An exploratory study of EEG connectivity during the first year of life in preterm and full-term infants

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Abstract

Aim: to evaluate EEG connectivity during the first year of age in healthy full-term infants and preterm infants with prenatal and perinatal risk factors for perinatal brain damage.

Methods: Three groups of infants were studied: healthy at full-term infants (n = 71), moderate and late preterm infants (n = 54), and very preterm infants (n = 56). All preterm infants had perinatal or/and perinatal risk factors for brain damage. EEG was obtained during phase II of natural NREM sleep. EEG analysis was performed in 24 segments of 2.56 s free of artifacts. For the calculation of EEG sources, the spectral Structured Sparse Bayesian Learning (sSSBL) was used. Connectivity was computed by the phase-lag index.

Results: In healthy full-term infants, EEG interhemispheric connectivity in the different frequency bands followed similar trends with age to those reported in each frequency band: delta connectivity decreases, theta increases at the end of the year, in the alpha band, different trends were observed according to the region studied, and beta interhemispheric connectivity decreases with age. EEG connectivity in preterm infants showed differences from the results of the term group.

Discussion: Important structural findings may explain the differences observed in EEG connectivity between the term and preterm groups.

Conclusion: The study of EEG connectivity during the first year of age gives essential information on normal and abnormal brain development.

Introduction

Electroencephalographic brain connectivity in different spectral bands is associated with diverse mechanisms underlying brain development function (1). Band-specific synchronized -spectral-connectivity is the underlying mechanism for large-scale brain integration of functionally specialized regions from which coherent behavior and cognition emerge (2–5). This mechanism relies mainly on the neural architecture and interactions within layers at the microscopic level of description of cortical columns (6,7). However, in isolation, its topological organization -spatial distribution and connectivity pattern- at the macroscopic level possesses a tremendous descriptive power on the developing brain of the preterm neonates (8).

An essential part in describing the development of neural networks involves mapping its spatial distribution alone by the localization of responsive areas at the observational level of experimental techniques, which could be gathered by Magnetic Resonance Imaging (MRI) and Electroencephalogram (EEG) (9). For either approach, this mapping is indirect. However, the spectral composition of fMRI signals is severely distorted by the slow metabolic-hemodynamic cascade of the process following the actual neural activity (10,11). Several MRI studies have shown aberrant structural characteristics and even abnormal connectivity in preterm infants (12), suggesting white matter tracts may underlie the neurodevelopmental impairments common in this population. It has also been suggested that abnormalities in the functional connectivity between the cortex and thalamus underlie neurocognitive impairments seen after preterm birth (13). The development of thalamocortical connections and how such development relates to cognitive processes during the earliest stages of life at ages one and two years have been described during the last decade (14).

Furthermore, the thalamus–sensorimotor and thalamus–salience connectivity networks had been shown to be already present in neonates, whereas the thalamus– medial visual and thalamus–default mode network connectivity emerged later, at one year of age (14). Also important is the observation that the working memory performance measured at one and two years of age has significant correlations with the thalamus–salience network connectivity. Studies have compared the connectivity between very preterm infants (VPT) and full-term infants (FTI) using MRI procedures (15). They showed that the most decreased connectivity strength in VPT was the frontotemporal, fronto-limbic, and posterior cingulate gyrus, at gestational ages of 39.6 + 1,2 weeks (FTI) and 40.3 + 0.6 weeks (VPT).

Although many references exist studying structural connectivity by MRI procedures, there is a lack of references using EEG to measure functional connectivity. EEG recordings in neonates and infants have shown that quantitative EEG analyses are a reliable and valuable procedure to evaluate functional and maturational changes (16–18). The study of EEG connectivity is relevant since coherent brain rhythmic activity plays a role in communication between neural populations engaged in functional and cognitive processes (19). It has also been shown that neural synchrony plays a role in synaptic plasticity (20). Therefore, the early study of EEG connectivity in preterm and term infants may give essential knowledge of brain development. However, EEG signals are affected by their low spatial resolution and volume conduction effects (21,22). These pitfalls have been tackled by deploying generations of Electrophysiological Source Imaging (ESI) methods during the last decades (23). ESI methods combine the best spatial resolution of MRI for the head model estimation with a more excellent time resolution of EEG for inference of neural activity and connectivity at the brain level (24–28).

The World Health Organization estimates the prevalence of preterm birth to be 5–18% across 184 countries worldwide (29). The causes for premature birth comprise mainly biological, genetic, and environmental factors (30). Despite advances in prenatal and neonatal care and decreased perinatal mortality of preterm newborns, the number of survivors with neurological and cognitive deficits constitutes a public health problem (31). Furthermore, preterm birth is a leading risk factor for (i) cerebral palsy (32,33), (ii) delayed mental and/or psychomotor development (34,35), (iii) executive dysfunction (36), (iv) neurosensory disability (37), (v) language and reading deficits (38), (vi) academic underachievement (39,40), (vii) attention deficit hyperactivity disorder, and (viii) autism spectrum disorders (12,41).

In this work, we focus on the temporal dynamics of neural networks in the millisecond range to study early neural integration. We present a longitudinal study of EEG connectivity during preterm and full-term infants' first year of life using a measure based on instantaneous phase differences.

1 Methods

Ethical permission was granted by the Ethics Committee of the Instituto de Neurobiología of the Universidad Nacional Autónoma de México, which complies with the Ethical Principles for Medical Research Involving Human Subjects by the Helsinki Declaration. Informed consent from the parents was obtained for all study participants.

1.1 Participants

Three groups of infants were studied: i) healthy full-term infants without any antecedent for perinatal brain damage; ii) a group of moderate and late preterm infants with gestational age (GA) between 32 and 37 weeks, and iii) a group of very preterm infants with a GA of 27 to 31 weeks. All preterm babies had prenatal and/or perinatal risk factors for perinatal brain damage. However, participants with congenital and hereditary brain malformations, infectious or parasitic diseases were excluded from this study. After the infants were discharged from the hospital where they were born, their parents were invited to participate in a unique project of the Neurodevelopmental Research Unit at the Institute of Neurobiology of the National Autonomous University of Mexico in Queretaro. Information regarding each group is included in Table 1.

1.2 EEG data analysis

EEG was acquired from infants while they were in phase II sleep and were in his/her mother's lap in a dimly lit room with acoustic isolation. No sedation was used. Referential EEGs recordings for 20 minutes were obtained from 19 electrodes according to the 10/20 system using linked ears as reference. MEDICID IV System with a gain of 20,000, amplifier bandwidth between 0.5 to 100 Hz, and sample rate was 200 Hz. Some participants were recorded twice or more times during their first year of life. Therefore, EEG data were selected from a data set of 297 recordings collected between 2016 and 2020 as part of an ongoing project investigating the characterization of preterm brain development.

Later, EEG data was segmented by visual inspection into 24 artifact-free segments of 2.56s duration. The idea behind this processing was to avoid transforming original data by using preprocessing techniques like independent component analysis to remove artifacts (eye movement and blinks) or interpolation to fix "bad" channels. These methods could modify profoundly the connectivity information relayed on the electrophysiology signal leading us to a wrong interpretation of the data. The frequency analysis was set up from 0.3 Hz to 20 Hz. After EEG data collection and edition, the data analysis continued with two main steps: inference of EEG source space data using ESI method and finally, the connectivity analysis based on the phase-lag connectivity measure.

1.3 Inference of EEG source space data

ESI methods aim to infer local neural currents based on EEG and MRI data (42,43). However, this process is subject to distortions due to the system of linear equations being highly ill-conditioned, and the possible solutions lie within a high-dimensional space. These distortions can indeed reach unacceptable levels, as shown repeatedly in simulations (21,22,44).

In this paper, we estimated the cortical neural activity using a third generation of ESI methods, spectral Structured Sparse Bayesian Learning (sSSBL) (45). sSSBL pursues estimation of the neural activity through a maximum "evidence" search via the Expectation-Maximization algorithm (46). Where evidence is defined as the conditional probabilities of two groups of parameters: (i) variances of spectral EEG source activity, which controls the statistical relevance of the source cross-spectral components; and (ii) variances of spectral EEG noise, which controls the level of noise of the observations.

Furthermore, this approach is based on an iterated scheme that produces an approximated representation of the evidence (expectation) followed by its maximization, guaranteeing convergence to a local maximum. The maximization step is carried out via estimation formulas of the vector regression Elastic Net (47) and the Sparse Bayesian Learning (48) through the arithmetic mean of typical vector regression inputs corresponding to the samples. The global sparsity level is handled by estimating the regularization parameters in the completely analogous form to the procedure described by Paz-Linares and collaborators (47).

The cortical activity inference was set up on a cortical manifold space defined as 5000 points at the gray matter, with coordinates on the pediatric MNI brain template (http://www.bic.mni.mcgill.ca). The scalp sensors space was built on 19 electrodes within a 10-20 EEG sensors system (49). The lead fields were computed by the boundary element method (BEM) integration method accounting for a model of five head compartments (gray matter, cerebrospinal fluid, inner skull, outer skull, scalp) (50). The initial cortical surface parcellation based on ninety regions of Tzourio-Mazoyer's atlas (51) was manually gathered into five large regions per hemisphere: frontal, sensorimotor, parietal, temporal, and occipital.

1.4 Connectivity analysis through phase-lag based measure

In neuroscience, phase-locking has become the primary measure for neural connectivity to evaluate the synchronization between neural groups. In this study, we compute the phase-lag index (PLI) (52,53) between cortical structures. PLI is one of the most popular methods for synchronization inference since its near "immunity" against the volume conduction effects (54). This approach applies spatial filters to the EEG data that reduce volume conduction effects leading to the correct interpretation of connectivity information.

In this work, an all-to-all PLI connectivity matrix was computed between the ten cortical regions, five per hemisphere, at each frequency point from 0.3 Hz to 20 Hz. This procedure resulted in a 3-D matrix (ROI-ROI-frequency). Finally, the global efficiency was computed to assess the connectivity information per cortical region and to summarize the connectivity matrices. Efficiency is based on the inverse of the average distance from each vertex (ROI) to any other vertex (path lengths), which explains that higher efficiency values correspond to more direct connections. Furthermore, global efficiency has been proved to be helpful to evaluate pathological networks since its robust again networks that are not fully connected (55,56).

1.5 Statistical analysis

For the statistical analysis, a 3-D efficiency matrix (ROI-frequency-age) was created for each group under analysis. One point to note is that our data did not cover every age value between 0 and 1 year. Figure 1 shows some small gaps in the age distribution of each group. To solve this pitfall and to estimate with more critical details the development connectivity surfaces along the first year of life, a locally weighted scatterplot smoothing (LOWESS) method was applied (57). The LOWESS approach overcomes classical methods through a linear and no linear least squares regression. This regression fits simple models with subsets of the data to build up a function that describes the deterministic part of the variation in the data instead of requiring a global function to fit a model to the entire data. Later, we compute a linear regression model for each row of the development connectivity surface to evaluate the connectivity behavior for each frequency value along the first year of life. The slope-based curve provides evidence to compare the connectivity develop for the three groups under analysis.

2 Results

The results of the LOWESS approach for global efficiency measure in full-term and preterm infants are shown in Figure 2. In this figure, the term group shows a decrease of the connectivity with age in the frequencies within the delta band (0.5 Hz - 3.0 Hz), whereas, in both groups of preterm infants, an increase is observed. Connectivity in the theta and alpha bands decreases in the three groups. In the low beta band, EEG connectivity increases in term and very preterm groups and decreases in the moderate and late preterm group. Connectivity at frequencies at 15 and above Hz decreases in all groups. As it is difficult to interpret the results of the global power of the connectivity, and almost all references have studied the interhemispheric connectivity, we present the results of the interhemispheric connectivity for each cortical region under analysis.

2.1 Left-right frontal connectivity (LRFC)

Results of the LRFC are shown in Figure 3. In the delta band, LRFC tended to decrease, although at age 0.1 years (36.5 days) different connectivity values are observed for the different frequencies in the delta band. In the moderate and late preterm, this interhemispheric delta connectivity decreases, although at 0.5 Hz - 1.0 Hz is possible to observe an increase with age. In the very preterm group, the decrease in interhemispheric frontal connectivity with increasing age is evident. LRFC in the theta band showed in term subjects an increase with age. Meanwhile, in the moderate and late preterm, there was a decrease in connectivity with age that was even more marked in the very preterm group. LRFC in the alpha band in term and moderate and late preterm decreased with age. As this band of frequency decreased in power, the result was expected. However, there were differences in the trend of connectivity between groups in the beta band: term infants had a decreasing trend during the first year of life, but both groups of preterm infants showed increasing values with age.

2.2 Left-right sensorimotor connectivity (LRSC)

Results are shown in Figure 4. LRSC in the delta band in term infants decreases during the first six months of age, and later on, it increases. At the end of the first year, this increase was also observed in moderate and late preterm and with great intensity in the very preterm. This last group also showed this increase in LRSC at frequencies in the theta band; meanwhile, a decrease in LRSC was observed in infants at term and in moderate and late preterm. It was possible to see a constant increase in the range of 5-8 Hz in term infants. This may be corresponding to a rhythmical central activity that has been reported as a precursor of the mu or sensorimotor rhythm (58). Moderate and late preterm showed a decrease in theta connectivity, and in very preterm, this activity has a constant decrease. In the alpha band, LRSC decrease with age in term and moderate and late preterm. In both groups at three months, there was robust alpha connectivity that decreased slowly. However, in the very preterm, there was a substantial decrease during the whole year. Around 15 Hz LRSC decreased during the whole year in term and very preterm infants, and an unexpected increase at the end of the year was present in the moderate and late preterm.

2.3 Left-right parietal connectivity (LRPC)

Results of the LRPC are shown in Figure 5. LRPC in term infants shows a decrease with age in all frequencies between 5 Hz and 10 Hz. However, in moderate and late preterm LRPC in the delta frequencies and the band from 6 Hz to 10 Hz shows high values at age 3.65 months that progressively decrease with age. In this group, connectivity from 11 Hz to 18 Hz decreases, but connectivity increases with age at the end of the year.

2.4 Left-right temporal connectivity (LRTC)

Figure 6 shows the results of LRTC. In the delta band, this connectivity at three months is robust, decreases with age in term infants. Moderate and late preterm, and very preterm infants, shown a reverse trend, increasing with age. In term infants' LRTC at frequencies from 6 to 8 Hz increases during the year. At 10 Hz to 12 Hz, LRTC decreases with age up to 6 months and later increases. LRTC at frequencies within the beta band decreases with age in term infants. LRTC in both preterm groups decreases with age from 10 Hz to 18 Hz.

2.5 Left-right occipital connectivity (LROC)

In Figure 7, the results for LROC are shown. Full-term infants showed a progressive decrease with age in frequencies of the delta band. In the alpha band, connectivity decreased during the first six months and increased in the last six months of the year. Late and moderate preterm and very preterm infants showed a completely different connectivity behavior across the first year of age.

3 Discussion

In our work, EEG connectivity in preterm infants was described. However, most papers reporting preterm brain connectivity use magnetic resonance images (30,59–61), and prominent differences between networks identified in term control versus premature infants at term equivalent have been described (62). These authors also reported that putative precursors of the default mode network were detected in term control infants but were not identified in preterm infants, including those at term equivalent. In a follow-up of preterm children at seven years, (63) demonstrated that children born very preterm have less connected and less complex brain networks compared with typically developing term-born children and that even these structural abnormalities are observed in a follow-up of seven years. The structural information about the connectivity observed in preterm infants demonstrates alterations related to motor, linguistic and cognitive deficits (64). All this information was the basis for studying the EEG connectivity in preterm infants.

The pioneer studies of (65) reported EEG coherence from eight left and eight right intrahemispheric electrode pairs from 253 children ranging in mean age from 6 months to 7 years. The results support the view that the functions of the left and right hemispheres are established early in human development through complementary developmental sequences. These sequences appear to recapitulate differences in adult hemispheric function. However, posterior studies in infants have mainly analyzed the correlation between homologous left and right hemispheres.

Previous studies analyzing the correlation between homologous left and right hemispheres (66) described that the median correlation value decreased significantly (between -40% and -60% decrease) in infants from 27 to 37 weeks of gestational age. For postnatal maturation, only the central-temporal channel showed a decreasing trend. These authors conclude that the decreasing median correlation values in all homologous channels indicate a decrease in similarity in signal shape with advancing gestational age. González et al., in 2011 studied EEG inter and intrahemispheric connectivity measuring coherence between regions and the measure of phase synchronization (67). They found significant differences between term and preterm infants during active and quiet sleep, with term infants with greater magnitude values of coherence than preterm infants. The interhemispheric PLI values were different during active sleep between term and preterm infants in the delta band.

Similarly, the intrahemispheric PLI values in the beta band differed between term and preterm infants during quiet sleep. Our results showed that term infants have different results during quiet sleep than preterm infants in EEG connectivity in all frequency bands. The data go through two main steps: inference of EEG source space data using a novel ESI method and finally, the connectivity analysis based on the phase-lag connectivity measure. Differences in the EEG analysis may explain the contradiction with González results.

Significant structural findings may explain the differences observed in EEG connectivity between the term and preterm groups. The corpus callosum (CC), is the anatomic structure that has axons is an anatomical structure constituted by axons connecting homologous cortical regions. A rapid growth in its volume occurs during the first 20 months of age (68). The midsagittal area of the CC has been commonly used as a sensitive marker of brain development and maturation since the CC area is related to the number of axons and morphology, such as axon diameter and myelination (69). On the other hand, the development of the corpus callosum in preterm infants is affected by prematurity (70), and in preterm infants, the decrease of its volume is frequently observed (71,72). This structural abnormality may explain many differences noted between term and preterm infants in the interhemispheric EEG connectivity, which we consider the leading cause of the results obtained.

Another important aspect is that cortical synaptogenesis has a different pattern of development of the cortex, with a more rapid increase in the auditory cortex than the prefrontal cortex (73), which may explain the asynchrony of cortical maturation in the infant's brain (74). These facts, together with the maturational process of myelination that shows that it ends at a different time in different regions: the auditory and visual cortex myelination ends at 18-24 months, whereas in the Broca's area, it ends at five years and in the prefrontal cortex at nine years of age (75). These statements may produce essential differences in the topography of EEG connectivity along the first year of age. On the other hand, myelination in preterm babies is severely affected since MRI studies have shown that diffuse white matter injury is one of the most frequent abnormalities observed in preterm infants (76). The structural differences between term and preterm babies strongly support the differences observed between this group in EEG connectivity.

In the group of term infants, the results obtained may be explained by the studies of EEG development in normal infants (77). In all regions studied, the EEG connectivity in the delta band decreased with age. EEG development in this frequency band has also shown a decrease with age, which may explain the results observed in the connectivity. The EEG connectivity in the theta band shows differences in development according to the region study. LRFC showed a significant increase with age which is consistent with the observation that at term infant's theta absolute and relative power in frontal leads increase during the first year (77). LRTC also showed an increase at the end of the year, which also coincided with the EEG neurodevelopmental findings.

In the range from 5 Hz to 8 Hz in full-term infants, it was possible to see in LRFC a constant increase, as well as in LRTC and LRSC. This may be corresponding to a rhythmical central activity that has been reported as a precursor of the mu or sensorimotor rhythm (58). The moderate and late preterm group showed a decrease in connectivity, and in the very preterm group, this activity has a constant decrease. Our finding is consistent with (78). There a clear sensorimotor rhythm is described in the range of 5.47-7.03 Hz with contralateral activity to free movement in awake at full-term infants around the four months of life. Furthermore, there the preterm infant group with periventricular leukomalacia did not show any electroencephalographic sign of the presence of this rhythm.

In the alpha band, EEG connectivity in term infants has a different trend in the different regions. In frontal, temporal, and sensorimotor regions, the interhemispheric connectivity decreases with age during the whole year. However, LPOC showed at the early months a sharp decrease that changed to a progressive increase in the second semester of the year. This changing trend was not detected in the studies of EEG development, maybe because they have used linear regression for the analysis (77).

EEG beta band connectivity decreases in all regions. Our results were limited to a small range of frequencies, from 13 to 20 Hz. Therefore, it is difficult to compare with studies of EEG development of other references.

4 Conclusions

Our exploratory study of EEG connectivity between left and right cortical areas in healthy at full-term infants during the first year of age showed a similar trend that has been reported by the different frequency bands in similar groups of healthy full-term infants. EEG interhemispheric connectivity in all preterm infants studied with a gestational age from 26 to 37 weeks and prenatal and perinatal risk factors for brain damage has great differences with the group of healthy at full-term infants. Such differences in EEG connectivity may be due to the structural brain abnormalities that have been described in preterm infants.

5 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

6 Author Contributions

The Author Contributions section is mandatory for all articles, including articles by sole authors. If an appropriate statement is not provided on submission, a standard one will be inserted during the production process. The Author Contributions statement must describe the contributions of individual authors referred to by their initials and, in doing so, all authors agree to be accountable for the content of the work. Please see here for full authorship criteria.

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10 Supplementary Material

Supplementary Material should be uploaded separately on submission, if there are Supplementary Figures, please include the caption in the same file as the figure. Supplementary Material templates can be found in the Frontiers Word Templates file.

Please see the Supplementary Material section of the Author guidelines for details on the different file types accepted.

11 Data Availability Statement

The datasets [GENERATED/ANALYZED] for this study can be found in the [NAME OF REPOSITORY] [LINK]. Please see the Data Availability section of the Author guidelines for more details.

Table 1. Demographic information for full term and preterm infants.

Age Group	N	Sex (females)	EEGs	GA (wks)
Term	71	29	82	40 (38-41)
Moderate and Late preterm	54	25	112	35 (32-37)

Very preterm	56	27	103	29 (27-31)

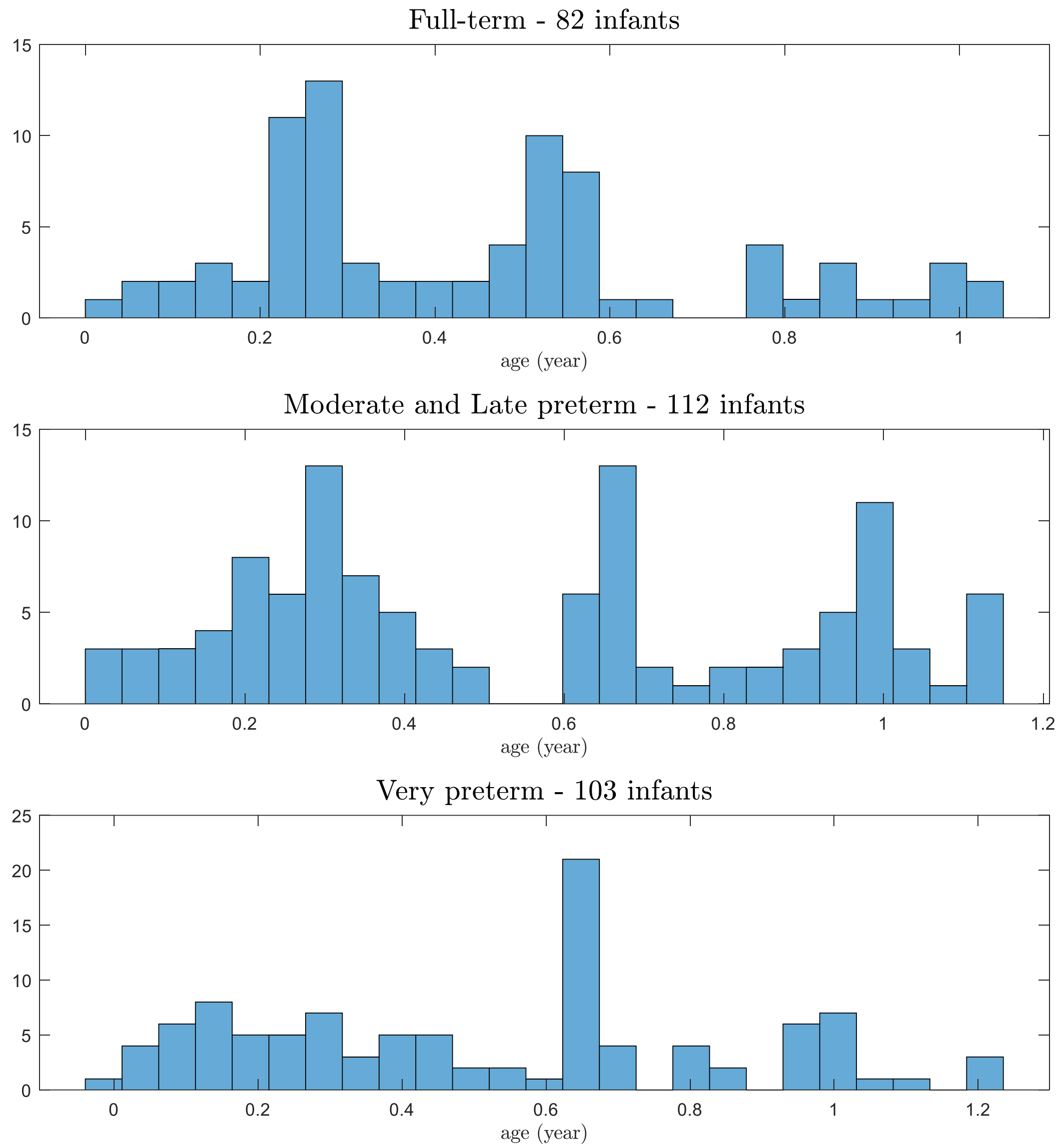

Fig 1: *Histogram by age groups showing some small gaps along the first year on EEG data recordings.*

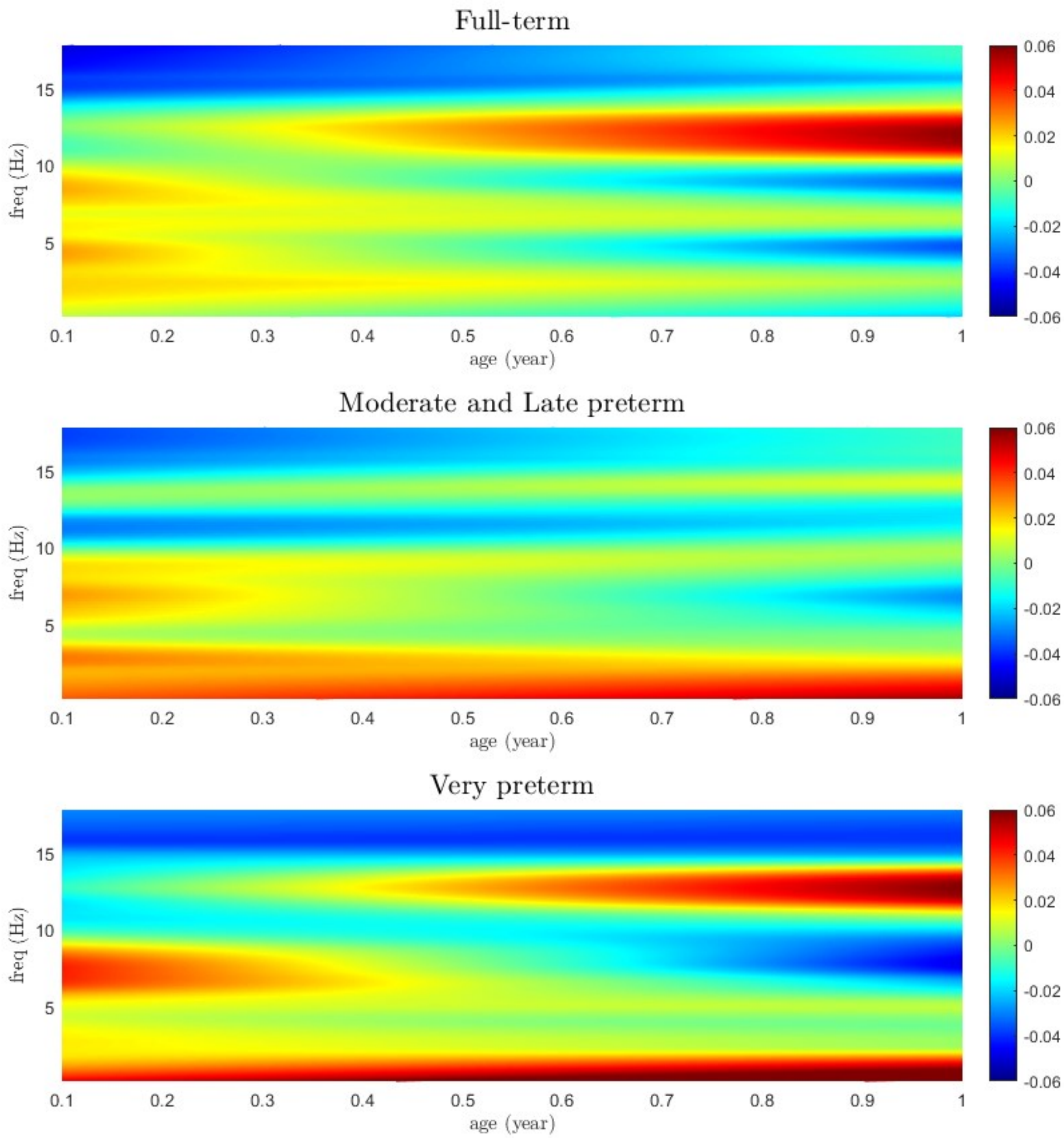

Fig 2: *Global connectivity pattern for the three groups of infants: full term, late preterm, and very preterm.*

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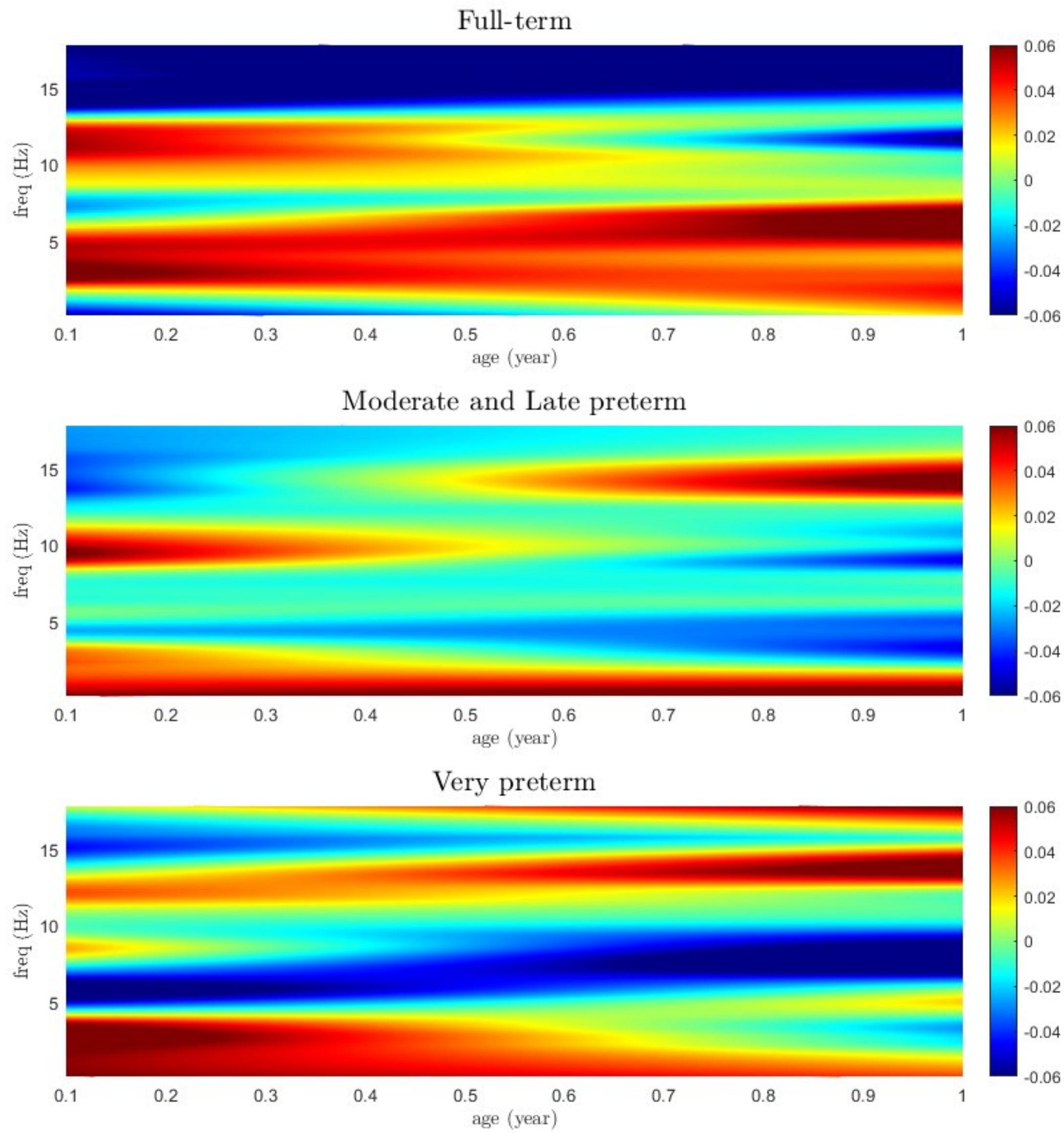

Fig 3: *Local connectivity pattern for the three groups of infants (full term, late preterm, and very preterm) at frontal cortical regions.*

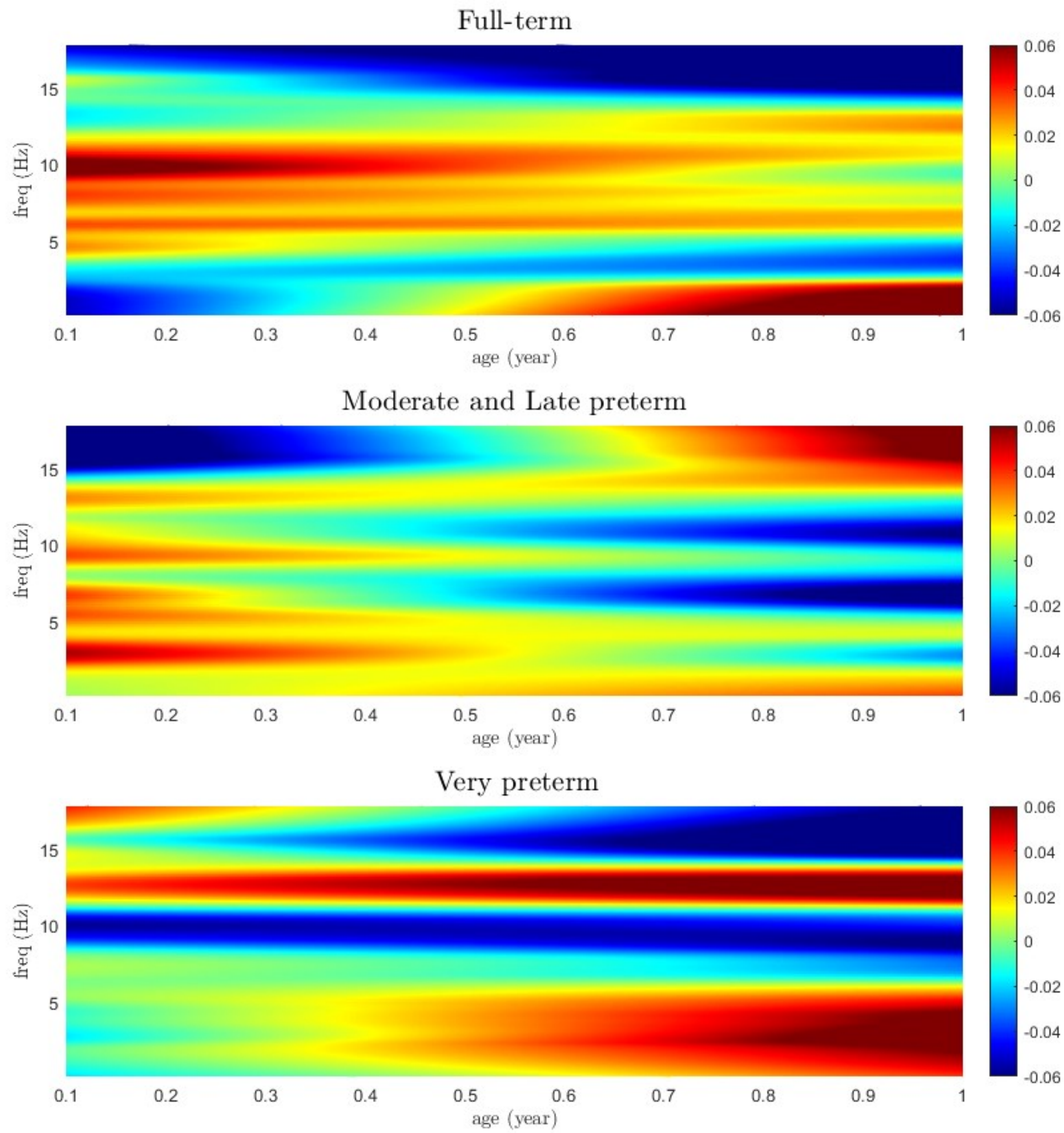

Fig 4: *Local connectivity pattern for the three groups of infants (full term, late preterm, and very preterm) at sensorimotor cortical regions.*

628

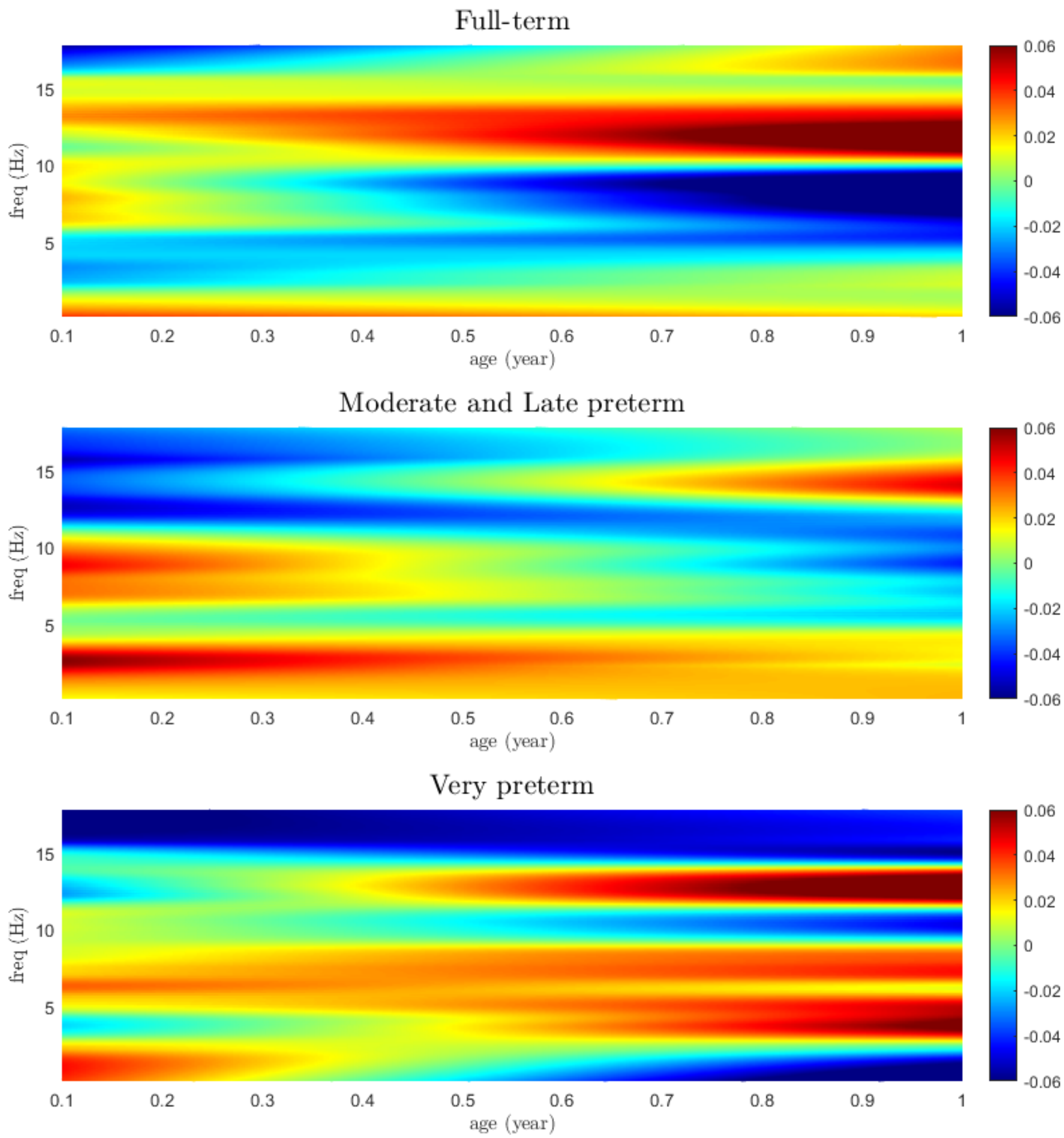

Fig 5: *Local connectivity pattern for the three groups of infants (full term, late preterm, and very preterm) at parietal cortical regions.*

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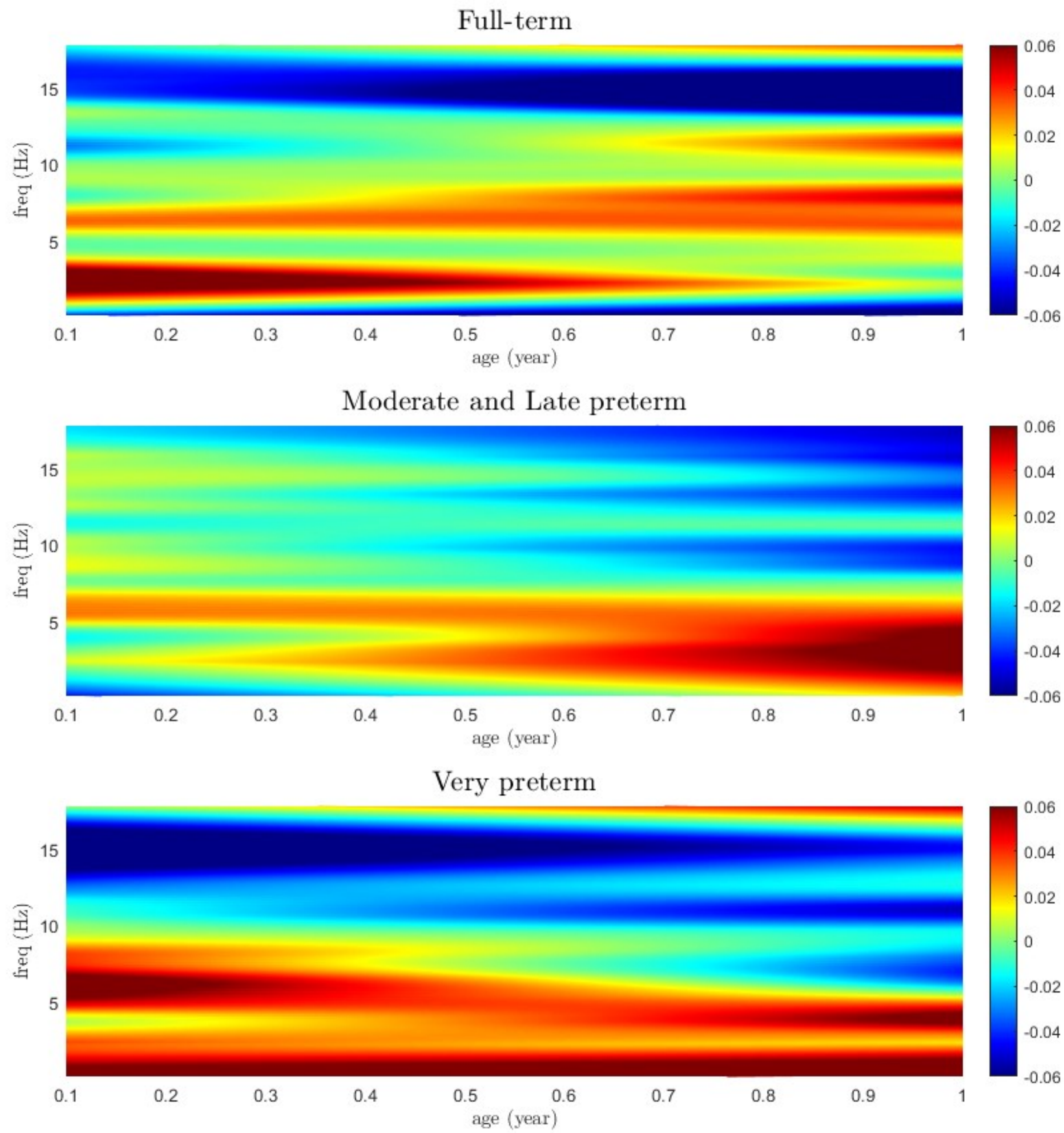

Fig 6: *Local connectivity pattern for the three groups of infants (full term, late preterm, and very preterm) at temporal cortical regions.*

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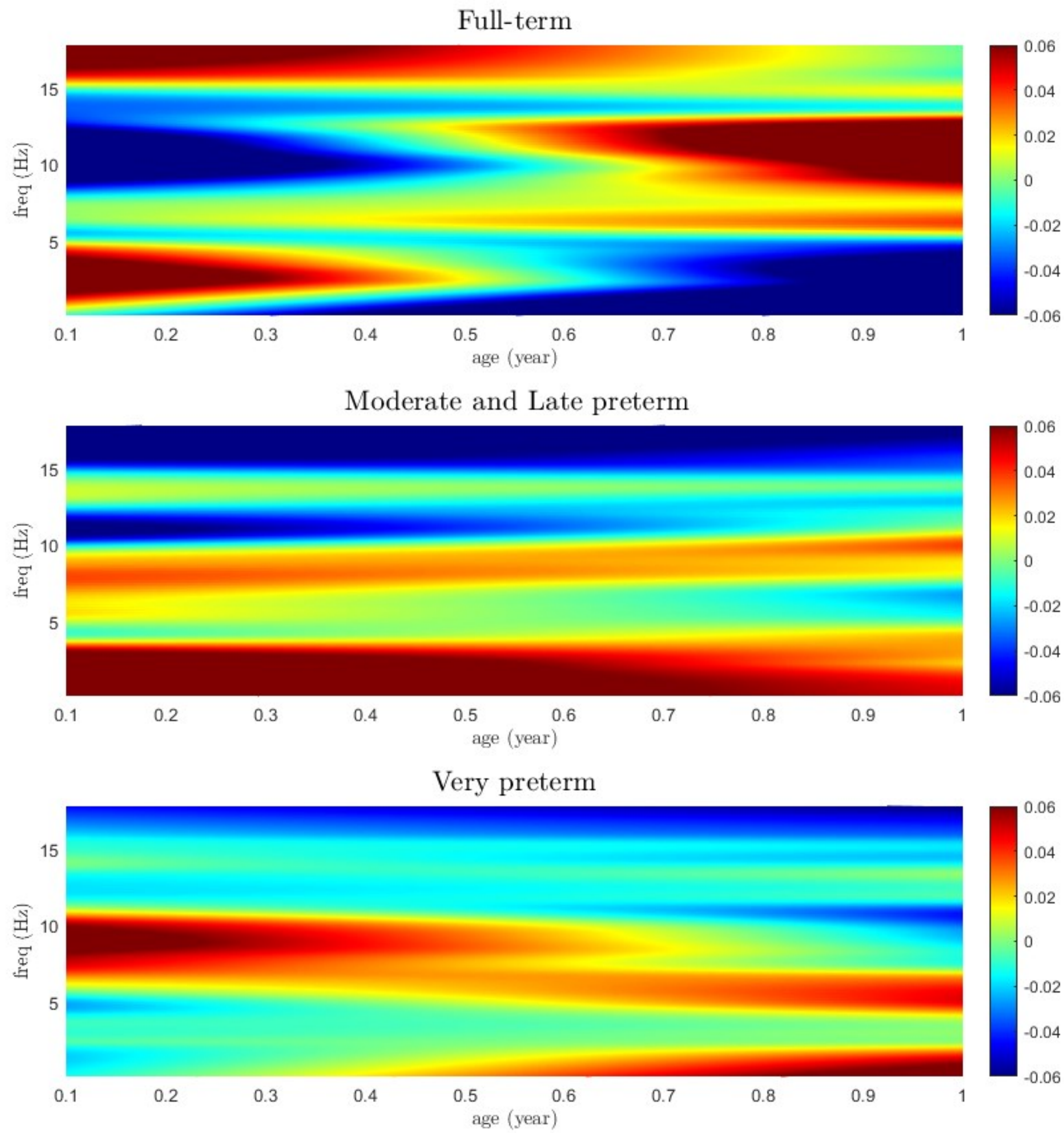

Fig 7: *Local connectivity pattern for the three groups of infants (full term, late preterm, and very preterm) at sensorimotor occipital regions.*

631