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 electroencephalography (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 full-term infants (n = 71), moderate/late-preterm infants (n = 54), and very preterm infants (n = 56). All preterm infants had perinatal and/or perinatal risk factors for brain damage. EEG was obtained during phase II of natural nonrapid eye movement (NREM) sleep. EEG analysis was performed in 24 2.56-s artifact-free segments. For the calculation of EEG sources, spectral structured sparse Bayesian learning 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 decreased, theta increased at the end of the year, the alpha band showed different trends based on the region studied, and beta interhemispheric connectivity decreased 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 provides 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 of cortical columns at the microscopic level of description (6,7). However, in isolation, its topological organization—spatial distribution and connectivity pattern at the macroscopic level possesses tremendous descriptive power with regard to the developing brain of preterm neonates (8).

An essential aspect of describing the development of neural networks involves mapping their spatial distribution alone by the localization of responsive areas at the observational level of experimental techniques, which can be collected by magnetic resonance imaging (MRI) and electroencephalography (EEG) (9). With either approach, this mapping is indirect. However, the spectral composition of functional MRI (fMRI) signals is severely distorted by the slow metabolic-hemodynamic cascade of the process that follows actual neural activity (10,11). Several MRI studies have shown aberrant structural characteristics and even abnormal connectivity in preterm infants (12), suggesting that disrupted 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, e.g., at ages of one and two years, have been described during the last decade (14).

Furthermore, the thalamus–sensorimotor and thalamus–salience connectivity networks have been shown to be already present in neonates, whereas the thalamus–medial visual and thalamus–default mode network connectivity were shown to emerge later, at one year of age (14). The observation that working memory performance measured at one and two years of age has significant correlations with the thalamus–salience network connectivity is also important. Studies have compared the connectivity between very preterm infants (VPTs) and full-term infants (FTIs) using MRI procedures (15). These studies showed that the most decreased connectivity strength in VPTs was the frontotemporal, fronto-limbic, and posterior cingulate gyrus at gestational ages (GAs) of 39.6 ± 1.2 weeks (FTI) and 40.3 ± 0.6 weeks (VPT).

Although many studies have evaluated 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 study of EEG connectivity in preterm and term infants early in life may provide essential knowledge regarding brain development. However, EEG signals are affected by their low spatial resolution and volume conduction effects (21,22). These pitfalls have been addressed by deploying generations of electrophysiological source imaging (ESI) methods during recent decades (23). ESI methods combine the best spatial resolution of MRI for head model

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estimation with the better 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 study, we focused on the temporal dynamics of neural networks in the millisecond range to study early neural integration. We present a longitudinal study of EEG connectivity in preterm infants and FTIs during the 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 FTIs without any antecedent for perinatal brain damage; ii) a group of moderate/late-preterm infants with GA between 32 and 37 weeks; and iii) a group of VPTs 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 or 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 or her mother's lap in a dimly lit room with acoustic isolation. No sedation was used. Referential EEG recordings for 20 minutes were obtained from 19 electrodes based on the 10/20 system using linked ears as a reference. The MEDICID IV System with a gain of 20,000, amplifier bandwidth between 0.5 and 100 Hz, and sample rate of 200 Hz was used. Some participants were recorded two or more times during their first year of life. Therefore, EEG data were selected from a dataset of 297 recordings collected between 2016 and 2020 as part of an ongoing project investigating the characterization of brain development in preterm infants.

Later, EEG data were segmented by visual inspection into 24 artifact-free segments of 2.56-s duration. The idea behind this processing was to avoid transforming original data by using

preprocessing techniques such as independent component analysis to remove artifacts (eye movement and blinks) or interpolation to fix "bad" channels. These methods could profoundly modify the connectivity information relayed in the electrophysiology signal, leading us to an incorrect interpretation of the data. The frequency analysis was set up from 0.3 Hz to 20 Hz. After EEG data collection and selection, the data analysis continued with two main steps: inference of EEG source space data using an ESI method and 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 because the possible solutions lie within a high-dimensional space. These distortions can reach unacceptable levels as repeatedly shown in simulations (21,22,44).

In this paper, we estimated cortical neural activity using a third generation ESI method, spectral structured sparse Bayesian learning (sSSBL) (45). sSSBL pursues estimation of neural activity through a maximum "evidence" search via the expectation-maximization algorithm (46). Evidence is defined as the conditional probabilities of two groups of parameters: (i) variances in spectral EEG source activity, which controls the statistical relevance of the source cross-spectral components; and (ii) variances in spectral EEG noise, which controls the level of noise in the observations.

Furthermore, this approach is based on an iterative 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 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 a 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 Montreal Neurological Institute (MNI) brain template (http://www.bic.mni.mcgill.ca). The scalp sensor space was built on 19 electrodes within a 10-20 EEG sensor system (49). The lead fields were computed by the boundary element method (BEM) integration method accounting for a model with 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 categorized into five large regions per hemisphere: frontal, sensorimotor, parietal, temporal, and occipital regions.

1.4 Connectivity analysis through phase-lag based measures

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

In this study, 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

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matrix (ROI-ROI-frequency). Finally, 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 why higher efficiency values correspond to more direct connections. Furthermore, global efficiency has been proven to be helpful in evaluating pathological networks since it is robust against 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 address this pitfall and to estimate with more critical details the development connectivity surfaces during 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 nonlinear 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 dataset. Later, we computed a linear regression model for each row of the development connectivity surface to evaluate the connectivity behavior for each frequency value during the first year of life. The slope-based curve provides evidence to compare the connectivity developed for the three groups under analysis.

2 Results

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

2.1 Left-right frontal connectivity (LRFC)

LRFC results are shown in Figure 2b. In the delta band, LRFC tended to decrease, although at age 0.1 years (36.5 days), different connectivity values were observed in different delta band frequencies. In the moderate/late-preterm group, this interhemispheric delta connectivity decreased, although at 0.5 Hz–1.0 Hz there was an increase with age. In the very preterm group, a decrease in interhemispheric frontal connectivity with increasing age was evident. LRFC in the theta band showed an increase in full-term subjects with age. Meanwhile, in the moderate/late-preterm group, there was a decrease in connectivity with age that was more marked in the very preterm group. LRFC in the alpha band in term and moderate/late-preterm infants decreased with age. As power in this frequency band decreased, this result was expected. However, there were differences in connectivity trends between groups in the beta band: full-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)

These results are shown in Figure 2c. LRSC in the delta band in term infants decreased during the first six months of age and subsequently increased. At the end of the first year, this increase was also observed in the moderate/late-preterm infants and with great intensity in the VPTs. This latter group also showed this increase in LRSC at frequencies in the theta band; meanwhile, a decrease in LRSC in the theta band was observed in full-term infants and in moderate/late-preterm infants. There was a constant increase in the 5 Hz–8 Hz range in term infants. This may correspond to rhythmic central activity that has been reported as a precursor to the mu or sensorimotor rhythm (58). Moderate/late-preterm infants showed a decrease in theta connectivity, and theta connectivity in VPTs showed a constant decrease. In the alpha band, LRSC decreased with age in term and moderate/late-preterm infants. In both groups at three months, robust alpha connectivity slowly decreased. However, in the VPTs, there was a substantial decrease across the whole year. LRSC at approximately 15 Hz decreased across the whole year in term infants and VPTs, and there was an unexpected increase at the end of the year in the moderate/late-preterm infants.

2.3 Left-right parietal connectivity (LRPC)

The results regarding LRPC are shown in Figure 2d. LRPC in term infants showed a decrease with age at all frequencies between 5 Hz and 10 Hz. However, in moderate/late-preterm infants, LRPC in the delta frequencies and the band from 6 Hz to 10 Hz showed high values at 3.65 months of age that progressively decreased with increasing age. In this group, connectivity in the band from 11 Hz to 18 Hz decreased, but connectivity had increased with age at the end of the year.

2.4 Left-right temporal connectivity (LRTC)

Figure 2e shows the results for LRTC. In the delta band, this connectivity at three months was robust and decreased with age in term infants. Moderate/late-preterm infants and VPTs showed the reverse trend, i.e., increases with age. In term infants, LRTC at frequencies from 6 to 8 Hz increased during the year. At 10 Hz to 12 Hz, LRTC decreased with age up to 6 months and subsequently increased. LRTC at frequencies within the beta band decreased with age in term infants. LRTC in both preterm groups decreased with age in the band from 10 Hz to 18 Hz.

2.5 Left-right occipital connectivity (LROC)

In Figure 2f, the results regarding LROC are shown. FTIs showed a progressive decrease with age in delta band frequencies. In the alpha band, connectivity decreased during the first six months and increased in the last six months of the year. Moderate/late-preterm infants and VPTs showed completely different patterns of connectivity behavior across the first year of age.

3 Discussion

In this study, EEG connectivity in preterm infants was described. Most papers reporting brain connectivity in preterm infants have used MRI (30,59–61), and prominent differences between networks identified in term control versus premature infants at term-equivalent ages 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 ages. In a follow-up study of preterm children at seven years of age, (63) demonstrated that children born very preterm had less connected and less complex brain networks than typically developing term-born children and that these structural abnormalities were observed after a follow-up of seven years. Structural information about the connectivity observed in preterm infants

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demonstrated alterations related to motor, linguistic and cognitive deficits (64). All this information was the basis for studying EEG connectivity in preterm infants.

The pioneering 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 supported the view that the functions of the left and right hemispheres are established early in human development through complementary developmental sequences. These sequences appeared to recapitulate differences in adult hemispheric function. However, subsequent studies in infants have mainly analyzed the correlation between homologous left and right hemispheres.

Previous studies analyzing the correlations between homologous left and right hemispheres (66) have described that median correlation values significantly decreased (between -40% and -60% decrease) in infants from 27 to 37 weeks of GA. Regarding postnatal maturation, only the central-temporal channel showed a decreasing trend. These authors concluded that the decreasing median correlation values in all homologous channels indicated a decrease in similarity in signal shape with increasing GA. González et al., in 2011, studied EEG inter- and intrahemispheric connectivity measuring coherence between regions and a measure of phase synchronization (67). They found significant differences between term and preterm infants during active and quiet sleep, with term infants having 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 full-term infants had different EEG connectivity results during quiet sleep than preterm infants in all frequency bands. Differences in the EEG analysis may explain the contradiction with the González results.

Significant structural differences may explain the findings observed in EEG connectivity between the term and preterm groups. Several studies have shown that preterm infants with risk factors for perinatal brain damage, especially those born before 32 gestational weeks, exhibit cerebral white and gray matter abnormalities (31). For example, brain MRI studies report that 50 to 80% of extreme and very premature infants present mild-to-moderate abnormalities in the cerebral white matter (68). Myelination delays in the posterior limb of the internal capsule and/or corona radiata, enlargement of the lateral ventricles (due to cerebral white matter loss) and thinning of the corpus callosum (CC) have frequently been observed on MRI. This last neuroradiological finding can range from a partial thinning of the CC with a decrease in the isthmus and/or body to a global thinning in the CC (69). It is important to mention that the CC is a cerebral structure constituted by axons connecting homologous cortical regions. Rapid growth in its volume occurs during the first 20 months of age (68,70). The midsagittal area of the CC has been commonly used as a sensitive marker of brain development and maturation since the area of the CC is related to the number of axons and their morphology, such as axon diameter and myelination (71). Furthermore, the loss of CC at the level of the isthmus and the mid-body has been associated with alterations in sensorimotor interhemispheric connectivity due to the loss of transcallosal connections, which affects maturation of the motor control network (72,73). This spectrum of structural abnormalities may explain many differences noted between term and preterm infants in interhemispheric EEG connectivity, especially in the sensorimotor region. Therefore, the development of the corpus callosum in preterm infants is affected by prematurity (74), and in preterm infants, a decrease in its volume has frequently been observed (69). 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 shows different patterns of development across the cortex, with a more rapid increase in the auditory cortex than in the prefrontal cortex (75), which may explain the asynchrony in cortical maturation in the infant's brain (76). These facts, together with the maturational process of myelination, show that it ends at a different time in different regions: auditory and visual cortex myelination ends at 18-24 months, whereas these processes end in Broca's area at five years and in the prefrontal cortex at nine years of age (77). These findings may explain essential differences in the topography of EEG connectivity during 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 (78). 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 studies of EEG development in normal infants (79). In all regions studied, EEG connectivity in the delta band decreased with age. EEG development in this frequency band has also been shown to decrease with age, which may explain the results observed in connectivity. EEG connectivity in the theta band shows differences in development based on the region being studied. LRFC showed a significant increase with age, which is consistent with the observation that in term infants' theta, absolute and relative power in frontal leads increase during the first year (79). LRTC also showed an increase at the end of the year, which coincided with the EEG neurodevelopmental findings.

In the range from 5 Hz to 8 Hz in FTIs, there was a constant increase in LRFC, as well as in LRTC and LRSC. This may correspond to rhythmic central activity that has been reported as a precursor to the mu or sensorimotor rhythm (58). The moderate/late-preterm group showed a decrease in connectivity, and in the very preterm group, this activity constantly decreased. Our findings are consistent with (80). A clear sensorimotor rhythm was described in the range of 5.47–7.03 Hz with contralateral activity in response to free movement while awake FTIs around the four months of life. Furthermore, 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 showed different trends in the different regions. In the frontal, temporal, and sensorimotor regions, interhemispheric connectivity decreased with age across the whole year. However, LROC showed a sharp decrease in the early months 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, perhaps because they used linear regression for the analysis (79).

EEG beta band connectivity decreased 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 other studies of EEG development.

4 Conclusions

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

5 Conflict of Interest

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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

TH conceived the project and contributed to the design of the study and validations. EGM contributed to the design of the study, data analysis, validations, and drafted the figures. DPL and AAG contributed to the design of the software tool implementation, carried out computational experiments and validations. LCR, MHR and PAVS contributed to the design of the study and supervised validations. All authors contributed to the final manuscript.

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

Age Group	N	Sex (females)	EEGs	GA (wks)
Full-term	71	29	82	40 (38-41)
Moderate/late preterm	54	25	112	35 (32-37)
Very preterm	56	27	103	29 (27-31)

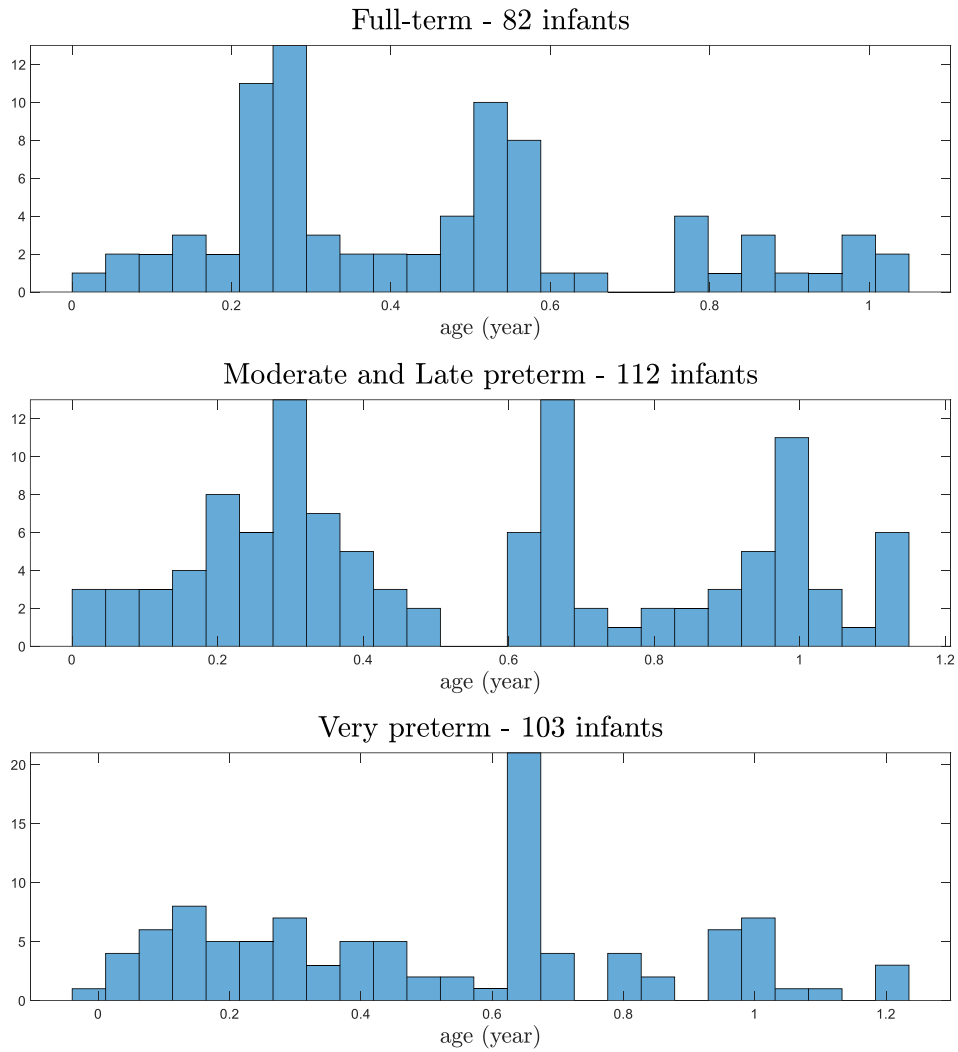

Fig 1: *Histogram by age groups showing some small gaps in EEG data recordings during the first year.*

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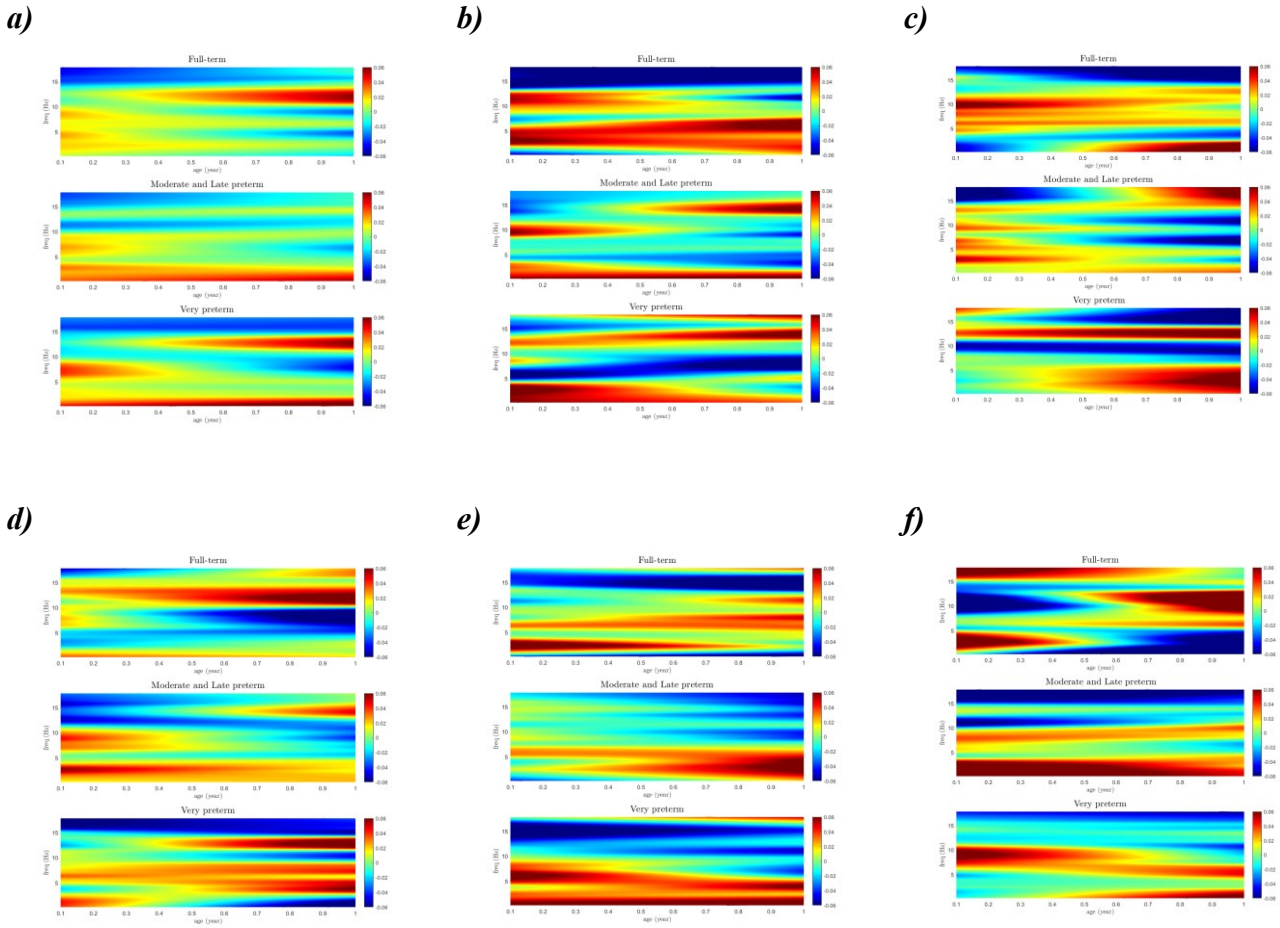

Fig 2: *Connectivity patterns in the three groups of infants: full-term, moderate/late preterm, and very preterm: a) global connectivity patterns, b) interhemispheric frontal cortical connectivity patterns, c) interhemispheric sensorimotor cortical regions connectivity patterns, d) interhemispheric parietal cortical regions connectivity patterns, e) interhemispheric temporal cortical regions connectivity patterns, f) interhemispheric occipital regions connectivity patterns.*

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