Published in final edited form as:

Brain Struct Funct. 2016 July ; 221(6): 3211–3222. doi:10.1007/s00429-015-1096-6.

Preterm birth alters neonatal, functional rich club organization

Dustin Scheinost^{1,*}, Soo Hyun Kwon², Xilin Shen¹, Cheryl Lacadie¹, Karen C Schneider², Feng Dai³, Laura R Ment^{2,4}, and R. Todd Constable^{1,5}

¹Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, CT

²Department of Pediatrics, Yale University School of Medicine, New Haven, CT

³Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, CT

⁴Department of Neurology, Yale University School of Medicine, New Haven, CT

⁵Department of Neurosurgery, Yale University School of Medicine, New Haven, CT

Abstract

Alterations in neural networks are associated with the cognitive difficulties of the prematurely born. Using functional magnetic resonance imaging, we analyzed functional connectivity for preterm (PT) and term neonates at term equivalent age. Specifically, we constructed whole-brain networks and examined rich club (RC) organization, a common construct among complex systems where important (or “rich”) nodes connect preferentially to other important nodes. Both, PT and term neonates showed RC organization with PT neonates exhibiting significantly reduced connections between these RC nodes. Additionally, PT neonates showed evidence of weaker functional segregation. Our results suggest that PT birth is associated with fundamental changes of functional organization in the developing brain.

Keywords

rich club; network theory; preterm birth; connectivity; neonate

Introduction

Preterm (PT) birth represents a major public health problem (Beck et al. 2010) with deficits in language processing, motor abilities, executive function, and attention for PT children as a cause of school failure (Pritchard et al. 2014). One in three PT children is diagnosed with language delay by preschool age (Foster-Cohen et al. 2010) and over half require special services at school age (Pritchard et al. 2014). These difficulties persist through adolescence and young adulthood and may be exacerbated by disorders of executive function and attention. Over the past decade, multiple magnetic resonance imaging (MRI) studies of brain connectivity suggest that these difficulties of the prematurely born are related to alterations in functional and structural networks (Kim et al. 2014; Constable et al. 2012; White et al.

*corresponding author: Dustin Scheinost, Ph.D., Magnetic Resonance Research Center, 300 Cedar St, PO Box 208043, New Haven, CT 06520-8043, Tel: (203) 785-6148, Fax: (203) 785-6534, dustin.scheinost@yale.edu.

2014; Salvan et al. 2013). Similarly, PT neonates show disruptions in connectivity (Smyser et al. 2010; Doria et al. 2010), suggesting that PT birth results in both proximate and long-lasting changes in functional organization of the developing brain.

Rich club (RC) organization is a common construct among complex systems where important (or “rich”) nodes connect preferentially to other important nodes (van den Heuvel and Sporns 2011). Structural connections in the human brain show RC organization in infancy, childhood and adulthood (Ball et al. 2014; Grayson et al. 2014; Kim et al. 2014; van den Heuvel et al. 2014). PT birth results in significant disruption of structural RC in neonates (Ball et al. 2014) and adolescents (Kim et al. 2014). Emerging evidence suggest that functional RCs evolve during development to a greater extent than structural RCs (Grayson et al. 2014). Alterations in functional RCs for PT neonates compared to term controls have yet to be explored.

In this report, we used resting-state functional MRI (rs-fMRI) data to examine alterations in neonatal RC organization and other measures of network topology associated with PT birth. We hypothesized that PT neonates would show a decrease in measures of functional integration and segregation.

Methods

This study was approved by the Yale University Human Investigation Committee. All participants' parents provided written consent.

Participants

Twelve PT and 25 term non-sedated neonates without evidence of brain injury underwent rs-fMRI on a 3 T Siemens TIM Trio system at term equivalent age. PT neonates with a birth weight (BW) between 500–1500 grams and healthy term controls born between 37 and 41 weeks' postmenstrual age (PMA) were eligible for the protocol and prospectively enrolled between September 1, 2010 and April 30, 2014. Term neonates were inborn and appropriate for gestational age. Exclusion criteria included evidence of congenital infections, congenital malformations and/or chromosomal disorders, seizures, intraventricular hemorrhage (IVH), periventricular leukomalacia and focal abnormalities on a previous or study MRI. Demographic information is presented in Table 1. Participants were scanned during natural sleep induced by food, comfort, and warmth (Saunders et al. 2007) without sedation with a 32-channel parallel receiver head coil.

Imaging parameters

Localizer images were acquired for prescribing the functional image volumes, aligning the seventh or eighth slice to the plane transecting the anterior and posterior commissures (AC-PC). T1-weighted 2D anatomical images were collected (TR=300ms, TE=2.47ms, FoV=220mm, matrix size=256×256, slice thickness=4mm, Flip Angle=60°, Bandwidth=300Hz/pixel with 25 slices) with 25 AC-PC aligned axial-oblique slices in addition to 3D anatomical scans using Magnetization Prepared Rapid Gradient Echo (MPRAGE) (176 contiguous sagittal slices, slice thickness=1mm, matrix size=256×256, FoV=256mm, TR=2530ms, TE=2.77ms, Flip Angle=7°, Bandwidth=179Hz/pixel). After

these structural images, acquisition of functional data began in the same slice locations as the axial-oblique T1-weighted data. Functional images were collected using an echo-planar image gradient echo pulse sequence (TR=1500ms, TE=27ms, FoV=220mm, matrix size=64×64, slice thickness=4mm, Flip Angle=60°, Bandwidth=2520Hz/pixel with 25 slices) with 186 volumes per run. The first 6 volumes were removed to allow magnetization to reach the steady-state. The number of functional runs was dependent on participant cooperation. There were no group differences in the number of functional runs (term=2.32±0.69, preterm=2.25±0.45, p=0.72).

Connectivity preprocessing

Data analyses were performed as previously described (Kwon et al. 2014a). Briefly, images were slice-time-corrected and motion-corrected using SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5/>). All further analysis was performed using BioImage Suite (Joshi et al. 2011). Several covariates of no interest were regressed from the data including linear and quadratic drift, six rigid-body motion parameters, mean cerebral-spinal-fluid (CSF) signal, and mean white-matter signal. The global gray matter signal was not regressed. The data were temporally smoothed with a zero mean unit variance Gaussian filter (approximate cutoff frequency=0.12Hz). A gray-matter mask was applied to the data so only voxels in the gray matter were used in the calculation. Blocks of data with a displacement greater than 1.5 mm or a rotation greater than 2 degrees were removed. All participants had at least 4 minutes of resting state data and there were no group differences in the amount of data used (p=0.73), or the amount of data removed (p=0.97).

Motion analysis

As motion has been shown to confound connectivity studies (Van Dijk et al. 2012), the frame-to-frame displacement averaged across all functional volumes was calculated for each participant. When preterm neonates were compared to term controls, there were no significant differences in frame-to-frame motion (p=0.73).

Neonatal functional parcellation

A major consideration in applying network theory to functional data is how to delineate brain regions for further analysis. We used a novel group-wise parcellation method to divide each hemisphere of the brain into nodes containing optimal within node similarity (Shen et al. 2013). The optimal number of nodes was determined as the maximum number of nodes that produced an overall reproducibility of at least 75% (Finn et al. 2013; Shen et al. 2013). Reproducibility was obtained by computing the parcellation for mutually exclusive groups of neonates and calculating the Dice's coefficient between the resultant parcellations. We performed the division 20 times with a random permutation of participants. This resulted in a 50 node parcellation of the left hemisphere and a 45 node parcellation of the right hemisphere. Only term neonates were used to construct the functional parcellation similar to other published reports comparing PT and term neonates (Smyser et al. 2014). Although parcellations were defined using data from term participants, we calculated ROI inhomogeneity for each ROI and participants to examine if parcellation preferential fit the term neonates. Inhomogeneity was defined as the Euclidean distance between the timecourse of an individual voxel and the mean timecourse of the node to which it belongs; the whole-

brain homogeneity index for an individual subject is calculated by summing Euclidian distances for all voxels. There was no difference in whole-brain inhomogeneity scores between the PT and term groups ($p=0.30$), suggesting that the choice of atlas was not biased towards the term neonates. The whole-brain functional parcellation is shown in Figure 1.

Common space registration

To define our neonatal functional parcellation, a term neonate scan from a participant that was not part of this study was used as a template. Rs-fMRI data from the term neonates were warped to this template through the concatenation of a series of linear and non-linear registrations. The functional series were linearly registered to the T1 axial-oblique image. The T1 axial-oblique image was linearly registered to the MPRAGE image. The MPRAGE image was non-linearly registered to the template brain. All transformation pairs were calculated independently and combined into a single transform, warping the single participant results into common space. This single transformation allows the single participant images to be transformed to common space with only one transformation, reducing interpolation error. Once the parcellation was defined in the template space, it was transformed back into each participant's individual space through the inverse of the single combined transformation. All transformations were estimated using the intensity-only component of the method implemented by BioImage Suite (Joshi et al. 2011).

Network construction

The mean time-course for each of the 95 nodes was calculated and these mean time courses were correlated with each other forming a 95×95 weighted connectivity matrix. The correlations were normalized to Z scores with the Fisher transformation. To create weighted networks, the edge weights between nodes were assumed to be the correlation coefficients between brain regions with negative correlations and self-loops removed as in previous reports of neonatal connectomics (van den Heuvel et al. 2014). While negative correlations may be an important feature rs-fMRI, no consensus of how best to model these correlations exist. Additionally, removing negative correlations acts as an implicit threshold, ensuring that all nodes do not have the same degree needed for RC calculations.

To create binary networks, the correlation matrices were thresholded using one of two thresholding methods with any edge greater than the threshold set to 1 and any edge less than the threshold set to 0. We used both absolute thresholding with correlation thresholds of 0.05 and 0.15 and proportional thresholding with density thresholds of 50% and 75%. Using multiple definitions of the network model helps to ensure group differences are not dependent on arbitrary factors such as thresholds (Scheinost et al. 2012).

Functional rich club organization

Similar to recent reports (van den Heuvel and Sporns 2011), we quantified RC organization using weighted and binary networks (Opsahl et al. 2008; Colizza et al. 2006). To quantify RC organization for weighted networks, all connections are ranked by their weight creating a vector of weights (V) and all nodes with degree k are removed in an iterative procedure over a range of k values. For the resulting sub-network at each k value, the sum of all connection weights (W), the number of connections (E), the sum of the E strongest weights

in $V(S)$ are computed. The RC coefficient ($\phi(k)$) for any k value is the ratio of W and S and the formal equation is: $\phi(k) = \frac{w}{s}$, where $s = \sum_{i=1}^E V_i$. To quantify RC organization for binary networks, all nodes with degree k are removed in an iterative procedure over a range of k values. The RC coefficient ($\phi(k)$) for any k value is the ratio of connections (E) present between the remaining nodes and the total number of possible connections for a fully connected network with the same number of nodes (N). The formal equation is:

$$\phi(k) = \frac{2E}{N(N-1)}.$$

Since PT neonates engage alternate pathways for language and executive function (Wilke et al. 2014; Salvan et al. 2013; Scheinost et al. 2014), RC coefficients were calculated for each participant separately over a range of k values (35 $\leq k \leq 85$) resulting in a RC curve for each participant. This method is in contrast to other reports where RC coefficients were calculated on group averaged networks (Grayson et al. 2014).

As random network may exhibit increasing RC organization because high degree node have a greater likelihood of being interconnected by chance alone, each participant's RC curve was normalized by a set of random networks. These random networks were created by randomizing the individual connections within each network. For each participant, 1000 random networks were created, and for each random network, RC curves were computed. These random RC curves were then averaged, resulting in a single random RC curve (ϕ_{random}) per participant. Normalized RC curves ($\phi_{normalized}$) were computed as a participant's ϕ divided by a participant's ϕ_{random} , or $\phi_{normalized} = \phi / \phi_{random}$. All RC curves and random networks were generated using the Brain Connectivity Toolbox (<https://sites.google.com/site/bctnet/>).

Definition of RC nodes

To examine the spatial location of RC nodes, individual RC were defined as the 10 nodes with the highest degree. Defining RC nodes as the highest degree nodes, rather than by k level, controls for possible individual differences in degree distribution.

Rich club, feeder, and local connections

RC connections (connections between RC nodes), feeder connections (connections between RC nodes and non-RC nodes), and local connections (connections between two non-RC nodes) were classified based on individually defined rich club nodes. For RC, feeder, and local connection, strength was computed and normalized by the overall network strength (see below for description of strength).

Network organization metrics

In addition to rich club organization, several other network organization metrics were computed to examine overall network topology in PT and term neonates. These metrics included strength (S), the clustering coefficient (C), the characteristic path length (L), the modularity (Q), and the assortativity (R). Strength, clustering coefficient, and characteristic path length were averaged over all the node-specific values to provide measures of overall

network organization. Finally, clustering coefficient and characteristic path length were compared with the clustering coefficient (C_{random}) and characteristic path length (L_{random}) of a set of 1000 random networks, similar to the normalization applied to the RC curves. Additional details about these measures can be found elsewhere (Rubinov and Sporns 2010).

Statistics

RC coefficients were compared using two-tailed permutation testing and corrected for multiple comparisons using false discovery rate (FDR, $q < 0.05$). Categorical data were analyzed either using standard chi-squared statistics or using Fisher's exact test. Continuous valued data were analyzed either using t-tests or using Mann-Whitney u-tests when a normal distribution could not be assumed to compare groups. Finally, Pearson's correlations were performed to assess the relationship between RC and PMA. Analyses were performed using Matlab 2011b. For data other than RC coefficients, p-values < 0.05 were considered significant.

Results

Rich club organization

RC organization, defined as $\phi_{normalized} > 1$, was found for both PT and term neonates using weighted networks. Preterms showed RC organization for k level between 55 and 85 ($p < 0.01$ 10,000 permutations) and terms showed RC organization for k level between 45 and 85 ($p < 0.01$ 10,000 permutations). The normalized rich club curves of both the PT and term networks are shown in Figure 2. PT neonates displayed significantly reduced RC organization (49 $\leq$ k $\leq$ 67 and 70 $\leq$ k $\leq$ 75, $q < 0.05$, FDR corrected, 10,000 permutation). Similarly, RC organization defined using binary networks reveal RC organization for both groups and lower organization for PT neonates compared to terms over a similar range of k levels (Figure 3).

RC nodes were defined for individual networks as the ten nodes with the highest degree. Figures 4, 5, and 6 show the percent of subjects sharing each node in their individual RC for the weighted and binary networks, respectively. The most consistent nodes were similar for the weighted and binary networks and were located in the posterior cingulate cortex (PCC), inferior parietal/temporal lobes, and visual cortex. For the binary networks, nodes in the prefrontal lobe were also observed.

Using individually defined RC nodes and the weight network definitions, RC, feeder, and local connection strength were computed and normalized by the overall network strength S . Compared to preterms, term neonates displayed significantly greater RC connection strength (term = 0.25 ± 0.05 , PT = 0.22 ± 0.05 , $p = 0.03$, one-tail, 10,000 permutation), but not feeder (term = 0.99 ± 0.09 , PT = 1.02 ± 0.08 , $p = 0.41$, one-tail, 10,000 permutation) or local connection strength (term = 0.82 ± 0.03 , PT = 0.82 ± 0.05 , $p = 0.22$, one-tail, 10,000 permutation).

No significant correlations between gestational age and RC organization or connection strength were observed for the PT neonates. Similarly, no significant correlations between gestational age and RC organization or connection strength were observed for the PT neonates.

Network Topology

Average strength S was not different between PT and term neonates ($p=0.30$, 10,000 permutations). Using both weighted and binary networks, preterms showed evidence of reduced normalized clustering coefficient (C/C_{random}). However, these differences were dependent on the exact network definition. Normalized characteristic path length (L/L_{random}) was not significantly different between study groups for the weighted or binary networks. Similarly, modularity (Q) showed evidence of being reduced in PT neonates with significance varying by network definition. Independent of network definition, assortativity (R) was significantly lower in PT compared to term neonates, consistent with the observed RC results. The results for C/C_{random} , L/L_{random} , Q , and are summarized for the weighted networks in Table 2, and binary networks in Tables 3 and 4.

Discussion

Using measures of whole-brain functional organization, these data demonstrate that PT birth fundamentally alters network topology in the developing brain. Comparing PT at term equivalent age and term neonates, PT neonates showed a similar core set of RC nodes as term neonates yet exhibited reduced RC organization. This reduced RC organization appears to be driven by a significant reduction in strength between RC connections for PT neonates as strength, averaged over the whole network, was preserved. Similarly, PT neonates showed evidence of reduced clustering coefficient, assortativity, and modularity compared to term controls, but not characteristic path length. In general, these differences were consistent over several different network definitions suggesting that the results are not solely a function of arbitrary network definitions. The observed alterations in network topology foreshadow altered neural networks in older PT participants and may reflect a delay in maturation or the engagement of auxiliary systems in the prematurely born.

Increasingly, the organization of the brain is being recognized as a complex network that is both highly segregated (forming tight clusters or communities of similar nodes) and highly integrated (short commute time between these clusters) (Bullmore and Sporns 2009). To facilitate this organization, a small number of highly connected brain regions or “hubs” serve as high bandwidth bridges connecting different clusters (Achard et al. 2006; Crossley et al. 2014). Our results suggest a reduction in connectivity between these hubs for PT neonates. Both RC organization and assortativity are measures of the preference of hubs to connect to other hubs and are reduced in PT neonates. Additionally, PT neonates showed reduced correlation between RC nodes. A possible consequence of this reduction of connectivity between hubs in PT neonates is the observed decrease in functional segregation (measured by clustering coefficient and modularity). If communication between hubs is reduced, a network cannot form small clusters of nodes while maintaining high levels of integration (ie similar characteristic path length for the study groups). However, as random networks also maintain high levels of integration (Sporns 2013), the observed preservation of functional integration may not be as biologically relevant as the observed reduction in segregation and between hub communication in PT neonates.

PT birth results in early changes in cerebral functional and structural organization. PT neonates have weaker inter-hemispheric functional connections (Smyser et al. 2010), decreased functional lateralization (Kwon et al. 2014b), and reduced complexity of inter-network connections (Smyser et al. 2014). Similarly, alterations in structural networks (Brown et al. 2014; Pandit et al. 2014), particularly in structural RC organization (Ball et al. 2014; van den Heuvel et al. 2014), are observed in PT neonates. The development of functional and structure networks appear to be highly correlated in PT neonates (van den Heuvel et al. 2014) and evidence suggests that PT neonates with the greatest white matter injury have the weakest functional connections (Smyser et al. 2013). However, the association between alterations of functional and structural networks for PT neonates in comparison to term controls remains to be explored.

Prior imaging studies suggest that frontal, parietal, and insular regions are key RC nodes (Ball et al. 2014; van den Heuvel et al. 2014; van den Heuvel and Sporns 2011; Grayson et al. 2014). The presented RC nodes show clear overlap with these previous reports in the medial parietal/PCC, and lateral parietal lobes. Parietal lobe connections to the frontal lobes are involved in efficient communication (Cole et al. 2013) and are established by the third trimester (Kostovi and Jovanov-Milosevi 2006). However, instead of insular and frontal nodes, occipital nodes were observed. Likely, reported differences in the developmental trajectories of structural and functional RCs may explain these differences in observed RC nodes. Structural RCs appear to be similar between neonates, children, and adults (Grayson et al. 2014; Kim et al. 2014; van den Heuvel et al. 2014; van den Heuvel and Sporns 2011; Ball et al. 2014) whereas, functional RCs evolve across development (Grayson et al. 2014). In particular, the insula appears to become “richer” across development. Finally, gray matter in the frontal and occipital regions grows the fastest during the neonatal period (Gilmore et al. 2007; Nishida et al. 2006; Spann et al. 2014), which could influence the development of functional RC nodes.

Model systems for PT birth demonstrate both a lag in neuronal maturation (Komitova et al. 2013) and perturbations of dendritic arborization (Back and Miller 2014), suggesting alterations in connectivity in the developing brain. Although recent work has begun to explore neuronal populations of RC organization (Towlson et al. 2013), the cellular and molecular mechanisms contributing to RC organization in PT neonates remain largely unexplored. However, our data are consistent with a delay in maturation in the prematurely born.

The strengths of this study include innovative imaging strategies based on individual participant's networks rather than group average data, imaging of non-sedated neonates, and the inclusion of term controls at the same postmenstrual age as the PT neonates. The weaknesses include the small sample size which limits the analysis of neonatal risk factors and the lack of longitudinal imaging data to compare the course of RC development in PT neonates to that in typically-developing fetuses. In addition, cognitive and language testing measures are not yet available for our study participants. Finally, network measures and their interpretation in relation to brain function is an emerging science with heterogeneous methodology. As such, caution is required when interpreting these results in the context of development.

We show that PT neonates exhibit significantly reduced correlation between RC nodes. Atypical RC organization is a hallmark of disorders of neural connectivity (van den Heuvel et al. 2013; Crossley et al. 2014; Ray et al. 2014). If the goal of newborn intensive care is to promote improved developmental trajectories for the prematurely born (Bauer and Msall 2010), future studies must both identify those critical periods and regions of altered development and interrogate the epigenetic influences contributing to them.

Acknowledgements

Supported by NIH NS074022, T32 HD07094, T32 DA022975

References

- Achard S, Salvador R, Whitcher B, Suckling J, Bullmore E. A Resilient, Low-Frequency, Small-World Human Brain Functional Network with Highly Connected Association Cortical Hubs. *The Journal of Neuroscience*. 2006; 26(1):63–72. [PubMed: 16399673]
- Back SA, Miller SP. Brain injury in premature neonates: A primary cerebral dysmaturation disorder? *Ann Neurol*. 2014; 75(4):469–486. [PubMed: 24615937]
- Ball G, Aljabar P, Zebari S, Tusor N, Arichi T, Merchant N, Robinson EC, Ogundipe E, Rueckert D, Edwards AD, Counsell SJ. Rich-club organization of the newborn human brain. *Proc Natl Acad Sci U S A*. 2014; 111(20):7456–7461. [PubMed: 24799693]
- Bauer SC, Msall ME. Optimizing neurodevelopmental outcomes after prematurity: lessons in neuroprotection and early intervention. *Minerva Pediatr*. 2010; 62(5):485–497. doi:R15103597 [pii]. [PubMed: 20940682]
- Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, Rubens C, Menon R, Van Look PF. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bull World Health Organ*. 2010; 88(1):31–38. [PubMed: 20428351]
- Brown CJ, Miller SP, Booth BG, Andrews S, Chau V, Poskitt KJ, Hamarneh G. Structural network analysis of brain development in young preterm neonates. *Neuroimage*. 2014; 101:667–680. [PubMed: 25076107]
- Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci*. 2009; 10(3):186–198. [PubMed: 19190637]
- Cole MW, Reynolds JR, Power JD, Repovs G, Anticevic A, Braver TS. Multi-task connectivity reveals flexible hubs for adaptive task control. *Nat Neurosci*. 2013; 16(9):1348–1355. [PubMed: 23892552]
- Colizza V, Flammini A, Serrano MA, Vespignani A. Detecting rich-club ordering in complex networks. *Nat Phys*. 2006; 2(2):110–115.
- Constable RT, Vohr BR, Scheinost D, Benjamin JR, Fulbright RK, Lacadie C, Schneider KC, Katz KH, Zhang H, Papademetris X, Ment LR. A left cerebellar pathway mediates language in prematurely-born young adults. *Neuroimage*. 2012; 64C:371–378. doi:S1053-8119(12)00917-2 [pii] 10.1016/j.neuroimage.2012.09.008. [PubMed: 22982585]
- Crossley NA, Mechelli A, Scott J, Carletti F, Fox PT, McGuire P, Bullmore ET. The hubs of the human connectome are generally implicated in the anatomy of brain disorders. *Brain : a journal of neurology*. 2014; 137(Pt 8):2382–2395. [PubMed: 25057133]
- Doria V, Beckmann CF, Arichi T, Merchant N, Groppo M, Turkheimer FE, Counsell SJ, Murgasova M, Aljabar P, Nunes RG, Larkman DJ, Rees G, Edwards AD. Emergence of resting state networks in the preterm human brain. *Proceedings of the National Academy of Sciences of the United States of America*. 2010; 107(46):20015–20020. [PubMed: 21041625]
- Finn ES, Shen X, Holahan JM, Scheinost D, Lacadie C, Papademetris X, Shaywitz SE, Shaywitz BA, Constable RT. Disruption of Functional Networks in Dyslexia: A Whole-Brain, Data-Driven Analysis of Connectivity. *Biol Psychiatry*. 2013
- Foster-Cohen SH, Friesen MD, Champion PR, Woodward LJ. High prevalence/low severity language delay in preschool children born very preterm. *J Dev Behav Pediatr*. 2010; 31(8):658–667. [PubMed: 20613625]

- Gilmore JH, Lin W, Prastawa MW, Looney CB, Vetsa YS, Knickmeyer RC, Evans DD, Smith JK, Hamer RM, Lieberman JA, Gerig G. Regional gray matter growth, sexual dimorphism, and cerebral asymmetry in the neonatal brain. *J Neurosci*. 2007; 27(6):1255–1260. [PubMed: 17287499]
- Grayson DS, Ray S, Carpenter S, Iyer S, Dias TG, Stevens C, Nigg JT, Fair DA. Structural and functional rich club organization of the brain in children and adults. *PLoS One*. 2014; 9(2):e88297. [PubMed: 24505468]
- Joshi A, Scheinost D, Okuda H, Belhachemi D, Murphy I, Staib LH, Papademetris X. Unified framework for development, deployment and robust testing of neuroimaging algorithms. *Neuroinformatics*. 2011; 9(1):69–84. [PubMed: 21249532]
- Kim DJ, Davis EP, Sandman CA, Sporns O, O'Donnell BF, Buss C, Hetrick WP. Longer gestation is associated with more efficient brain networks in preadolescent children. *NeuroImage*. 2014; 100C: 619–627. [PubMed: 24983711]
- Komitova M, Xenos D, Salmaso N, Tran KM, Brand T, Schwartz ML, Ment L, Vaccarino FM. Hypoxia-induced developmental delays of inhibitory interneurons are reversed by environmental enrichment in the postnatal mouse forebrain. *J Neurosci*. 2013; 33(33):13375–13387. [PubMed: 23946395]
- Kostovi I, Jovanov-Milosevi N. The development of cerebral connections during the first 20–45 weeks' gestation. *Semin Fetal Neonatal Med*. 2006; 11(6):415–422. [PubMed: 16962836]
- Kwon SH, Scheinost D, Lacadie C, Benjamin J, Myers EH, Qiu M, Schneider KC, Rothman DL, Constable RT, Ment LR. GABA, Resting-State Connectivity and the Developing Brain. *Neonatology*. 2014a; 106(2):149–155. [PubMed: 24970028]
- Kwon SH, Scheinost D, Lacadie C, Sze G, Schneider KC, Dai F, Constable RT, Ment LR. Adaptive mechanisms of developing brain: Cerebral lateralization in the prematurely-born. *Neuroimage*. 2014b; 108C:144–150. [PubMed: 25528658]
- Nishida M, Makris N, Kennedy DN, Vangel M, Fischl B, Krishnamoorthy KS, Caviness VS, Grant PE. Detailed semiautomated MRI based morphometry of the neonatal brain: preliminary results. *Neuroimage*. 2006; 32(3):1041–1049. [PubMed: 16857388]
- Opsahl T, Colizza V, Panzarasa P, Ramasco JJ. Prominence and control: the weighted rich-club effect. *Phys Rev Lett*. 2008; 101(16):168702. [PubMed: 18999722]
- Pandit AS, Robinson E, Aljabar P, Ball G, Gousias IS, Wang Z, Hajnal JV, Rueckert D, Counsell SJ, Montana G, Edwards AD. Whole-brain mapping of structural connectivity in infants reveals altered connection strength associated with growth and preterm birth. *Cereb Cortex*. 2014; 24(9): 2324–2333. [PubMed: 23547135]
- Pritchard VE, Bora S, Austin NC, Levin KJ, Woodward LJ. Identifying very preterm children at educational risk using a school readiness framework. *Pediatrics*. 2014; 134(3):e825–e832. [PubMed: 25113296]
- Ray S, Miller M, Karalunas S, Robertson C, Grayson DS, Cary RP, Hawkey E, Painter JG, Kriz D, Fombonne E, Nigg JT, Fair DA. Structural and functional connectivity of the human brain in autism spectrum disorders and attention-deficit/hyperactivity disorder: A rich club-organization study. *Human brain mapping*. 2014
- Rubinov M, Sporns O. Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage*. 2010; 52(3):1059–1069. [PubMed: 19819337]
- Salvan P, Walsh SF, Allin MP, Walshe M, Murray RM, Bhattacharyya S, McGuire P, Williams SC, Nosarti C. Road work on memory lane-Functional and structural alterations to the learning and memory circuit in adults born very preterm. *NeuroImage*. 2013
- Saunders DE, Thompson C, Gunny R, Jones R, Cox T, Chong WK. Magnetic resonance imaging protocols for paediatric neuroradiology. *Pediatr Radiol*. 2007; 37(8):789–797. [PubMed: 17487479]
- Scheinost D, Benjamin J, Lacadie CM, Vohr B, Schneider KC, Ment LR, Papademetris X, Constable RT. The Intrinsic Connectivity Distribution: A Novel Contrast Measure Reflecting Voxel Level Functional Connectivity. *NeuroImage*. 2012
- Scheinost D, Lacadie C, Vohr BR, Schneider KC, Papademetris X, Constable RT, Ment LR. Cerebral Lateralization is Protective in the Very Prematurely Born. *Cereb Cortex*. 2014

- Shen X, Tokoglu F, Papademetris X, Constable RT. Groupwise whole-brain parcellation from resting-state fMRI data for network node identification. *Neuroimage*. 2013; 82:403–415. [PubMed: 23747961]
- Smyser CD, Inder TE, Shimony JS, Hill JE, Degnan AJ, Snyder AZ, Neil JJ. Longitudinal Analysis of Neural Network Development in Preterm Infants. *Cereb Cortex*. 2010 doi:bhq035 [pii] 10.1093/cercor/bhq035.
- 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. [PubMed: 23874510]
- Smyser CD, Snyder AZ, Shimony JS, Mitra A, Inder TE, Neil JJ. Resting-State Network Complexity and Magnitude Are Reduced in Prematurely Born Infants. *Cereb Cortex*. 2014
- Spann MN, Bansal R, Rosen TS, Peterson BS. Morphological features of the neonatal brain support development of subsequent cognitive, language, and motor abilities. *Hum Brain Mapp*. 2014; 35(9):4459–4474. [PubMed: 24615961]
- Sporns O. Network attributes for segregation and integration in the human brain. *Curr Opin Neurobiol*. 2013; 23(2):162–171. [PubMed: 23294553]
- Towlson EK, Vértes PE, Ahnert SE, Schafer WR, Bullmore ET. The rich club of the *C. elegans* neuronal connectome. *J Neurosci*. 2013; 33(15):6380–6387. [PubMed: 23575836]
- van den Heuvel MP, Kersbergen KJ, de Reus MA, Keunen K, Kahn RS, Groenendaal F, de Vries LS, Benders MJ. The Neonatal Connectome During Preterm Brain Development. *Cereb Cortex*. 2014
- van den Heuvel MP, Sporns O. Rich-club organization of the human connectome. *J Neurosci*. 2011; 31(44):15775–15786. [PubMed: 22049421]
- van den Heuvel MP, Sporns O, Collin G, Scheewe T, Mandl RC, Cahn W, Goni J, Hulshoff Pol HE, Kahn RS. Abnormal rich club organization and functional brain dynamics in schizophrenia. *JAMA psychiatry*. 2013; 70(8):783–792. [PubMed: 23739835]
- Van Dijk KR, Sabuncu MR, Buckner RL. The influence of head motion on intrinsic functional connectivity MRI. *Neuroimage*. 2012; 59(1):431–438. doi:S1053-8119(11)00821-4 [pii] 10.1016/j.neuroimage.2011.07.044. [PubMed: 21810475]
- White TP, Symington I, Castellanos NP, Brittain PJ, Froudish Walsh S, Nam KW, Sato JR, Allin MP, Shergill SS, Murray RM, Williams SC, Nosarti C. Dysconnectivity of neurocognitive networks at rest in very-preterm born adults. *Neuroimage Clin*. 2014; 4:352–365. [PubMed: 24567907]
- Wilke M, Hauser TK, Krageloh-Mann I, Lidzba K. Specific impairment of functional connectivity between language regions in former early preterms. *Human brain mapping*. 2014; 35(7):3372–3384. [PubMed: 24243552]

Figure 1.

Surface rendering and 2D slices of neonatal functional parcellation. We used a novel groupwise parcellation method to divide each hemisphere of the brain into nodes containing optimal within node similarity. In total, 95 nodes were used to compute functional networks and RC coefficients.

Figure 2.

Rich club (RC) organization of weighted networks for preterm and term subjects. RC coefficients (Φ) are plotted against degree (k). Preterm subjects display reduced RC organization over a range of k -levels. Asterisks indicate significance at $q < 0.05$, FDR corrected. The shade area represents standard error.

Figure 3.

Rich club curves for binary networks using absolute thresholding of A) $T=0.05$ and B) $T=0.15$ and using proportional thresholding of C) $T=50\%$ and D) $T=75\%$. RC coefficients (Φ) are plotted against degree (k). Preterm subjects display reduced RC organization over a range of k levels. Asterisks indicate significance at $q < 0.05$, FDR corrected. The shade area represents standard error.

Figure 4.

Rich club nodes for weighted networks. RC nodes were defined as the top ten highest degree nodes for each participant. Warmer colors indicate a node was included in a large percentage of individual participant's RC. The most consistent nodes were located in the posterior cingulate (PCC) and parietal lobes.

Figure 5.

Rich club nodes for binary networks created using absolute thresholding of A) $T=0.05$ and B) $T=0.15$. RC nodes were defined as the top ten highest degree nodes for each participant. Warmer colors indicate a node was included in a large percentage of individual participant's RC.

Figure 6.

Rich club nodes for binary networks created using proportional thresholding of A) $T=50\%$ and B) $T=75\%$. RC nodes were defined as the top ten highest degree nodes for each participant. Warmer colors indicate a node was included in a large percentage of individual participant's RC.

Table 1

Characteristics of study participants

	Preterm (n=12)	Term (n=25)	p-value
Postmenstrual age at birth (weeks)	27 ± 2.2	40 ± 1	< 0.001
Birth weight (grams)	1015 ± 330	3350 ± 380	< 0.001
Postmenstrual age at scan (weeks)	42.6 ± 1.0	42.3 ± 1.3	0.96
Male gender	3 (25%)	15 (60%)	0.08
Non-white	6 (50%)	7 (28%)	0.27
Bronchopulmonary dysplasia	3 (25%)		
Retinopathy of prematurity	4 (33%)		
Necrotizing enterocolitis	0 (0%)		
Late-onset sepsis	2 (17%)		

values are mean ± SD

Table 2

Comparison of network theory measures from weighted networks.

	Preterm	Term	P-value
Normalized Clustering Coefficient (C/C_{random})	1.15±0.09	1.23±0.09	0.02
Normalized Characteristic Path Length (L/L_{random})	1.29±0.06	1.34±0.09	0.11
Assortivity (R)	0.06±0.05	0.13±0.10	0.03
Strength (S)	18.1±4.09	17.0±2.21	0.30
Modularity (Q)	0.22±0.06	0.25±0.05	0.09

P values calculated using 2 tail permutation testing with 10,000 permutations.

Table 3

Comparison of network theory measures from binary networks using an absolute threshold.

	Preterm	Term	P-value
Threshold T=0.05			
Normalized Clustering Coefficient (C/C_random)	1.09±0.08	1.15±0.07	0.03
Normalized Characteristic Path Length (L/L_random)	1.00±0.00	1.00±0.00	0.94
Assortivity (R)	0.07±0.05	0.17±0.11	<0.01
Modularity (Q)	0.13±0.06	0.17±0.04	0.02
Threshold T=0.15			
Normalized Clustering Coefficient (C/C_random)	1.25±0.17	1.31±0.13	0.24
Normalized Characteristic Path Length (L/L_random)	1.00±0.01	1.01±0.01	0.11
Assortivity (R)	0.13±0.05	0.25±0.13	<0.01
Modularity (Q)	0.19±0.07	0.22±0.05	0.13

P values calculated using 2 tail permutation testing with 10,000 permutations. Standard deviation with value of 0.00 have values below two decimal points and are rounded down for display.

Table 4

Comparison of network theory measures from binary networks using a proportional threshold.

	Preterm	Term	P-value
Threshold T=50%			
Normalized Clustering Coefficient (C/C_random)	1.18±0.06	1.21±0.06	0.14
Normalized Characteristic Path Length (L/L_random)	1.00±0.01	1.00±0.00	0.93
Assortivity (R)	0.12±0.05	0.21±0.12	0.01
Modularity (Q)	0.17±0.04	0.19±0.03	0.08
Threshold T=75%			
Normalized Clustering Coefficient (C/C_random)	1.05±0.17	1.10±0.13	0.02
Normalized Characteristic Path Length (L/L_random)	1.00±0.01	1.00±0.01	0.91
Assortivity (R)	0.04±0.04	0.12±0.10	<0.01
Modularity (Q)	0.10±0.04	0.14±0.04	0.01

P values calculated using 2-tail permutation testing with 10,000 permutations. Standard deviation with value of 0.00 have values below two decimal points and are rounded down for display