Decrease in functional network segregation in infants with congenital heart defects

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Introduction

Children with complex congenital heart defects (CHD) are at risk for a variety of neurocognitive deficits in domains including executive function, attention, visual-spatial processing, and memory[1, 2]. Neuroimaging studies have identified a variety of brain differences in children and adults with CHD (termed "encephalopathy of CHD") which may underlie these deficits[3]. However, the effects of CHD on early brain development are less well understood. We applied graph analysis to neonatal CHD patients and neonatal healthy controls in order to better understand the impact of CHD on functional network topology in infants.

Materials and Methods

Participants: Complex CHD and healthy term neonates were prospectively recruited from two large CHD surgical centers (Children's Hospital of Pittsburgh and Children's Hospital Los Angeles) over a five year period (2009-2014). The CHD cohort comprised pathologies including single physiology, aortic arch obstruction, fetal mixing, conotruncal, aortic valve outflow obstruction and heterotaxy based upon a pre- or postnatal echocardiogram reviewed by a fetal cardiologist.

Ic-fMRI Scans: Intrinsic connectivity fMRI (ic-fMRI) scans were collected preoperatively from unsedated neonates on a 3 T scanner using a multichannel coil. Scanning parameters were: TR = 2000 ms, 150 volumes collected for a total scanning time of 5 minutes.

Preprocessing: The data analysis approach closely followed that of Power et al.[4] in order to minimize the risk of spurious findings due to participant motion. Slice timing correction using sinc interpolation was followed by motion correction using a 12-parameter transform. The reference frames were spatially normalized to a neonatal template[5] using routines in SPM8 (Wellcome Dept. of Cognitive Neurology, London, UK). A study-specific template was constructed by averaging the normalized reference frames and coregistering to the neonatal template, and the spatial normalization was repeated using the study-specific template. The slice-timing corrected ic-fMRI dataset was normalized into the template frame and motion corrected in a single transformation (using the parameters found from the motion correction routine) and resampled to 3 mm isotropic resolution. Each dataset was normalized to grand mean = 1000. Time courses were extracted for each region for each participant according to the 90-region neonatal parcellation atlas[5]. The framewise displacement (FD) and DVARS (intensity-related) parameters were computed as measures of participant motion.

Graphs: Frames with FD > 0.2 mm or DVARS > 20 were discarded as suffering from excess motion. The entire dataset was discarded if there were not at least 100 usable frames. Usable data was collected from 69 participants (26 CHD, 43 TD; post-conceptional age (PCA) at scan: 41.5 +/- 3.65 weeks, range 37-51 weeks); data from 35 participants was rejected due to excessive motion. Nuisance parameters, including global signal, linear and quadratic drift, and all parameters from the motion correction were regressed out. The time courses were then band-pass filtered with pass band between 0.009 and 0.08 Hz. Weighted graphs were constructed as the absolute value of the correlation coefficient between two time courses (with nuisance parameters regressed out and band-pass filtered).

Graph analysis: Graph metrics were computed using routines in Brain Connectivity Toolbox (Indiana University, Bloomington, IN) and IDL (http://www.ittvis.com, Boulder, CO). Graphs were thresholded at cost values ranging from 0.05 to 0.45 (step 0.05).

Statistical analysis: Graph metrics were analyzed using a General Linear Model with CHD status the variable of interest and sex, PCA at birth, and PCA at scan as covariates of no interest. Due to the multiple values of cost threshold, a bootstrap analysis (resampling with replacement; 10,000 iterations) was performed and statistical tests were run on the sum of the regression parameter over all values of cost. For global metrics results were deemed significant at $p < 0.05$; for nodal metrics, results were deemed significant at False Discovery Rate (FDR) corrected $q < 0.05$ (*IBHLog* procedure)[6-8].

Results

CHD neonates displayed a marked decrease in segregation metrics including transitivity ($p < 0.01$) and modularity ($p < 0.001$) in contrast to greater global efficiency ($p = 0.025$). Strikingly, CHD neonates displayed smaller clustering coefficient in multiple regions mainly in the left hemisphere (Figure 1), and greater participation coefficient in multiple regions in both hemispheres (Figure 2). CHD neonates also displayed greater nodal efficiency in frontal regions in the right hemisphere but also smaller nodal efficiency in posterior regions (Figure 3).

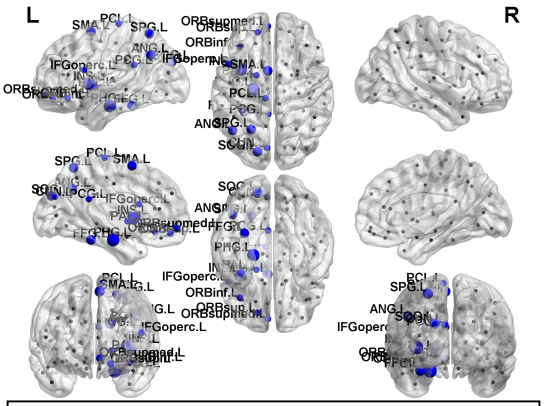

Figure 1. Regions with decreased clustering coefficient (large blue dots) in neonates with CHD compared to normal healthy controls. All regions significant with nominal $p < 0.01$, FDR-corrected $q < 0.05$.

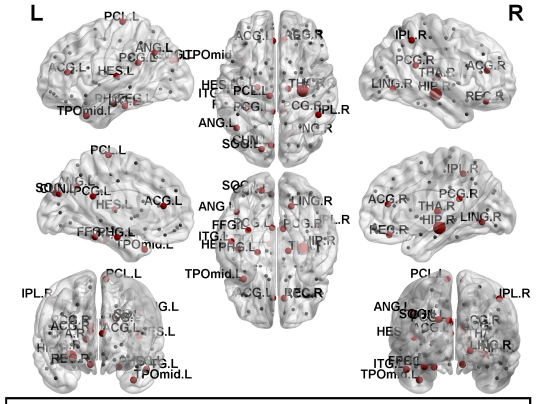

Figure 2. Regions with increased participation coefficient (large red dots) in neonates with CHD compared to normal healthy controls. All regions significant with nominal $p < 0.01$, FDR-corrected $q < 0.05$.

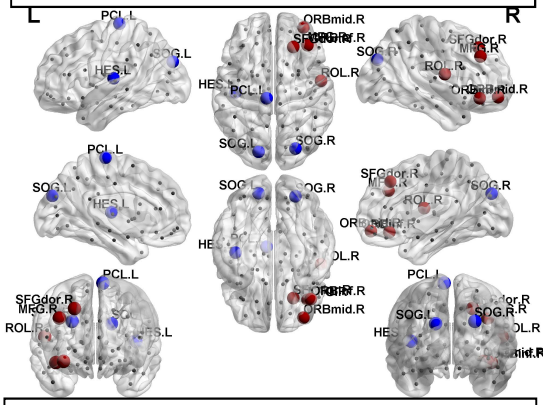

Figure 3. Regions with increased (large red dots) and decreased (large blue dots) nodal efficiency in neonates with CHD compared to normal healthy controls. All regions significant with nominal $p < 0.01$, FDR-corrected $q < 0.05$.

Discussion

These results indicate that the functional network topology in CHD neonates is less segregated, both at a nodal level, driven by decreased clustering coefficient in many regions in the left hemisphere; and also at a more regional level, indicated by greater participation coefficient in many regions in both hemispheres. This is likely the result of a less mature brain in CHD neonates resulting in a lower degree of short-range functional connectivity. The functional topology is also somewhat more integrated, driven by greater nodal efficiency in right hemisphere frontal regions; however, this effect is counteracted by less nodal efficiency in left hemisphere regions. Further research will investigate possible differential effects of subtypes of CHD on network topology and correlation with neurodevelopmental outcomes.

Conclusion

CHD is shown to affect the development of functional network topology *in utero*, as neonatal CHD patients exhibit a markedly less segregated topology overall, suggesting global immature brain development.

References

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