

# Structural Covariance Brain Networks in Preterm and Term Neonates

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**INTRODUCTION** The structural covariance can reflect synchronized development between brain regions<sup>1</sup>. Previously, structural covariance networks (SCNs) have been used to study the connectivity patterns in adult brains<sup>1</sup>. However, the connectivity pattern in neonatal especially preterm neonatal brains remains largely unknown. In this study, SCNs of preterm and term neonatal brains were constructed based on regional volume correlation. By examining the global topological properties, inter-hemispheric connections, and nodal centrality shift, we aim to investigate the distinct features of preterm and term neonates, which may provide new insights into the characteristics of neonatal brains and early brain development.

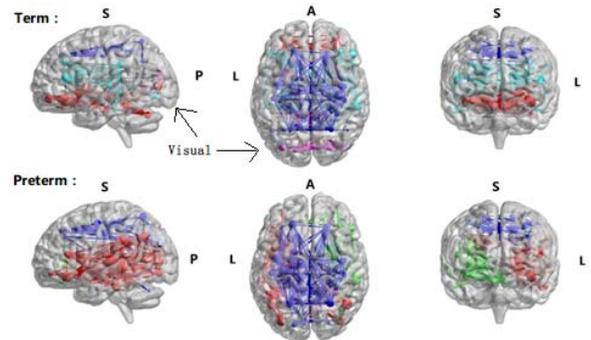
**METHODS** 11 preterm neonates (gestational age =  $34.08 \pm 0.83$  weeks) and 11 term neonates (gestational age =  $41.34 \pm 0.84$  weeks) were included in this study with parents written consent. The neonates were sedated before scanning. 3D-T1 FSPGR were acquired on a 3T scanner (GE, Signa HDxt) with 8-channel head coil and parameters were TR=10.28ms, TE=4.616 ms, TI=400 ms, 110-140 slices, voxel size=0.94\*0.94\*1 mm. The images were normalized to John Hopkins University neonatal brain atlas using FSL. From the resulting affine matrices and Jacobian determinants<sup>2</sup>, we estimated the volumes of 64 cortical and subcortical grey matter regions<sup>3</sup>. For each group, the regional volumes were corrected by multiple linear regression to remove the effect of age, gender, and total brain volume. The connection between every two regions was measured by the inter-subject Pearson correlation coefficient of their corrected volumes within each group. A minimum threshold 0.55 was applied to obtain fully connected binary networks. We computed average degree, small-worldness, global efficiency, and local efficiency and identified modules defined by graph theory using NetworkX. Similar analysis was performed again on inter-hemispheric sub-networks. Finally, we computed the nodal betweenness centrality (BC) variance from preterm to term neonates group, as a measure of regional centrality shift in network. Permutation tests were performed to evaluate the difference between two groups.

**RESULTS** The average degree, global efficiency, and average local efficiency in preterm neonatal brains were all lower than those in term neonatal brains (Tab. 1). The two networks had similar degree distributions (Fig. 3) in low degree (<10) but preterm neonatal SCN contained fewer high degree nodes (>20). Both SCNs were small-world networks (small-worldness >> 1). Five modules (including sensory-motor and visual sub-networks etc.) were identified in term neonatal SCN and three modules (including sensory-motor and two unilateral sub-networks) in preterm (Fig. 1). In addition, the inter-hemispheric connections (Fig. 2, Tab. 1) in preterm neonatal SCNs were significantly fewer than those in term. From preterm to term SCNs, nodes with largest BC increase were mainly in occipital lobe and a few in frontal lobe (Fig. 4).

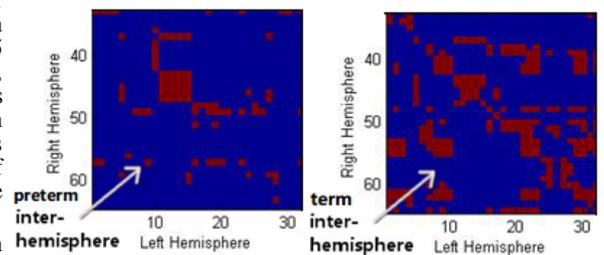
**DISCUSSION AND CONCLUSION** The degree distributions showed that the regions in preterm neonatal brains were less intensively connected than in term neonatal brains. Particularly the lack of high degree nodes (potential hubs) and inter-hemispheric connections in preterm neonatal brains may account largely for its relatively low global efficiency, which indicates the higher cost of regional interaction in preterm neonatal brains. More modules with specific functions were found in term neonatal SCN, and this may be resulted from the on-going functional integration of brain regions. Furthermore, as quantified by the centrality shift, the regions involved in visual processing and emotion more frequently acted as a bridge between other nodes in term neonatal brains than in preterm. Considering these functions can be crucial for cognition and social behaviors, term neonates may hereby have advantages in adapting themselves to the after-birth environment. In conclusion, our finding suggests that the brain connectivity pattern may change dramatically during the several weeks before term. Although the preterm neonatal brains had basic characteristics such as small-world and modules to facilitate information flow, term neonatal brains gained better topological organization with precisely enhanced regional interaction and integration.

## REFERENCES

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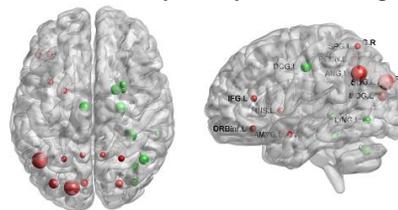
**Fig. 1** 3D models of term and preterm SCNs visualized using BrainNet Viewer. Different colors indicate modules. The sizes of nodes indicate their degree. Motor-sensory modules (blue) were found in both groups, yet visual module (purple) only emerged in term neonatal brain.



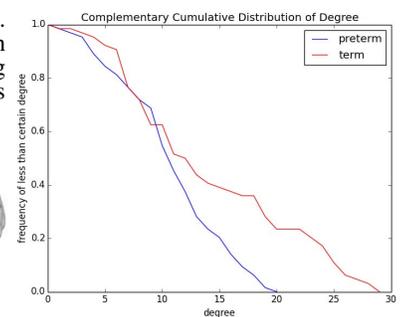
**Fig. 2** Inter-hemispheric parts of connection matrices of preterm (left) and term (right) neonatal SCNs. A red point(x,y) indicates connection between region x and region y. Region 1 to 32 are in the left hemisphere and their contralateral regions are numbered from 33 to 64 in the same order.

| Group   | Deg  | SW   | GE   | LE   | Inter_Deg* | Inter_GE |
|---------|------|------|------|------|------------|----------|
| Preterm | 11.0 | 2.88 | 0.41 | 0.79 | 2.81       | 0.117    |
| Term    | 14.4 | 2.34 | 0.47 | 0.85 | 7.47       | 0.312    |

**Tab. 1** Global parameters. Deg for Degree, SW for small-worldness, GE for global efficiency, LE for local efficiency, Inter for inter-hemispheric. \* p < 0.05.



**Fig. 4** The nodes with large BC variance (absolute value > 0.05) from preterm to term neonatal SCNs. The red means increase and green means decrease.



**Fig. 3** Complementary cumulative distribution of degree of two SCNs. The point(x,y) on the curve indicates that the proportion of nodes with degree larger than x is y.