Altered Structural and Functional Connectivity in Late Preterm Preadolescents

Jessica L Wisnowski[1,2], Vincent J Schmithorst[2], Rafael C Ceschin[2,3], Patricia Corby[4], Hanna Damasio[1], and Ashok Panigrahy[2]

[1]Brain and Creativity Institute, University of Southern California, Los Angeles, CA, United States, [2]Radiology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, United States, [3]Biomedical Informatics, University of Pittsburgh, Pittsburgh, PA, United States, [4]Dentistry, New York University, New York, NY, United States

Target Audience

Researchers who are interested in brain development, connectomics and those who model brain network topology using DTI and fMRI methods.

Purpose

Long-range corticocortical and thalamocortical connections form the basis for the default mode network (DMN) and other brain networks. These networks undergo critical periods of development during the third trimester of fetal gestation[1]. Preterm birth is a risk factor for injury to the developing white matter and it is not known how such injury affects the long-term development of these networks or network topology. We hypothesized that preadolescent children who were born preterm would have a decrement in long-range inter- and intrahemispheric connectivity, and concomitantly, a decrease in the overall efficiency of their functional connectome.

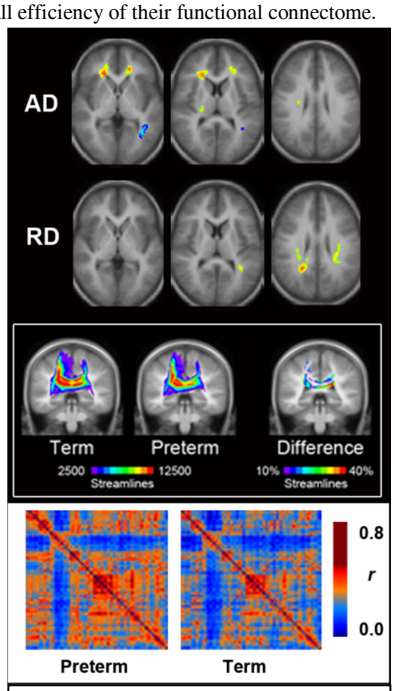
Methods

The participant population consisted of a community sample of pre-adolescent twin pairs (ages 9-13 years) born late preterm (>32 weeks) and at full term recruited from a developing region in northeast Brazil (Montes Claros, pop. ca. 410,000) as part of an ongoing longitudinal international collaborative research program investigating the genetic and environmental influences relating prematurity, long-term neurocognitive functioning and health outcomes.

MRI scanning was performed on a Philips 1.5T Achieva system. DTI scans were acquired with the following parameters: TR = 6000 ms, TE = 90 ms, slice thickness = 2 mm, matrix = 112 X 112, FOV = 22.4 X 22.4 cm, b value = 1000 s/mm^2; 32 diffusion-encoding gradients. Pre-processing included motion and eddy current correction and slice dropout removal according to routines written in FSL. Diffusion tensor components were computed and fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD) maps were spatially normalized into MNI space. Only voxels with FA > 0.25 and white matter probability > 0.9 were retained for further analysis in order to minimize the risk of spurious results obtained from imperfect spatial normalization. For the second-level analysis, a voxelwise mixed-effects model was applied with preterm/term status as the variable of interest and age, sex, and neurocognitive performance (i.e., complex figure task, raw score) as covariates of no interest. The random effects were between-family and between-genotype (e.g. non-monozygotic twin sibling) variance. The fit was performed using restricted maximum-likelihood (ReML) estimation and an expectation-maximization (EM) algorithm using customized code written in IDL (Exelis, Boulder, CO). After the fit converged, the resulting T-scores were converted into Z-scores. Results were spatially filtered (in only the white matter) with $\sigma = 3$ mm. An intensity threshold of $Z > 6.5$ and spatial extent threshold of 150 voxels was used, shown to correspond to a family-wise-error (FWE) $p<0.05$ via Monte Carlo simulation.

Between-group probabilistic tractography analysis was carried out in a similar manner as that used by Rykhlevskaia and colleagues[2]. Seed regions corresponding to the posterior and anterior hubs in the DMN were defined from the AAL template[3] and transformed into native space. Using the FSL bedpost and probtrackx routines, 1000 streamlines per voxel were generated using parameters of: curvature threshold (0.2), maximum steps (1000) and step length (0.5 mm). No way point or termination masks were included. Streamline maps from each subject were then normalized, transformed back into MNI space and analyzed according to a mixed-effects model, as above.

Ic-fMRI was acquired with scan parameters: TR = 3000 ms, TE = 50 ms, FOV = 211.2 X 211.2 mm, imaging matrix = 80 X 80, slice thickness = 4 mm, 30 slices acquired covering the whole brain, SENSE factor = 2, 100 volumes acquired for a total scan time of 5 minutes per run. Two scan runs were acquired: one with the child asked to keep his eyes open, and one with eyes closed. After motion correction, an intensity-based cost function was used to discard frames corrupted by motion, with a threshold determined via visual inspection. Datasets were then transformed into MNI space using SPM8. Cerebral regions were parcellated out for each child using the 90-region AAL template[3]. Time-courses were extracted for each participant for each region and low-pass filtered with a cutoff frequency of 0.1 Hz, corrected for baseline drift, and variance-normalized. The time courses from the two runs from each subject were concatenated into a single time course. For each participant, correlations were calculated between the time courses from each set of two regions, resulting in a 90-X-90 correlation matrix. The correlation matrices were then thresholded and binarized, resulting in an undirected, unweighted graph. For each graph corresponding to each participant, global efficiency (a measure of network integration) and transitivity (a measure of network segregation) were calculated[4]. Each parameter was marginalized over all values of network cost in order to avoid threshold-specific effects.



[Top] Voxelwise DTI analyses revealed areas of increased (red-yellow) and decreased (blue) AD and RD in preterms compared to terms. Similar results were obtained for FA (not pictured). [Middle] Probabilistic tractography demonstrated fewer streamlines connecting the posterior DMN hub regions and the anterior DMN hub and the thalamus on the right (not pictured). [Bottom] ic-fMRI analyses revealed increased connectivity in the preterms, characterized by an increase in shorter-range connections and resulting in a decreased overall in the topology of the preterm preadolescent connectome.

Results

In preadolescents born late preterm, DTI revealed microstructural differences in posterior and anterior deep white matter regions containing a myriad of crossing fiber bundles, including connections from the DMN hub regions to other cortical and subcortical regions. Probabilistic tractography revealed fewer streamlines in the splenium of the callosum connecting the posterior DMN hub regions bilaterally, as well as fewer streamlines between the anterior DMN hub and the thalamus on the right. Ic-fMRI revealed differences in whole-brain functional connectivity, namely, a marked increase in short-range cortico-cortical connectivity and a resultant decrease in the overall cost-efficiency ($p < 0.05$) of the network organization on a global scale. There was also a trend toward decreased efficiency ($p < 0.1$) but no difference in transitivity.

Discussion

This is the first study, to our knowledge, to apply multimodal DTI and fMRI to examine the longitudinal impact of preterm birth on the preadolescent connectome. Prior research has demonstrated that the white matter adjacent to the anterior horn and trigone of the lateral ventricles, regions that contain a numerous crossing fiber bundles including those containing fibers connecting the DMN hub regions to other cortical and subcortical hubs, is exquisitely vulnerable to injury in preterm infants. Here, using voxelwise DTI analyses, we demonstrated that preterm birth was associated with differences in the tissue microstructure of these regions in a sample of preadolescent children. Furthermore, these changes were associated with decreased interhemispheric connectivity of the posterior DMN hub regions, and concomitantly, with decreased cost-efficiency in the network topology of the functional connectome.

Conclusion

Long-range corticocortical connections undergo critical periods of development during the late third trimester. Altering these connections as a result of injury or environmental stress may result in large-scale differences in the developing network topology of the functional connectome into preadolescence.

References: [1] Kostović I, Milošević NJ. The development of cerebral connections during the first 20-45 weeks' gestation. *Semin Fetal Neonat M* 2006;11:415-422. [2] Rykhlevskaia E, Uddin LQ, Kondos L, Menon V. Neuroanatomical correlates of developmental dyscalculia: combined evidence from morphometry and tractography. *Front Hum Neurosci* 2009;3:51 [3] Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage.* Jan 2002;15(1):273-289. [4] Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage.* Sep 2010;52(3):1059-1069.

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