Altered Functional Brain Network Integration, Segregation, and Modularity in Infants Born Very Preterm at Term-Equivalent Age

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Objectives To determine the functional network organization of the brain in infants born very preterm at term-equivalent age and to relate network alterations to known clinical risk factors for poor neurologic outcomes in prematurity.

Study design Resting-state functional magnetic resonance imaging data from 66 infants born very preterm (gestational age <32 weeks and birth weight <1500 g) and 66 healthy neonates born at full term, acquired as part of a prospective, cross-sectional study, were compared at term age using graph theory. Features of resting-state networks, including integration, segregation, and modularity, were derived from correlated hemodynamic activity arising from 93 cortical and subcortical regions of interest and compared between groups.

Results Despite preserved small-world topology and modular organization, resting-state networks of infants born very preterm at term-equivalent age were less segregated and less integrated than those of infants born full term. Chronic respiratory illness (ie, bronchopulmonary dysplasia and the length of oxygen support) was associated with decreased global efficiency and increased path lengths ($P < .05$). In both cohorts, 4 functional modules with similar composition were observed (parietal/temporal, frontal, subcortical/limbic, and occipital). The density of connections in 3 of the 4 modules was decreased in the very preterm network ($P < .01$); however, in the occipital/visual cortex module, connectivity was increased in infants born very preterm relative to control infants ($P < .0001$).

Conclusions Early exposure to the ex utero environment is associated with altered resting-state network functional organization in infants born very preterm at term-equivalent age, likely reflecting disrupted brain maturational processes. *(J Pediatr 2019;213:13-21).*

R esting-state functional magnetic resonance imaging (rs-fMRI) is an imaging technique that reveals, without any explicit external stimulation, consistent and reproducible patterns of interacting brain regions called resting-state networks that correspond to known functionally relevant brain systems (ie, visual, sensorimotor, and auditory, among others).[1,2] In infants born preterm, rs-fMRI has allowed researchers to begin to characterize the effects of early exposure to the extrauterine environment on the neurodevelopment of infants born preterm.[3-6] rs-fMRI estimates neuronal activity by measuring spontaneous, low-frequency fluctuations in blood oxygen level−dependent (BOLD) signals. Because rs-fMRI is noninvasive, rapidly acquired, requires no input from the participant, and investigates multiple brain systems simultaneously,[2] it has emerged as a promising tool for evaluating pediatric brain function. In infants born preterm, rs-fMRI has shown intact resting-state network patterns but with reduced complexity and altered connectivity strengths in some neural networks.[4,6-8] Connectivity changes in the brains of infants born preterm also have been shown to correlate with long-term neurologic outcomes.[9,10]

Studies of preterm resting-state networks using a mathematical approach known as graph theory[11-13] showed that the organization of preterm brains for specialized and distributed processing of information differed from healthy, full-term controls. Building on these network studies, we compared the functional organization of resting-state neural networks in a sample of unsedated infants born preterm without or with mild brain injury and healthy newborns born full term. We investigated the effects of clinical risk factors on network connectivity and hy-

BOLD	Blood oxygen level−dependent
BPD	Bronchopulmonary dysplasia
Cc	Clustering coefficient
GE	Global efficiency
L	Characteristic path length
lE	Local efficiency
MRI	Magnetic resonance imaging
ROI	Region of interest
rs-fMRI	Resting-state functional magnetic resonance imaging

pothesized that the effect of prematurity would be associated with measurable alterations in strength and organization of the resting-state networks.

Methods

Infants born very preterm and healthy controls born at full term were enrolled in 2 prospective observational studies.[14] For the very preterm cohort, inclusion criteria were gestational age at birth <32 weeks and birth weight <1500 g. Exclusion criteria included chromosomal anomalies, dysmorphic features, congenital brain malformations, central nervous system infection, and metabolic disorders. Only infants born very preterm without brain injury or with mild brain injury (eg, low-grade intraventricular hemorrhage or mild white matter injury; Figure 1 [available at www.jpeds.com]) based on the brain magnetic resonance imaging (MRI) scoring system of Kidokoro et al were included.[15] All healthy control infants born full term were born without delivery complications and had normal MRI scans of the brain. Exclusion criteria for the control group were maternal drug use and disease (eg, gestational diabetes, psychiatric disorders), congenital infections, chromosomal abnormalities, and dysmorphic features.

Demographic and clinical information was collected from medical record reviews. In the preterm cohort, several risk factors were chosen a priori based on previous literature for their potential adverse effect on brain development; these included the presence of mild brain injury (yes/no), moderate-to-severe bronchopulmonary dysplasia (BPD), the length of supplemental oxygen requirement, postnatal steroid treatment, necrotizing enterocolitis diagnosis, need for cardiac vasopressor support, and need for patent ductus arteriosus surgical ligation.[16-25]

Image Acquisition and Processing

All infants were scanned without sedation using the same 3T GE scanner (GE Healthcare, Milwaukee, Wisconsin). Acquisition parameters are detailed in Appendix 1 (available at www.jpeds.com). Resting-state data were preprocessed using a previously validated pipeline that employed a series of temporal and spatial denoising strategies to minimize the influence of noise from head motion, scanner drift, and subject physiology (ie, respiration), among others, on the measured BOLD signal.[26] BOLD signals were measured from 93 regions of interest (ROIs): 90 cortical and subcortical ROIs defined using an automated anatomical labelling atlas[27] mapped to a neonatal brain[28] and 3 infratentorial ROIs derived from Draw-EM segmentation (BioMedIA, Biomedical Image Analysis Group, Department of Computing, Imperial College London, London, United Kingdom).[29] Correlation (Pearson r) between BOLD signals from all possible ROI pairs were then computed and used for network analyses. Appendix 1 includes additional information.

Network Analyses

We compared network functional organization between the 2 groups using the following graph metrics: (1) clustering coefficient (Cc), (2) local efficiency (lE), (3) characteristic path length (L), (4) global efficiency (GE), (5) small world architecture, and (6) modular organization (see Appendix 2; available at www.jpeds.com).[30] Clustering coefficient and local efficiency are segregation parameters. Segregation reflects the extent to which densely connected regions of the brain (modules or clusters) perform specialized functions.[31] Segregated networks have high Cc and high lE. Network integration refers to the ability of resting state networks to share information globally and is captured by the metrics characteristic path length and global efficiency. Integrated networks have short L and high GE. Small-world topology, quantified with the small world index (σ) that relates Cc and L, refers to the balance between network specialization and integration observed in complex networks like the brain[11,32-36]; if $\sigma > 1$, meaning Cc is high and L is low, then the network is considered small-world. Modularity is related to segregation and reflects the tendency of networks to subdivide into functionally meaningful clusters. A module refers to a group of nodes that are highly connected to each other but are sparsely connected to others outside of their group.[37] This relationship is reflected by the modularity index (Q^{38}). For a mathematical description of these measures, please refer to the work of Rubinov and Sporns.[30]

In the preterm cohort, we studied the relationship between clinical risk factors and global properties of the resting-state networks. We computed the averaged global network metrics (Cc, L, GE, lE) over the range of correlation thresholds and assessed the relationship between risk factors associated with prematurity and global resting state networks properties using ANCOVA.

Statistical Analyses

Statistical analyses were performed using Matlab 2017a (MathWorks, Inc, Natick, Massachusetts) and SAS 9.3 (SAS Institute, Cary, North Carolina). Between the preterm cohort and healthy full-term group, we compared segregation and integration metrics from individual network using permutation testing (100 000 iterations) on the residuals adjusted for postmenstrual age at MRI, sex, and motion. Modularity was evaluated on group-averaged connectomes at a density of 15% (sparsest density with the least probability of spurious connections). We then identified modular communities using 10 000 iterations of the Louvain algorithm.[39] Between the preterm cohort and healthy full-term group, we compared the modularity index and the intramodular functional connectivity using 2-sided 2-samples t-test and the intramodular density using χ^2 test. Finally, the relationship between risk factors associated with prematurity and global resting-state networks properties was assessed using ANCOVA analysis, controlling for sex, gestational age at birth, day of life at MRI, and motion.

Table I. Clinical characteristics of infants born very preterm and control infants born full term

Characteristics	Infants born very preterm, n = 66	Healthy infants born full term, n = 66	P value
Perinatal			
Birth gestational age, mean ± SD, wk	27.36 ± 2.68	39.48 ± 0.99	<.0001
Range	22.4-32	37.3-41.3	
Birth weight, g, mean ± SD	931 ± 305	3373 ± 356	<.0001
Range	480-1500	2590-4011	
Small for gestational age*, n (%)	9 (14)	6 (9)	.41
Male, n (%)	29 (44)	36 (55)	.76
Native American; Hispanic; white	0; 15 (23); 9 (14)	2 (3); 6 (9); 16 (24)	.021
Asian; black; Multiethnic, n (%)	0; 39 (59); 3 (4)	5 (8); 24 (51); 3 (5)	
Vaginal delivery, n (%)	27 (40)	45 (68)	.0017
Apgar score at 5 min, median (range)	8 (1-9)	9 (8-10)	<.001
Maternal age, y, mean ± SD	27.91 ± 5.9	29.2 ± 7.18	.26
MRI			
Postmenstrual age at MRI, wk, mean ± SD	40.21 ± 1.56	41.1 ± 1.1	.0002
Range	37.4-44.4	38.4-44.3	
Day of life at MRI, d, mean ± SD	89.97 ± 21.4	11.21 ± 4.88	<.0001
Range	41-137	4-20	
Head circumference at MRI, cm, mean ± SD	33.26 ± 2	35.71 ± 1.09	<.0001
Range	27-37	32-39	
Weight at MRI, g, mean ± SD	2818 ± 681	3596 ± 422	<.0001
Range	1870-5400	2475-4470	

*Small for gestational age if birth weight <10% percentile for sex and gestational age, based on the Fenton growth chart.

Results

We studied 132 infants: 66 infants born very preterm at term-equivalent age and 66 healthy control infants born at full term. Of the 66 infants born very preterm, 21 had mild brain injury: 7 with low-grade intraventricular hemorrhage (grade I-II), 13 with mild white matter injury, and 1 with small cerebellar punctate hemorrhage. Postmenstrual age at MRI was greater in the full-term group; this was used as a covariate in the rest of the analysis. Table I summarizes the demographic and clinical characteristics of the cohorts.

Network Segregation, Integration, and Small-World Architecture

Resting-state networks of infants born very preterm and full term exhibited small-world topology ($\sigma > 1$). This balance between network integration and segregation suggested that even in the infants born very preterm, efficient global processing of information was preserved. However, segregation and integration measures per se were reduced in infants born very preterm compared with healthy newborns (Figure 2). Segregation parameters Cc and lE and L and GE were all significantly decreased in infants born very preterm.

Modular Organization

The resting-state networks of the infants born very preterm and full term showed modular organization (Figure 3). The modularity index, however, was significantly lower in the infants born very preterm compared with the infants born at full term, suggesting reduced density of connections within modules in the infants born very preterm. Although modules in the resting-state networks of infants born very preterm tend to be less connected, their composition was highly similar to newborns born full term

(Figure 3). In both cohorts, resting-state networks were divided into 4 modules (Table II and Figure 3), namely: (1) Module 1, primary somatosensory, motor, and auditory cortices and association areas within the parietal/temporal cortices; (2) Module 2, regions in the frontal cortex; (3) Module 3, subcortical, limbic, and paralimbic brain regions; and (4) Module 4, primary and association visual cortices/occipital cortex.

When we compared the number of connections within each module at a density threshold of 15 % (ie, same total number of connections in very preterm and full-term group-averaged functional connectome), density and connectivity strength within each module were perturbed in infants born very preterm (Table II). Infants born very preterm had significant lower density in all modules except Module 4 (ie, occipital areas), where connection density was greater. Connectivity strength was significantly reduced in infants born very preterm in the parietotemporal and subcortical/limbic modules (Table II).

Clinical Risk Factors

In the preterm cohort, we showed that both moderate-to-severe BPD and prolonged need for supplemental oxygen were associated with increased path length ($\beta > 0$) and decreased global efficiency ($\beta < 0$) (Table III), suggesting reduced integrative abilities in infants born very preterm. In addition, longer period of oxygen support also was associated with decreased local efficiency ($\beta < 0$), suggesting decreased specialization in very preterm resting-state networks (Table III).

Discussion

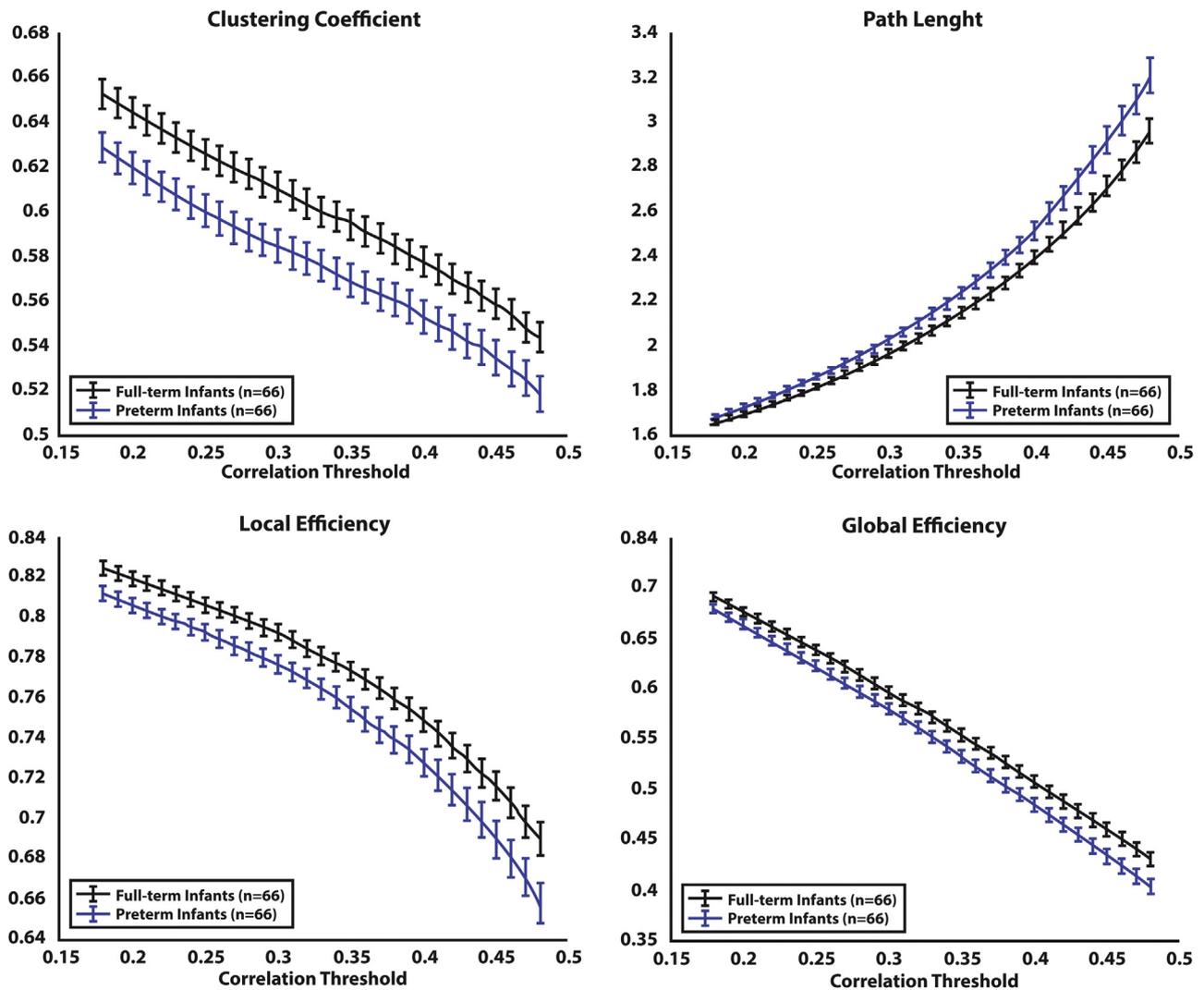Our study revealed aberrant functional network organization in a large sample of infants born very preterm scanned at

Figure 2. Cc, L, and GE and IE in infants born very preterm (*blue*) and full term (*black*). Metrics were significantly different between groups at all tested thresholds using permutation testing (*P* < .05); tests controlled for sex, postmenstrual age at MRI, and motion.

term-equivalent age. Compared with healthy newborn infants at term, infants born very preterm with no or mild brain injury had reduced-resting state network segregation and integration measures and altered modular connectivity. Among the risk factors analyzed, only the clinical indicators of severity of respiratory illness (ie, moderate-to-severe BPD and prolonged supplemental oxygen support) were associated with network alterations in infants born very preterm. These findings underscore the potential detrimental link between respiratory illness severity and functional brain development in infants born very preterm.

We showed small-world organization in infants born very preterm and full term consistent with previous studies using rs-fMRI.[3,11-13,40] This organization, reflective of efficient, specialized, and integrated neuronal communication,[41] likely emerges before the 31st week of gestation and continues to mature as gestation progresses.[13] Although small-world ar-

chitecture was preserved, resting state networks of infants born very preterm were less segregated (ie, lower clustering coefficients and reduced local efficiency) and integrated (ie, longer path lengths and reduced global efficiency). Reduced clustering was previously reported by Scheinost et al in a smaller cohort (12 infants born preterm)[12]; they, however, did not observe differences in path lengths between infants born premature and at term, possibly due to the smaller sample size. Our results suggest that preterm birth somehow reconfigures connections among brain regions. In infants born preterm, longitudinal studies have reported age-dependent increases in functional connectivity strength,[4,6,7] network complexity and magnitude,[7] integration,[11,13] and modularity[11,13] during the third trimester, suggesting a vulnerability window. Thus, it is not surprising that in some networks at term-equivalent age, infants born preterm exhibit reductions in connectivity strength,[7] decreased

Preterm Infants

Full-term Infants

● Module 1 - parieto-temporal   ● Module 3 – subcortical/limbic/paralimbic
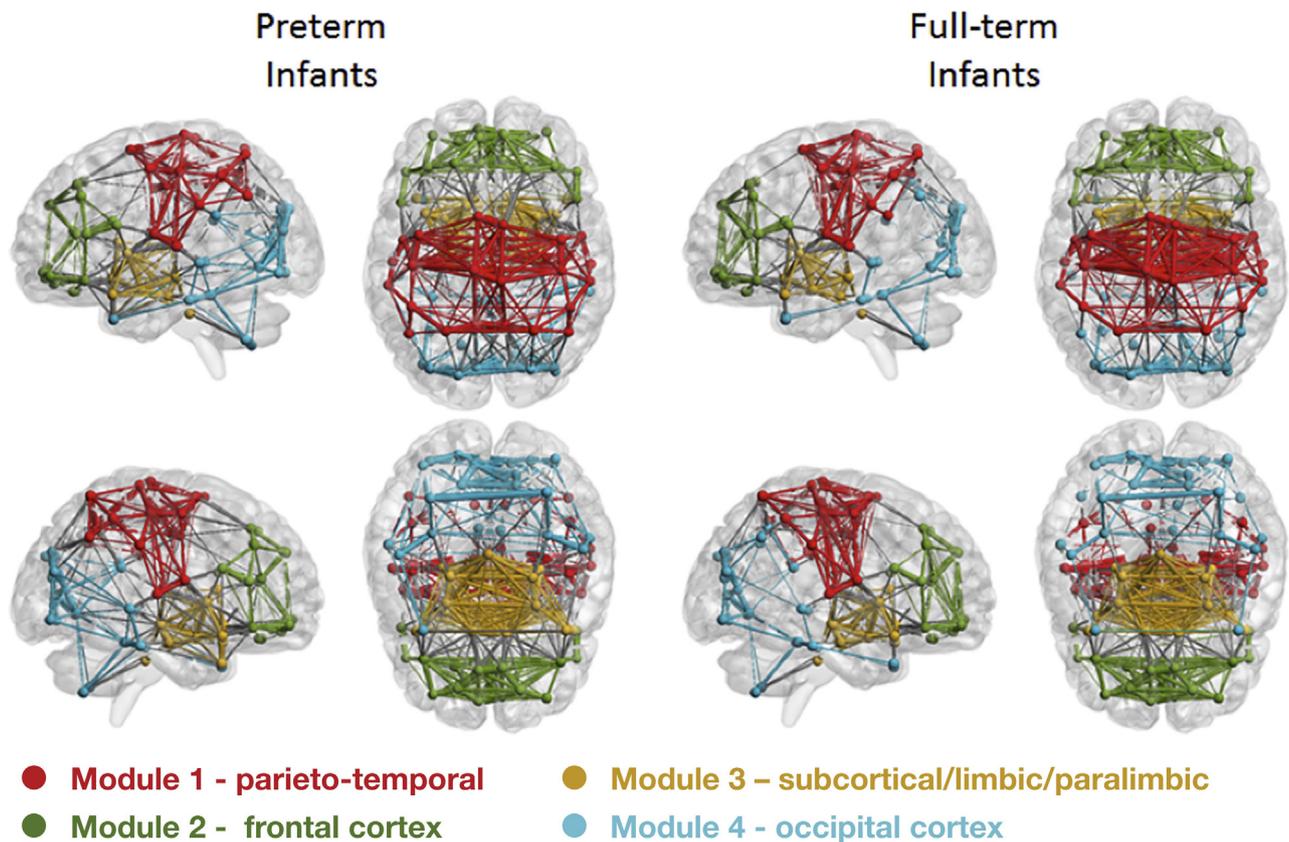● Module 2 - frontal cortex   ● Module 4 - occipital cortex

Figure 3. Modular brain organization in infants born very preterm and full term. *Spheres* are nodes, *lines* are edges; *color* represent module membership. Note reduced number of connection between nodes in modules 1-3 (1: *red*, 2: *green*, and 3: *yellow*) and increased density in module 4 (*blue*) in infants born very preterm compared with infants born full term.

interhemispheric connectivity,[5,6] altered lateralization of language areas,[42] altered thalamocortical connectivity,[8,43] and impaired basal ganglia–frontal cortex connectivity,[44] and it provides additional support to the likely effects of preterm birth on the organization of emerging functional networks. Our understanding of how functional connectivity in infants born very preterm evolves over time remains incomplete, but available follow-up studies already suggest that functional connectivity remains compromised in adults born very preterm.[45-49]

Interestingly, only the clinical risk factors linked to respiratory disturbances showed a negative association with resting-state network organization: moderate-to-severe BPD and length of oxygen support were linked to reduced global and/or local efficiency of the resting-state networks. Respiratory issues such as BPD and prolonged need for oxygen support have been associated with impaired brain development and adverse cognitive functioning.[19,20,50,51] Hypoxic episodes resulting from respiratory disturbances are thought to underlie the pathophysiological mechanisms responsible for these cerebral alterations.[52-56] Hypoxic—ischemic events are a major cause of prematurity-related brain injury,[57-59] and disturbances in cerebral oxygenation also have been associated with subtler delays in structural brain maturation in

high-risk neonatal population.[60,61] Taken together, these findings emphasize the crucial role of adequate oxygen supply in the early establishment of the neural circuitry.

Mild brain injury was not related to alterations in global properties of the resting-state networks in our study. Because white matter injury has been associated with altered functional connectivity in infants born preterm,[5,43,62] we hypothesize that the degree of brain injury severity plays a crucial role; thus, the potential functional connectivity disturbances following mild brain injury still remain to be elucidated.

Small-world topology of networks relate closely to its modular organization.[32,63] Modular systems with functionally specialized subsets of brain regions that are sparsely connected to other modules, such as what we observed in resting state networks of infants born very preterm at term-equivalent age and newborns born full term, tend to be small world (ie, high segregation balanced with high integration[64]). Modular organization of the developing brain has been described in fetuses during the third trimester,[65] infants born preterm,[11,13] and healthy neonates.[11,40] We also reported modular organization of resting-state networks in infants born very preterm at term-equivalent age, but with reduced modularity compared with infants born full term.

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Table II. Modular brain organization differences between infants born very preterm and full term

Modularities (Q)	Infants born very preterm, N = 66 0.49 ± 0.005	Control infants born full term, n = 66 0.51 ± 0.002	P value <.001
Module 1: parietal/temporal			
Node	26	24	
Density	42.2%	52.5%	**.01**
Connectivity strength	0.49 ± 0.2	0.54 ± 0.22	**.0086**
Module 2: frontal			
Node	22	22	
Density	36.4%	49.4%	**.0048**
Connectivity strength	0.55 ± 0.25	0.55 ± 0.25	.68
Module 3: subcortical/limbic			
Node	22	21	
Density	69.7%	80.5%	**.0092**
Connectivity strength	0.51 ± 0.21	0.56 ± 0.2	**.0023**
Module 4: occipital			
Node	23	26	
Density	41.5%	23.7%	**<.0001**
Connectivity strength	0.51 ± 0.25	0.535 ± 0.22	.239
Between module connections			
Density	4.8%	4.2 %	.44
Connectivity strength	0.39 ± 0.11	0.42 ± 0.13	**.0256**

P values in bold indicate statistically significant results.

Four functional modules with similar composition to infants born full term were identified. Consistent with previous work, modules in infants were mostly anatomically constrained[3,40,66]; adjacent areas/regions belonging to the same lobe tend to belong to the same module. In contrast, adult modules are composed of neighboring (ie, subcortical module), as well as spatially distant, but functionally associated regions such as the default-mode and attention modules (frontoparietal).[37,64,67,68] Cognitive networks are immature at birth[69] and the default-mode network only starts to exhibit adult-like properties during the first years of life[69-71]; thus, it is not surprising that the modular organization at term age

Table III. Relationship between clinical risk factors and global network properties in the preterm cohort

Risk factors studied	Infants born very preterm, n = 66	Global network metric	Model P value	Association with global network metrics
Mild brain injury	21 (32%)	Cc	.002	$\beta = 0.001$; $P = .94$
		L	.002	$\beta = 0.01$; $P = .85$
		GE	.011	$\beta = -0.001$; $P = .86$
		IE	.0008	$\beta = 0.002$; $P = .85$
Moderate-to-severe BPD*	24 (37%)	Cc	.0005	$\beta = -0.02$; $P = .15$
		L	<.0001	**$\beta = 0.17$; $P = .01$***
		GE	<.0001	**$\beta = -0.03$; $P = .02$***
		IE	.0001	$\beta = -0.02$; $P = .05$
Length of oxygen support, d	67 ± 41 0-172	Cc	.0006	$\beta = -0.0004$; $P = .36$
		L	.0001	**L: $\beta = 0.0027$; $P = .03$***
		GE	.0001	**GE: $\beta = -0.004$; $P = .01$***
		IE	<.0001	**IE: $\beta = -0.0004$; $P = .026$***
Postnatal steroid treatment	21 (32%)	Cc	.0013	$\beta = -0.001$; $P = .92$
		L	.0012	$\beta = -0.038$; $P = .58$
		GE	.0006	$\beta = 2.2 \times 10^{-6}$; $P = .99$
		IE	.0006	$\beta = 0.005$; $P = .69$
Necrotizing enterocolitis	19 (29%)	Cc	.0019	$\beta = -0.004$; $P = .78$
		L	.0017	$\beta = -0.05$; $P = .42$
		GE	.0011	$\beta = 0.002$; $P = .84$
		IE	.0007	$\beta = 0.006$; $P = .63$
Cardiac vasopressor treatment	19 (30%)	Cc	.0006	$\beta = 0.021$; $P = .18$
		L	.0014	$\beta = -0.02$; $P = .76$
		GE	.0006	$\beta = -9.9 \times 10^{-6}$; $P = .99$
		IE	.0003	$\beta = 0.016$; $P = .18$
Surgical ligation of patent ductus arteriosus	12 (18%)	Cc	.002	$\beta = 0.0018$; $P = .92$
		L	.0023	$\beta = 3.6 \times 10^{-4}$; $P = .99$
		GE	.0011	$\beta = -0.002$; $P = .86$
		IE	.0008	$\beta = 7 \times 10^{-4}$; $P = .96$

*Severity of BPD in infants born very preterm: treatment with oxygen for at least 28 days and need for more than 21% oxygen support (moderate: <30% oxygen; severe: >30% oxygen) at discharge or at 36 weeks of postmenstrual age, whichever comes first.[30]
Significant associations are in bold.

does not include cognitive module yet. Due to the postnatal development of cognitive processes and establishment of long-range connections during early childhood, regional organization of the resting-state networks evolve from a local organization during childhood to a distributed organization in adulthood.[63,72,73]

Preterm networks, although still modular, were less segregated (ie, lower modularity index) compared with full-term resting-state networks. Previous work has shown that networks become more segregated with increasing age in the first 2 years of life.[74] This reduced specialization in infants born very preterm may suggest less-mature brain networks compared with their full-term counterparts. Examining the density of connections within each module, however, suggests a more nuanced picture in which, depending on the neural network, both delayed and accelerated maturation seem to occur. In infants born preterm, connection density was reduced in 3 of the 4 modules—parieto-temporal, frontal, and subcortical/limbic. Interestingly, infants born very preterm had an increased number of connections in the occipital/visual module. This finding converges with the results of Padilla et al, which demonstrated increased volumes of areas involved in visual processing in infants born extremely preterm at term-equivalent age compared with healthy control infants.[75] This increased connection density in the visual cortex is likely due to experience-dependent processes. Early extrauterine exposure is likely associated with increased visual stimulation during a critical period of development for the visual system.[76-78] Synaptic density of the visual cortex dramatically increases from mid-gestation to the first months of postnatal life.[76,77,79,80] Increased visual inputs during this critical period might have lasting consequences on visual processing.[78,81,82] Additional studies are needed to elucidate the relationship between early visual experiences, functional organization of the visual cortex, and impairments in cortical visual processing. It would be intriguing to explore whether other sensory areas of the brain (ie, auditory cortex) that are prematurely exposed to ex utero stimulation also would present with increased connection density. The modular analysis performed was not suited to elucidate the possible link between prematurity and the functional development of other sensory areas sensitive to exogenous stimulation during the third trimester.

Our study limitations deserve mention. First, our understanding of the biological mechanisms underlying BOLD responses remains incomplete,[83] even more so in newborn infants than in adults.[84] As such, interpreting and comparing findings must be done carefully. Having said that, there is a high degree of consistency between our findings and other published reports in newborn infants. In addition, observed emergence of resting-state networks coincide with the timing of established developmental processes (ie, development of somatosensory and motor before higher cognitive/association networks). Second, recent work has shown that the disruption of resting-state networks in infants born preterm may begin in utero[85] with an additive negative effect of fetal growth restriction.[86] Thus, prenatal, in addition to postnatal

risk factors associated with preterm birth, also may impact the early development of the resting-state networks. Next, similar to other studies,[34] only positive correlations were included in our network analyses because most existing graph methods were optimized for networks with positive correlations.[87-89] To evaluate negatively correlated brain activity, newer approaches accounting for anticorrelated activity need to be used.[30,89,90] Last, newborn imaging poses numerous technical challenges, one of which is motion correction. To minimize the influence of motion, we removed ("scrubbed") high motion volumes and used motion parameters and their derivatives as regressors in our statistical analyses. Correcting geometric distortion in echo-planar images is another technical issue. We did not perform distortion correction in our study; however, rigorous visual evaluation of our echo-planar images show minimal shape distortion. We have now included field map acquisition in our newborn MRI sequences so we can systematically evaluate distortion effects on connectivity measures.

To summarize, we report reduced segregation and integration in resting-state networks of infants born very preterm at term-equivalent age and their association with prematurity-related respiratory illness severity. Notably, these network alterations were present despite intact small-world topology and modularity. Longitudinal studies covering the prenatal (ie, healthy fetal controls) and early school age periods would be necessary to provide additional insights into the role of premature birth on the development of functional brain networks, including possibly identifying the onset of these alterations, and to understand its long-term impact on neurobehavior. ∎

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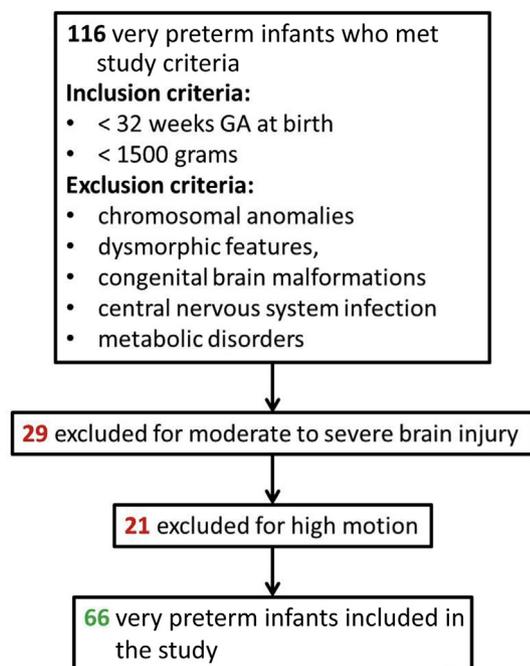Altered Functional Brain Network Integration, Segregation, and Modularity in Infants Born Very Preterm at Term-Equivalent Age

21

116 very preterm infants who met
   study criteria
Inclusion criteria:
- < 32 weeks GA at birth
- < 1500 grams

Exclusion criteria:
- chromosomal anomalies
- dysmorphic features,
- congenital brain malformations
- central nervous system infection
- metabolic disorders

29 excluded for moderate to severe brain injury

21 excluded for high motion

66 very preterm infants included in
   the study

Figure 1. Inclusion and exclusion criteria for infants born very preterm. *GA*, gestational age.