopy.

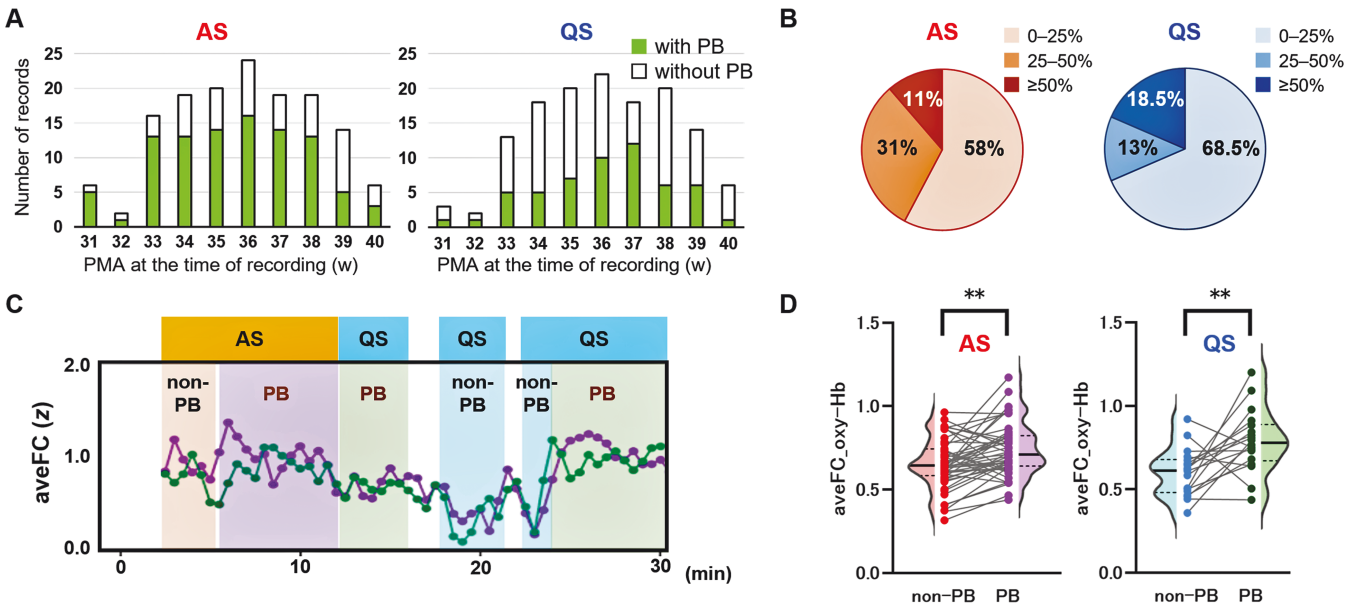


Figure 2. Periodic breathing (PB) in preterm infants. (A) Bar charts illustrating the numbers of records with and without PB according to postmenstrual age (PMA) at the time of recording in active sleep (AS, left) and quiet sleep (QS, right). (B) The proportion of time containing PB to the total recording time is depicted in pie charts for the records containing PB. (C) Representative 30-minute time-course of average functional connectivity (aveFC). Oxy-hemoglobin (Hb) data and deoxy-Hb data are represented by different colored dots, both showing similar trends. (D) AveFC for oxy-Hb signals in non-PB and PB segments in AS (left) and QS (right). Data from 49 AS and 18 QS records, including both non-PB and PB segments, were compared using a paired *t*-test (AS, $p < .001$; QS, $p = .004$). $^{**}p < .01$.

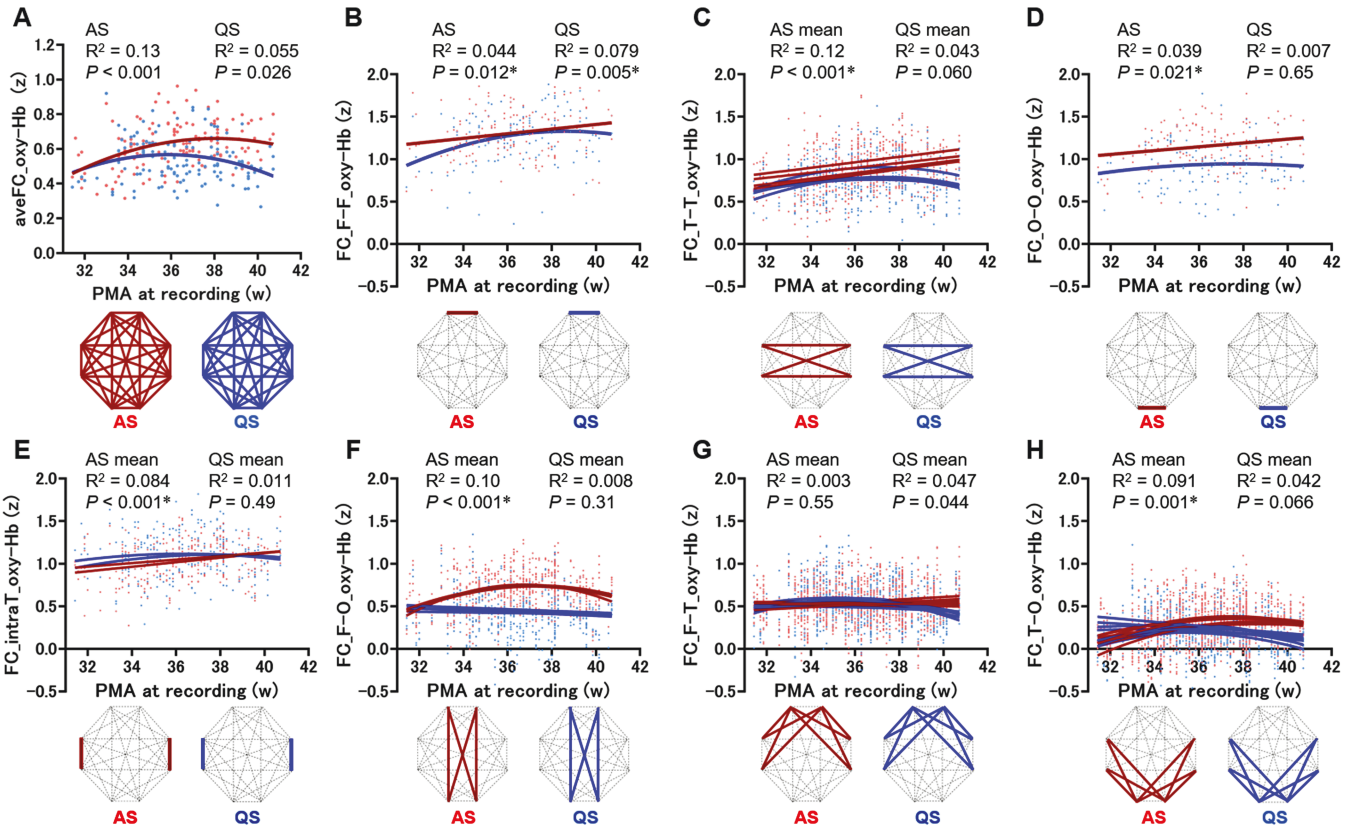


Figure 3. Developmental trajectories of functional connectivity in preterm infants (oxy-hemoglobin [Hb]). (A–H) Scatter plots and regression lines show the average functional connectivity (aveFC) of 28 connections (A) and the functional connectivity (FC) for individual connections (B–H) in oxy-Hb signals according to sleep state. FC values were calculated using non-periodic breathing data extracted from 143 records obtained during active sleep (AS) and 132 records obtained during quiet sleep (QS). The x-axis indicates postmenstrual age (PMA) at the time of recording, and the y-axis indicates aveFC (A) and FC (B–H) in oxy-Hb signals (z scores). The FC in AS and QS are represented in different colors. The connections were categorized into seven types (B–H), as shown in the lower column, based on brain regions and FC values. Linear or nonlinear regression analysis was conducted depending on the mean FC for each connection type. *P*-values calculated before the false discovery rate (FDR) adjustment are shown. *$p < .05$ after FDR adjustment.

Impact of sleep states and preterm birth on FC.

We conducted additional analyses to clarify the differences in FC between AS and QS, as well as between preterm infants at term and term-born infants. These analyses were conducted using oxy-Hb signals, given their more pronounced changes over time compared to deoxy-Hb signals [33, 51]. The use of this method was further justified by the observed similarities in the developmental trajectories of FC (based on oxy-Hb and deoxy-Hb signals) between the preterm and term periods, as mentioned in the preceding section.

AS versus QS in preterm infants at term.

A total of 42 preterm infants underwent EEG-fNIRS recordings between 37 and 41 weeks PMA. The median (range) PMA and mean (standard deviation) head circumference at the time of recording were 38.9 (37.0–40.7) weeks and 31.9 (1.4) cm, respectively. In AS, the aveFC for oxy-Hb was higher than in QS in preterm infants at term ($n = 42$, $t = 5.14$, $p < .001$; Figure 4). Furthermore, we compared FC in oxy-Hb signals between AS and QS using preterm datasets recorded at term. After FDR adjustment, FC values for frontal–occipital and temporal–occipital connections, as well as for inter-hemispheric temporal and occipital connections, were significantly stronger in AS than in QS (Supplementary Table S1). Remarkably, this stronger FC in AS included connections exhibiting an ascending trajectory as a function of PMA, as discussed in the preceding section (Figure 3, C, D, F, and H). However, no connections showed significantly lower FC values for AS than QS in preterm infants at term.

AS versus QS in term-born infants.

Next, we compared FC in oxy-Hb signals between AS and QS (within the same records) in 44 term-born infants. The median (range) PMA and mean (standard deviation) head circumference at the time of recording were 39.3 (37.9–40.9) weeks and 33.9 (1.2) cm, respectively. In term-born infants, aveFC values for oxy-Hb were higher in AS than in QS ($n = 44$, $t = 2.50$, $p = .016$; Figure 4). Next, FC was compared between AS and QS. Interestingly, the finding of significantly higher FC values for AS than for QS was similar to what was observed in preterm infants at term in frontal–occipital, temporal–occipital, and inter-hemispheric occipital connections (Supplementary Table S2). By contrast, FC values for intra-hemispheric temporal connections were significantly lower in AS than in QS in term-born infants.

FC comparison between preterm infants at term and term-born infants.

At the time of recording, the head circumference was significantly larger in term-born infants compared to preterm infants at term ($n = 86$, $t = -6.83$, $p < .001$), whereas PMA at the time of recording showed no statistically significant difference between

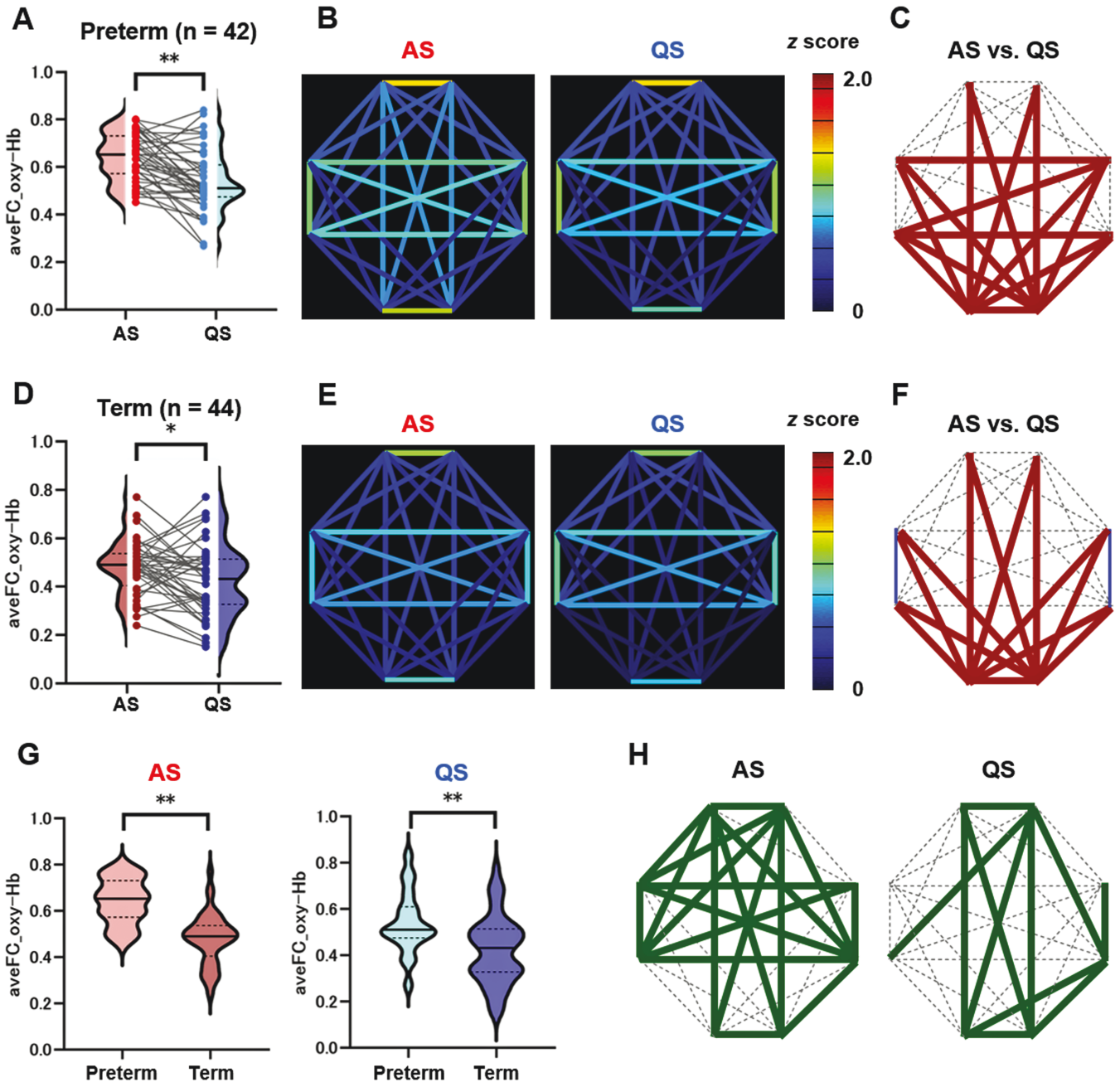


Figure 4. Disparities in functional connectivity (FC) between active sleep (AS) and quiet sleep (QS), and between preterm infants at term and term-born infants. (A) The average functional connectivity (aveFC) in oxy-hemoglobin (Hb) signals was compared between AS and QS in preterm infants at term using a paired *t*-test ($p < .001$). (B) Analysis of FC using oxy-Hb data from 42 preterm infants at term, in AS and QS, with FC strength indicated by the color bar. (C) Comparison of FC between AS and QS in preterm infants at term. A paired *t*-test was conducted to analyze the FC of all connections and connections that were significantly stronger in AS are depicted by bold solid lines. (D) AveFC for oxy-Hb signals in term-born infants: comparison between AS and QS using a paired *t*-test ($p = .016$). (E) Analysis of FC using oxy-Hb data from 44 term-born infants in AS and QS. (F) Comparison of FC between AS and QS in term-born infants. A paired *t*-test was conducted to analyze all FC connections; connections that were significantly stronger in AS are depicted by bold solid lines, and connections that were significantly weaker in AS are represented by thin solid lines (bilateral intra-hemispheric temporal connections). (G) AveFC for oxy-Hb signals recorded during AS and QS were compared between preterm infants at term and term-born infants using a two-sample *t*-test (AS, $p < .001$; QS, $p < .001$). (H) Comparison of FC between preterm infants at term and term-born infants in AS and QS. A two-sample *t*-test was conducted to analyze all FC connections and connections that were significantly stronger in preterm infants than in term-born infants are depicted by solid lines. No FC connections were significantly weaker in preterm infants than in term-born infants. Two-tailed *p*-values < .05 for aveFC, and for FC in individual connections after false discovery rate adjustment, were considered statistically significant. $^{*}p < .05$; $^{**}p < .01$. Detailed FC data are presented in Supplementary Tables S1–S4.

preterm infants at term and term-born infants ($p = .053$). The aveFC for oxy-Hb was higher in preterm infants at term than in term-born infants during both AS and QS ($n = 86$, $t = 7.10$, $p < .001$ for AS; and $n = 86$, $t = 3.87$, $p < .001$ for QS [Figure 4]). After FDR adjustment, the FC values for inter-hemispheric frontal and occipital connections, as well as for frontal–occipital connections, were significantly higher in preterm infants at term than in term-born infants, in both AS and QS (Supplementary Tables S3 and

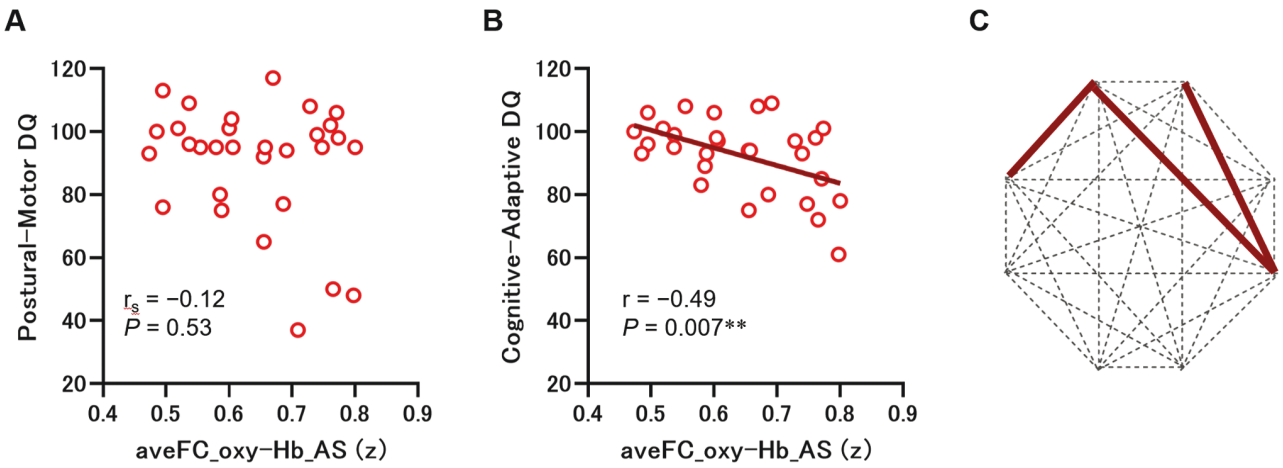


Figure 5. Association between the average functional connectivity (aveFC) at term and developmental quotient (DQ) in preterm infants. (A) Correlation between the aveFC for oxy-hemoglobin (Hb) signals at term in active sleep (AS) and the postural–motor DQ at 10 months of corrected age in preterm infants. (B) Correlation between the aveFC for oxy-Hb at term in AS and the cognitive–adaptive DQ at 10 months of corrected age in preterm infants. (C) Connections with functional connectivity (FC) values that were significantly negatively correlated (two-tailed p-value < .05 after false discovery rate adjustment) with the cognitive–adaptive DQ at 10 months of corrected age are represented by solid lines. Note that no FC connections showed a positive correlation with the cognitive–adaptive DQ. $^{**}p < .01$.

S4). In addition, in AS, the FC values for frontal–temporal, intra-hemispheric, and inter-hemispheric temporal connections were significantly higher in preterm infants at term than in term-born infants (Supplementary Table S3).

Associations between FC at term and clinical characteristics in preterm infants.

We assessed the associations between aveFC for oxy-Hb at term and clinical characteristics at birth in preterm infants ($n = 42$). The clinical characteristics included GA at birth (younger [<28 weeks], $n = 8$; older [≥28 weeks], $n = 34$), sex (male, $n = 19$; female, $n = 23$), and small for GA status (SGA, $n = 9$; non-SGA, $n = 33$). Because aveFC was influenced by PMA at the time of recording, aveFC data were adjusted for PMA before examining the associations with clinical variables. In multiple regression analyses, there were no significant associations except for a negative relationship between aveFC during QS and PMA at the time of recording.

Next, we evaluated the associations between aveFC at term and the postural–motor and cognitive–adaptive DQs at 10 months of corrected age ($n = 30$). Twelve infants were lost to follow-up, and one infant could be evaluated only in terms of the postural–motor DQ because of severe developmental delay. No significant association was found between aveFC in either sleep state and the postural–motor DQ ($r_s = -.12$, $p = .53$ in AS and $r_s = -.006$, $p = .98$ in QS; Figure 5) or aveFC for QS and the cognitive–adaptive DQ ($r = -.16$, $p = .40$). However, there was a significant negative correlation between aveFC for AS and the cognitive–adaptive DQ ($r = -.49$, $p = .007$). After FDR adjustment, significant negative correlations were observed between FC in 3 of the 28 connections, all of which were frontal–temporal connections, and the cognitive–adaptive DQ.

Finally, we investigated the associations between the cognitive–adaptive DQ and various clinical characteristics, including GA at birth, aveFC at term in AS, and SGA, using stepwise multiple regression analysis. In AS, the analysis revealed a positive relationship between the cognitive–adaptive DQ and GA at birth ($\beta = 1.9$, $p < .001$) and a negative relationship between the cognitive–adaptive DQ and aveFC at term ($\beta = -50.3$, $p = .004$). Notably, SGA was excluded from this final model, which was significant overall (adjusted $R^2 = 0.48$, $p < .001$).

Discussion

In this novel EEG-fNIRS study, we investigated the development of sleep state-dependent FC between the preterm and term periods. Our detailed analyses revealed clear differences in FC between AS and QS, as well as between preterm infants at term and term-born infants. Notably, preterm infants at term exhibited stronger FC across extensive brain regions during AS compared to QS. Furthermore, stronger FC within frontal–temporal connections in AS at term was negatively correlated with neurodevelopmental outcomes at 10 months of corrected age in preterm infants. Importantly, these significant findings were obtained after excluding PB segments, which have the potential to inflate FC values.

Our study provides the first definitive evidence of the impact of PB on analyses of FC in infants. The grand averages showed unequivocally that apnea in PB induced repetitive deoxygenation and reoxygenation of cerebral blood. This phenomenon, seen in multiple brain regions, is consistent with findings from a previous study that used single-channel NIRS [45] and supports the hypotheses of a previous fMRI study of healthy young adults [27]. In clinical settings, PB is generally recognized as a benign manifestation of immature respiratory regulation [45]. In our study, PB was frequently observed, being seen in 67% of AS records and 40% of QS records. Moreover, in 42% and 31.5% of AS and QS records, respectively, PB accounted for more than a quarter of the total recording duration. These observations align with previous studies [28, 52]. One reason why PB is considered a benign breathing pattern is that the relatively small declines in heart rate and oxygen saturation seen during PB episodes are typically insufficient to trigger alarms on bedside monitoring devices [28]. Given its significant impact on FC analyses and high prevalence, the identification of PB is crucial. This underscores the importance of respiratory monitoring, which is useful for detecting PB, particularly when employing modalities such as fMRI and fNIRS, to ensure the reliability and accuracy of FC assessments in this vulnerable population.

Our investigation indicated that FC exhibits distinct patterns across sleep states and brain regions. This represents a novel finding. Notably, the contrast in FC between AS and QS became increasingly evident toward term-equivalent age (see Figure 3 and Supplementary Figures S5 and S6). FC in inter-hemispheric homologous connections and connections related to occipital areas was notably strengthened during AS, whereas FC networks during QS included several connections, including inter-hemispheric homologous connections. AS and QS, which are precursors to REM sleep and non-REM sleep, respectively [42–44, 53], are considered to have distinct functions in brain development [53]. REM sleep, which is believed to promote early brain development by providing stimulation in the form of twitches [54] and REMs, is essential for activity-dependent development in the early stages of life. In a recent study on preterm infants, a higher proportion of AS during the preterm period was associated with increased white matter volume at term-equivalent age [55]. By contrast, non-REM sleep is hypothesized to aid brain development by optimizing neuronal networks through processes such as synaptic downscaling and pruning [56]. The results of our precise analyses, which showed enhanced FC in connections related to occipital areas in AS and weakened FC in all connections (except inter-hemispheric homologous connections) in QS, are consistent with the different developmental roles of each sleep state. Considering the predominance of AS in the prenatal and neonatal periods [53], our results indicate that FC is heightened in widespread brain regions during these early developmental stages. Subsequently, as non-REM sleep becomes dominant over the first 1–2 years of life [53], FC networks evolve toward an adult-like state, characterized by a weakening of short-range FC and selective strengthening of long-range FC [57, 58].

We identified stronger FC between occipital and spatially distant regions during AS in both preterm infants at term and term-born infants. This finding aligns with previous studies suggesting increased activation of the visual cortex, as well as strong FC in visual occipital regions, during REM sleep. Our results are concordant with an EEG study of preterm infants, in which AS was associated with heightened FC in visual occipital regions [26]. In addition, an adult NIRS study demonstrated an increase in oxy-Hb in a broader area including the visual cortex during REM periods [59]. Furthermore, a fMRI investigation of adults revealed REM-locked activation during sleep not only in the primary visual cortex but also in nonvisual sensory cortices, such as the motor cortex, as well as in language areas and the anterior cingulate gyrus [60]. Moreover, a mouse study that used mesoscale Ca^{2+} imaging revealed greater activation in the visual and somatosensory cortices during REM sleep [61]. Although the influence of REMs themselves on FC in occipital areas remains unclear, these findings strongly suggest that REM sleep plays a crucial role in the development of FC networks linked to the visual cortex.

The stronger FC observed in broad connections in preterm infants at term compared to term-born infants, during both AS and QS, was an additional notable finding of our study. This result is in line with previous EEG studies of FC [26, 62] and with an fMRI study that compared FC between preterm infants and fetuses [63]. Preterm infants may be exposed to a stimulus-enriched environment (relative to the in utero environment) during the crucial period of brain development characterized by activity-dependent processes [54]. It is important to acknowledge, however, that our results appear to contradict those of two fMRI studies that focused on specific networks, such as visual and thalamocortical networks; those studies reported that FC is weaker and restricted to a smaller area in preterm infants at term compared to term-born infants [13, 17], although they did not consider the role of sleep states. In addition, a functional ultrasound study suggested a significant decrease in the occurrence of thalamocortical networks during QS in very preterm infants compared to term-born infants [64]. This inconsistency in results may be attributable to the fact that these studies examined highly specific networks. Overall, our results align with previous fNIRS [65] and fMRI [12, 17, 18] studies indicating stronger FC in inter-hemispheric connections between homotopic regions, in both preterm and term-born infants. Considering that certain FC networks show functional specialization toward the end of the third trimester [12, 13, 16], we speculate that FC in major neuronal networks (such as inter-hemispheric homologous connections) strengthens with maturation, whereas FC in nonspecific connections may weaken, similar to what was seen during QS in this study. More studies on FC networks, particularly ones distinguishing between different sleep states, are needed to validate this speculation.

Contrary to our primary hypothesis, our results revealed inverse associations between FC within frontal–temporal connections at term in AS and DQs at 10 months of corrected age in preterm infants. This suggests that FC networks may be excessively strong in preterm infants, potentially leading to atypical neurodevelopmental outcomes. Our findings are consistent with a previous EEG study in which functional interactions between all pairs of cortical parcels were stronger in preterm infants receiving standard care compared to healthy term-born infants [62]. Intriguingly, no such difference was observed between healthy term-born infants and preterm infants who participated in the Family Nurture Intervention, a program designed to enhance emotional connections between mothers and infants in the NICU [62]. In addition, connectivity strength was negatively correlated with neurodevelopmental outcomes at 18 months of age [62]. Over-synchronized activities in broad brain regions may serve as a key pathogenic factor contributing to neurodevelopmental challenges in children and adults born preterm.

This study had several limitations. First, the fNIRS analysis was limited to only eight points across the entire brain surface. However, it is important to note that, for infants as young as 30 weeks PMA, the entire circumference of the head was covered at a specific latitude. Second, the brain regions and depth from the brain surface evaluated by NIRS may vary with head size. Even though, the comparison between PB and non-PB segments, as well as between AS and QS segments, was executed using paired samples, thereby mitigating individual differences (including in head circumference). In addition, the mean difference in head circumference between preterm infants at term and term-born infants was only 2 cm.

In conclusion, our study revealed distinct developmental trajectories of resting-state, low-frequency FC between AS and QS in preterm infants from 31 to 41 weeks PMA. Moreover, our results shed light on the significant impact of PB on FC analyses in infants. These results underscore the importance of respiratory and sleep monitoring for accurate FC analyses in infancy, particularly when using fNIRS and fMRI. Importantly, despite careful adjustment for PB and sleep state, there were differences in FC between preterm infants at term and healthy term-born infants, which suggests significant early-stage changes in the brain. These may be fundamental to the neurodevelopmental challenges that preterm infants often face in later life.

Supplementary material

Supplementary material is available at *SLEEP* online.

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Author Contribution

Anna Shiraki and Hiroyuki Kidokoro contributed to the conceptualization, recruitment, and follow-up of preterm infants, data acquisition, literature review, data analysis, result interpretation, and manuscript writing. Hama Watanabe and Gentaro Taga contributed to conceptualization, literature review, data analysis, and result interpretation, reviewing, and revising the manuscript. Takafumi Ushida contributed to the recruitment of term-born infants and revised the manuscript. Hajime Narita, Takamasa Mitsumatsu, Sumire Kumai, Ryosuke Suzui, Fumi Sawamura, Yuji Ito, Hiroyuki Yamamoto, Tomohiko Nakata, Yoshiaki Sato, Masahiro Hayakawa, Yoshiyuki Takahashi, and Jun Natsume contributed result interpretation, reviewed, and revised the manuscript.

Disclosure Statement

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Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author (H.K.).

References

1. Luhmann HJ, Kanold PO, Molnár Z, Vanhatalo S. Early brain activity: translations between bedside and laboratory. *Prog Neurobiol*. 2022;**213**:102268. doi: 10.1016/j.pneurobio.2022.102268
2. Molnar Z, Luhmann HJ, Kanold PO. Transient cortical circuits match spontaneous and sensory-driven activity during development. *Science*. 2020;**370**(6514):eabb2153. doi: 10.1126/science.abb2153
3. Inder TE, Volpe JJ, Anderson PJ. Defining the neurologic consequences of preterm birth. *N Engl J Med*. 2023;**389**(5):441–453. doi: 10.1056/NEJMra2303347
4. Pierrat V, Marchand-Martin L, Arnaud C, *et al*.; EPIPAGE-2 writing group. Neurodevelopmental outcome at 2 years for preterm children born at 22 to 34 weeks' gestation in France in 2011: EPIPAGE-2 cohort study. *BMJ*. 2017;**358**:j3448. doi: 10.1136/bmj.j3448
5. Cheong JLY, Olsen JE, Lee KJ, *et al*.; Victorian Infant Collaborative Study Group. Temporal trends in neurodevelopmental outcomes to 2 years after extremely preterm birth. *JAMA Pediatr*. 2021;**175**(10):1035–1042. doi: 10.1001/jamapediatrics.2021.2052
6. Agrawal S, Rao SC, Bulsara MK, Patole SK. Prevalence of Autism spectrum disorder in preterm infants a meta-analysis. *Pediatrics*. 2018;**142**(3):e20180134. doi: 10.1542/peds.2018-0134
7. Torio M, Iwayama M, Sawano T, *et al*. Neurodevelopmental outcomes of high-risk preterm infants: a prospective study in Japan. *Neurol Clin Pract*. 2021;**11**(5):398–405. doi: 10.1212/CPJ.0000000000000920
8. Brenner RG, Wheelock MD, Neil JJ, Smyser CD. Structural and functional connectivity in premature neonates. *Semin Perinatol*. 2021;**45**(7):151473. doi: 10.1016/j.semperi.2021.151473
9. Gerstein GL, Perkel DH. Simultaneously recorded trains of action potentials analysis and functional interpretation. *Science*. 1969;**164**(3881):828–830. doi: 10.1126/science.164.3881.828
10. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med*. 1995;**34**(4):537–541. doi: 10.1002/mrm.1910340409
11. Fransson P, Skiöld B, Horsch S, *et al*. Resting-state networks in the infant brain. *Proc Natl Acad Sci U S A*. 2007;**104**(39):15531–15536. doi: 10.1073/pnas.0704380104
12. Doria V, Beckmann CF, Arichi T, *et al*. Emergence of resting state networks in the preterm human brain. *Proc Natl Acad Sci U S A*. 2010;**107**(46):20015–20020. doi: 10.1073/pnas.1007921107
13. Smyser CD, Inder TE, Shimony JS, *et al*. Longitudinal analysis of neural network development in preterm infants. *Cereb Cortex*. 2010;**20**(12):2852–2862. doi: 10.1093/cercor/bhq035
14. Gao W, Alcauter S, Smith JK, Gilmore JH, Lin W. Development of human brain cortical network architecture during infancy. *Brain Struct Funct*. 2015;**220**(2):1173–1186. doi: 10.1007/s00429-014-0710-3
15. Smyser CD, Snyder AZ, Shimony JS, Blazey TM, Inder TE, Neil JJ. Effects of white matter injury on resting state fMRI measures in prematurely born infants. *PLoS One*. 2013;**8**(7):e68098. doi: 10.1371/journal.pone.0068098
16. Cao M, He Y, Dai Z, *et al*. Early development of functional network segregation revealed by connectomic analysis of the preterm human brain. *Cereb Cortex*. 2017;**27**(3):1949–1963. doi: 10.1093/cercor/bhw038
17. Eyre M, Fitzgibbon SP, Ciarrusta J, *et al*. The developing human connectome project: typical and disrupted perinatal functional connectivity. *Brain*. 2021;**144**(7):2199–2213. doi: 10.1093/brain/awab118
18. Dall'Orso S, Arichi T, Fitzgibbon SP, Edwards AD, Burdet E, Muceli S. Development of functional organization within the sensorimotor network across the perinatal period. *Hum Brain Mapp*. 2022;**43**(7):2249–2261. doi: 10.1002/hbm.25785
19. Jakab A, Schwartz E, Kasprian G, *et al*. Fetal functional imaging portrays heterogeneous development of emerging human brain networks. *Front Hum Neurosci*. 2014;**8**:852. doi: 10.3389/fnhum.2014.00852
20. Thomason ME, Grove LE, Lozon TA, *et al*. Age-related increases in long-range connectivity in fetal functional neural connectivity networks in utero. *Dev Cogn Neurosci*. 2015;**11**:96–104. doi: 10.1016/j.dcn.2014.09.001
21. Spoormaker VI, Schroter MS, Gleiser PM, *et al*. Development of a large-scale functional brain network during human non-rapid eye movement sleep. *J Neurosci*. 2010;**30**(34):11379–11387. doi: 10.1523/JNEUROSCI.2015-10.2010
22. Liu TT, Falahpour M. Vigilance effects in resting-State fMRI. *Front Neurosci*. 2020;**14**:321. doi: 10.3389/fnins.2020.00321
23. Damaraju E, Tagliazucchi E, Laufs H, Calhoun VD. Connectivity dynamics from wakefulness to sleep. *Neuroimage*. 2020;**220**:117047. doi: 10.1016/j.neuroimage.2020.117047

24. Lee CW, Blanco B, Dempsey L, *et al*. Sleep State modulates resting-state functional connectivity in neonates. *Front Neurosci*. 2020;**14**:347. doi: 10.3389/fnins.2020.00347
25. Uchitel J, Blanco B, Collins-Jones L, *et al*. Cot-side imaging of functional connectivity in the developing brain during sleep using wearable high-density diffuse optical tomography. *Neuroimage*. 2023;**265**:119784. doi: 10.1016/j.neuroimage.2022.119784
26. Tokariev A, Roberts JA, Zalesky A, *et al*. Large-scale brain modes reorganize between infant sleep states and carry prognostic information for preterms. *Nat Commun*. 2019;**10**(1):2619. doi: 10.1038/s41467-019-10467-8
27. Lynch CJ, Silver BM, Dubin MJ, *et al*. Prevalent and sex-biased breathing patterns modify functional connectivity MRI in young adults. *Nat Commun*. 2020;**11**(1):5290. doi: 10.1038/s41467-020-18974-9
28. Patel M, Mohr M, Lake D, *et al*. Clinical associations with immature breathing in preterm infants: part 2-periodic breathing. *Pediatr Res*. 2016;**80**(1):28–34. doi: 10.1038/pr.2016.58
29. Walter LM, Shepherd KL, Yee A, Horne RSC. Insights into the effects of sleep disordered breathing on the brain in infants and children: imaging and cerebral oxygenation measurements. *Sleep Med Rev*. 2020;**50**:101251. doi: 10.1016/j.smrv.2019.101251
30. Edwards BA, Sands SA, Berger PJ. Postnatal maturation of breathing stability and loop gain: the role of carotid chemoreceptor development. *Respir Physiol Neurobiol*. 2013;**185**(1):144–155. doi: 10.1016/j.resp.2012.06.003
31. Uchitel J, Vanhatalo S, Austin T. Early development of sleep and brain functional connectivity in term-born and preterm infants. *Pediatr Res*. 2022;**91**:771–786. doi: 10.1038/s41390-021-01497-4
32. Sasai S, Homae F, Watanabe H, *et al*. A NIRS-fMRI study of resting state network. *Neuroimage*. 2012;**63**(1):179–193. doi: 10.1016/j.neuroimage.2012.06.011
33. Ferradal SL, Liao SM, Eggebrecht AT, *et al*. Functional imaging of the developing brain at the bedside using diffuse optical tomography. *Cereb Cortex*. 2016;**26**(4):1558–1568. doi: 10.1093/cercor/bhu320
34. Arimitsu T, Shinohara N, Minagawa Y, Hoshino E, Hata M, Takahashi T. Differential age-dependent development of inter-area brain connectivity in term and preterm neonates. *Pediatr Res*. 2022;**92**(4):1017–1025. doi: 10.1038/s41390-022-01939-7
35. Taga G, Watanabe H, Homae F. Developmental changes in cortical sensory processing during wakefulness and sleep. *Neuroimage*. 2018;**178**:519–530. doi: 10.1016/j.neuroimage.2018.05.075
36. Homae F, Watanabe H, Otobe T, *et al*. Development of global cortical networks in early infancy. *J Neurosci*. 2010;**30**(14):4877–4882. doi: 10.1523/JNEUROSCI.5618-09.2010
37. Taga G, Homae F, Watanabe H. Effects of source-detector distance of near infrared spectroscopy on the measurement of the cortical hemodynamic response in infants. *Neuroimage*. 2007;**38**(3):452–460. doi: 10.1016/j.neuroimage.2007.07.050
38. Imai M, Watanabe H, Yasui K, *et al*. Functional connectivity of the cortex of term and preterm infants and infants with Down's syndrome. *Neuroimage*. 2014;**85 Pt 1**:272–278. doi: 10.1016/j.neuroimage.2013.04.080
39. Berry RB, Budhiraja R, Gottlieb DJ, *et al*.; American Academy of Sleep Medicine. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. *J Clin Sleep Med*. 2012;**8**(5):597–619. doi: 10.5664/jcsm.2172
40. Schmidt B, Roberts RS, Davis P, *et al*.; Caffeine for Apnea of Prematurity Trial Group. Caffeine therapy for apnea of prematurity. *N Engl J Med*. 2006;**354**(20):2112–2121. doi: 10.1056/NEJMoa054065
41. Tsuchida TN, Wusthoff CJ, Shellhaas RA, *et al*.; American Clinical Neurophysiology Society Critical Care Monitoring Committee. American Clinical Neurophysiology Society Standardized EEG Terminology and Categorization for the description of continuous EEG monitoring in neonates: report of the American Clinical Neurophysiology Society Critical Care Monitoring Committee. *J Clin Neurophysiol*. 2013;**30**:161–173. doi: 10.1097/WNP.0b013e3182872b24
42. André M, Lamblin MD, d'Allest AM, *et al*. Electroencephalography in premature and full-term infants. Developmental features and glossary. *Neurophysiol Clin*. 2010;**40**:59–124. doi: 10.1016/j.neucli.2010.02.002
43. Dereymaeker A, Pillay K, Vervisch J, *et al*. Review of sleep-EEG in preterm and term neonates. *Early Hum Dev*. 2017;**113**:87–103. doi: 10.1016/j.earlhumdev.2017.07.003
44. Grigg-Damberger MM. The visual scoring of sleep in infants 0 to 2 months of age. *J Clin Sleep Med*. 2016;**12**(3):429–445. doi: 10.5664/jcsm.5600
45. Urlesberger B, Pichler G, Gradnitzer E, Reiterer F, Zobel G, Müller W. Changes in cerebral blood volume and cerebral oxygenation during periodic breathing in term infants. *Neuropediatrics*. 2000;**31**(2):75–81. doi: 10.1055/s-2000-7477
46. Ikuzawa M, Matsushita Y, Nakase A. *Shinpan K Shiki Hattatsu Kensahou 2001 [The Kyoto Scale of Psychological Development Test 2001], Technical Manual*. Kyoto: Choyodo Printing Co.; 2002.
47. Kono Y, Yonemoto N, Kusuda S, *et al*. Developmental assessment of VLBW infants at 18 months of age: a comparison study between KSPD and Bayley III. *Brain Dev*. 2016;**38**(4):377–385. doi: 10.1016/j.braindev.2015.10.010
48. Nakanishi H, Suenaga H, Uchiyama A, Kono Y, Kusuda S; Neonatal Research Network, Japan. Trends in the neurodevelopmental outcomes among preterm infants from 2003–2012: a retrospective cohort study in Japan. *J Perinatol*. 2018;**38**(7):917–928. doi: 10.1038/s41372-018-0061-7
49. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B Stat Method*. 1995;**57**(1):289–300. doi: 10.1111/j.2517-6161.1995.tb02031.x
50. Glickman ME, Rao SR, Schultz MR. False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. *J Clin Epidemiol*. 2014;**67**:850–857. doi: 10.1016/j.jclinepi.2014.03.012
51. Homae F, Watanabe H, Nakano T, Taga G. Prosodic processing in the developing brain. *Neurosci Res*. 2007;**59**(1):29–39. doi: 10.1016/j.neures.2007.05.005
52. Decima PF, Fyfe KL, Odoi A, Wong FY, Horne RS. The longitudinal effects of persistent periodic breathing on cerebral oxygenation in preterm infants. *Sleep Med*. 2015;**16**(6):729–735. doi: 10.1016/j.sleep.2015.02.537
53. Knoop MS, de Groot ER, Dudink J. Current ideas about the roles of rapid eye movement and non–rapid eye movement sleep in brain development. *Acta Paediatr*. 2021;**110**(1):36–44. doi: 10.1111/apa.15485
54. Rio-Bermudez CD, Blumberg MS. Active Sleep promotes functional connectivity in developing sensorimotor networks. *Bioessays*. 2018;**40**(4):e1700234. doi: 10.1002/bies.201700234
55. Wang X, de Groot ER, Tataranno ML, *et al*. Machine learning-derived active sleep as an early predictor of white matter development in preterm infants. *J Neurosci*. 2024;**44**(5):e1024232023. doi: 10.1523/JNEUROSCI.1024-23.2023
56. Tononi G, Cirelli C. Sleep function and synaptic homeostasis. *Sleep Med Rev*. 2006;**10**(1):49–62. doi: 10.1016/j.smrv.2005.05.002

57. Gao W, Lin W, Grewen K, Gilmore JH. Functional connectivity of the infant human brain: plastic and modifiable. *Neuroscientist*. 2017;**23**(2):169–184. D oi: 10.1177/1073858416635986
58. Sylvester CM, Kaplan S, Myers MJ, *et al*. Network-specific selectivity of functional connections in the neonatal brain. *Cereb Cortex*. 2023;**33**(5):2200–2214. doi: 10.1093/cercor/bhac202
59. Igawa M, Atsumi Y, Takahashi K, *et al*. Activation of visual cortex in REM sleep measured by 24-channel NIRS imaging. *Psychiatry Clin Neurosci*. 2001;**55**(3):187–188. doi: 10.1046/j.1440-1819.2001.00819.x
60. Hong CC, Harris JC, Pearlson GD, *et al*. fMRI evidence for multisensory recruitment associated with rapid eye movements during sleep. *Hum Brain Mapp*. 2009;**30**(5):1705–1722. doi: 10.1002/hbm.20635
61. Wang Z, Fei X, Liu X, *et al*. REM sleep is associated with distinct global cortical dynamics and controlled by occipital cortex. *Nat Commun*. 2022;**13**(1):6896. doi: 10.1038/s41467-022-34720-9
62. Yrjölä P, Myers MM, Welch MG, Stevenson NJ, Tokariev A, Vanhatalo S. Facilitating early parent-infant emotional connection improves cortical networks in preterm infants. *Sci Transl Med*. 2022;**14**(664):eabq4786. doi: 10.1126/scitranslmed.abq4786
63. De Asis-Cruz J, Kapse K, Basu SK, *et al*. Functional brain connectivity in ex utero premature infants compared to in utero fetuses. *Neuroimage*. 2020;**219**:117043. doi: 10.1016/j.neuroimage.2020.117043
64. Baranger J, Demene C, Frerot A, *et al*. Bedside functional monitoring of the dynamic brain connectivity in human neonates. *Nat Commun*. 2021;**12**(1):1080. doi: 10.1038/s41467-021-21387-x
65. Fuchino Y, Naoi N, Shibata M, *et al*. Effects of preterm birth on intrinsic fluctuations in neonatal cerebral activity examined using optical imaging. *PLoS One*. 2013;**8**(6):e67432. doi: 10.1371/journal.pone.0067432