

# Sex Differences in Structural and Functional Network Topology are Present at Birth: A Multi-modal Graph Theory Study

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## Introduction

Male neonates have a higher incidence of white matter injury and poorer neurocognitive outcomes following perinatal stressors (such as preterm birth or congenital heart disease (CHD)) [1, 2] suggesting an underlying biological vulnerability. Moreover, sex differences in neurocognitive outcomes are also present among older preterm survivors, although emotional and limbic related disorders appear to have less of a sex difference when compared to frontal-executive difficulties [3]. While the etiology of these differences is likely related to hormones and cell death pathways [2], it is unknown how they may influence brain development at the macro-level. We investigated possible sex differences in structural and functional network topology in healthy neonates.

## Materials and Methods

34 healthy neonates (19M, 15F; mean post-conceptual age (PCA) = 42.4 weeks) were prospectively recruited and scanned at 3T without sedation using a feed-and-bundle technique. Diffusion tensor imaging (DTI;  $b = 700$  s/mm<sup>2</sup>, 25 directions) and resting-state BOLD fMRI (TR = 2 s, 5 min. total acquisition time) data were acquired.

Data was post-processed using in-house routines written in IDL (Exelis, Boulder, CO) and other software as indicated below. Binary unweighted adjacency matrices were computed as follows. **DTI**: Eigenvectors and eigenvalues of the diffusion tensor were computed using routines in FSL (FMRIB, Oxford, UK). Streamlines were computed (in native space) for each voxel with FA > 0.15 using deterministic fiber tractography using a turning threshold of 45 degrees. Data was normalized to a neonatal template [4] which parcellates the cerebrum into 90 cortical and subcortical regions using routines in SPM5 (Wellcome Dept. of Cognitive Neurology, London, UK). Using the inverse transformation the template was transformed back into native space for each participant. Each element of the adjacency matrix contained a value of 1 if there was at least one streamline connecting two brain regions, or 0 if not. **fMRI**: Datasets were co-registered using a pyramid iterative algorithm and normalized to the neonatal template. For each region in each participant, the average time course was extracted and low-pass filtered with cutoff frequency 0.1 Hz; frames with excessive motion (as determined by a least-squares cost function) were scrubbed from analysis. Correlation matrices were computed for each participant based on the full correlation coefficient between the time courses in each pair of regions; adjacency matrices were computed by thresholding the correlation matrices at various values of cost ranging from 0.05 to 0.45.

Graph metrics were computed using routines in Brain Connectivity Toolbox (Indiana University; Bloomington, IN). Global graph metrics computed include cost (for DTI only), efficiency, assortativity, small-worldness, and modularity. For DTI, a general linear model (GLM) was used with sex the variable of interest and PCA and cost covariates of no interest. For fMRI, the GLM was computed for all values of cost (0.05 – 0.45) and a bootstrapping procedure used to determine statistical significance of the sum of the regression parameter across all values of cost.

## Results

**DTI**: Females displayed significantly greater modularity ( $p < 0.02$ ), indicating greater segregation into sub-networks. There were no significant differences in cost, efficiency, assortativity, or small-worldness. Spring-loaded views (**Figure 1**) reveal overall quite similar network topology with the frontal interhemispheric network however more well-defined in females.

**fMRI**: Females displayed significantly greater modularity ( $p < 0.03$ ), greater efficiency ( $p < 0.02$ ) and greater small-worldness ( $p < 0.005$ ). There were no significant differences in assortativity. Spring-loaded views (**Figure 2**) again reveal similar overall network topology; however the frontal and fronto-temporo-parietal interhemispheric networks are more well-defined in females.

## Discussion

We show sex differences in structural and functional brain network topology in healthy term neonates, indicating that at least some sex differences arise during prenatal development. Interhemispheric frontal and temporo-fronto-parietal **functional** networks together with interhemispheric frontal **structural** networks appear more developed in females compared to males. These findings suggest that, at birth, there are sex-related differences in the vulnerability of frontal and frontal-parietal networks, which may not only explain the higher incidence of white matter injury in male preterm and CHD subjects (more intrinsic vulnerability of immature white matter), but also sex differences in frontal-executive dysfunction later. By contrast, male neonates have a similar degree of brain maturation in subcortical/limbic networks, which may explain some of the similar outcomes in emotional and limbic related behaviors between male and female neonates at risk for perinatal white matter injury.

## Conclusion

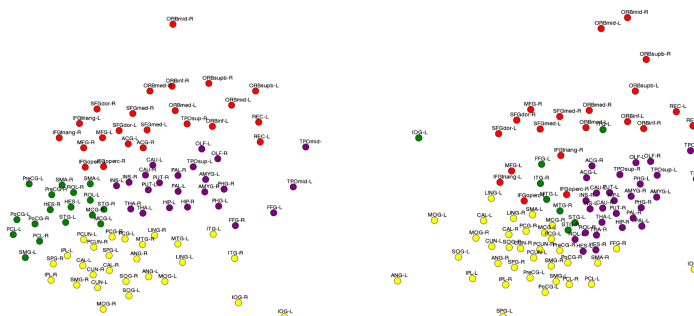
Structural and functional sex differences in brain network topology are present at birth, with female neonates displaying a greater degree of brain maturation at birth. These differences may underlie some sex differences found later in development and may explain some of the differences in vulnerability to injury and subsequent neurocognitive outcomes.

## References

[1] Goff DA et al., J Thorac Cardiovasc Surg, 2013 In Press. [2] Johnston MV, Hagberg H, Dev Med Child Neurol, 49, 74-8, 2007. [3] Hall J et al., Child and Adolescent Mental Health, 17, 238-45, 2012. [4] Shi F et al., PLoS One, 6, e18746, 2011.



**Figure 1.** Spring-loaded view of **structural** network topology for **female** neonates (**left**) and **male** neonates (**right**) as found from DTI deterministic tractography (strength determined by averaged adjacency matrices). Subnetworks found from modularity analysis are: frontal interhemispheric (**red**), posterior interhemispheric (**yellow**), right hemispheric (**green**), left hemispheric (**purple**). Note similarity in overall topology; the frontal interhemispheric subnetwork network is more separated in females, leading to overall greater modularity.



**Figure 2.** Spring-loaded view of **functional** network topology for **female** neonates (**left**) and **male** neonates (**right**) as found from resting-state fMRI (strength determined by averaged adjacency matrices for cost = 0.2). Subnetworks found from modularity analysis are: frontal interhemispheric (**red**), posterior interhemispheric (**yellow**), fronto-temporo-parietal interhemispheric (**green**), subcortical (**purple**). The frontal and fronto-temporo-parietal interhemispheric subnetworks are more separated in females, leading to overall greater modularity, efficiency, and small-worldness.