Regional functional hypoconnectivity in neonates with congenital heart disease
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**Background:** Congenital heart disease (CHD) is associated with a high-prevalence and wide spectrum of neurodevelopmental impairments. Available quantitative MRI studies have provided evidence for structural, metabolic and cerebral perfusion abnormalities in fetuses and newborns with CHD suggesting early-life disturbances in brain development. However, the extent to which brain function may be perturbed during this vulnerable period remains unexplored. To address this gap in our knowledge, we used resting state functional connectivity MRI (rs-fcMRI) and network-based analyses techniques to compare global and regional functional connectivity in neonates with CHD before open heart surgery and a control group of normal full term newborns.

**Methods:** In the context of an ongoing prospective study, we recruited newborns with complex CHD prior to open-heart surgery and healthy newborn controls. All newborns were imaged on a 3T GE scanner. After preprocessing, network measures were computed from weighted, undirected, Fisher’s z-transformed correlation matrices composed from 92 regions of interest (ROIs). To assess global connectivity, we measured small-world propensity (SWP); SWP > 0.6 suggests a small-world network or a balanced trade-off between network specialization and integration. To evaluate regional differences, we used the network-based statistic (NBS) to compare the strength of functional connections between all ROIs.

**Results:** We studied 24 CHD (6/24 with single ventricle physiology) and 24 control newborns at a mean gestational age at MRI of 39.41±1.24 wks (mean birthweight 2945.62±637.1g) and 39.82±0.70 wks (3202.1±474.1g), respectively. Small-world propensity values for CHD (0.86±0.060) and control (0.89±0.073) newborns were comparable suggesting preserved small-world architecture in CHD postnatally. While global properties were similar between the two groups, NBS revealed hypoconnectivity \( r \), control: 0.58±0.26, CHD: 0.29±0.28, \( p_{FWE} < 0.05 \) involving 21/92 ROIs in CHD, affecting predominantly the primary sensorimotor cortices (i.e. pre- and postcentral gyrus) and subcortical regions (i.e. putamen, caudate and globus pallidus).

**Conclusions:** We describe for the first time functional hypoconnectivity in newborns with CHD soon after birth, before undergoing open heart surgery. While global properties were preserved, local connections were weakened in regions that have been previously shown to be central to network function. These preliminary findings suggest early-life brain circuit dysfunction in infants with CHD which may be associated with neurodevelopmental impairment in the years following cardiac surgery. Whether these functional changes predate, coincide, or follow previously reported structural changes is an intriguing avenue of future research. Additional studies are needed to evaluate the prognostic, diagnostic and surveillance potential of these findings.

**References:**