Global structural network topology mediates neurocognitive outcome in children with congenital heart defects

Vincent Jerome Schmithorst[1], Ashok Panigrahy[1], Jessica Wisnowski[1], Chris Walsh[2], David Bellinger[2], Jane Newburger[2], and Michael Rivkin[2]
[1]*Radiology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, United States,* [2]*Boston Children's Hospital, Boston, MA, United States*

Introduction

Neurodevelopmental disabilities involving executive function, attention, visual-spatial, and memory deficits are the most common long-term complication of congenital heart defects (CHD) [1, 2]. Prior neuroimaging studies support the hypothesis that neurocognitive deficits in CHD are related to abnormal brain development and brain injury [3]. Yet, the precise connection between brain differences and neurocognitive outcomes remains poorly understood. We applied graph analysis to diffusion tensor imaging data acquired from 49 adolescents born with transposition of the great arteries (d-TGA), prospectively enrolled in the Boston Circulatory Arrest Study (BCAS) and corrected surgically in early infancy, and 29 typically developing (TD) controls. We used statistical mediation models to more precisely delineate the relation between d-TGA status, perioperative factors, global structural network topology, and neurocognitive outcomes.

Materials and Methods

Data acquisition and preprocessing: Adolescents (age = 15.7 ± 0.96 years; range = 13 – 17 years) were scanned on a GE Twin 1.5T system (General Electric, Milwaukee, WI) at Boston Children's Hospital. Acquisition parameters were: matrix = 64 X 64, TR/TE = 13000 ms/108 ms, slice thickness = 4 mm, b = 750 s/mm^2, FOV = 240 mm. DTI data were corrected for motion, eddy current, and slice dropout artifacts and DTI metrics including FA, S0, and direction of the principal eigenvector were computed using standard routines in FSL (FMRIB, Oxford UK). Deterministic tractography was performed using in-house software written in IDL (http://www.ittvis.com, Boulder, CO). Streamlines were computed from each white matter voxel (determined as all voxels with FA > 0.25) in both directions. Stopping thresholds for the tractography were turning angle > 45 degrees or FA < 0.25.

Graph analysis: The DTI data were segmented into 76 anatomical regions by applying the automated anatomic labeling (AAL) template after spatial normalization into native space using routines in SPM-8 (Wellcome Dept. of Cognitive Neurology, London, UK). Adjacency matrices were computed, with each non-diagonal element of the 76-X-76 matrix set to one if there was at least one streamline connecting the two corresponding nodes, and zero if not. Graph metrics (cost, global efficiency, modularity, transitivity and small-worldness) were computed via the C++ modules available from the Brain Connectivity Toolbox (BCT; Indiana University).

Differences between d-TGA patients and controls: Comparisons between d-TGA patients and normal controls were performed using a General Linear Model with d-TGA status as the variable of interest and age, sex, and square root of the number of retained DTI acquisitions as covariates of no interest.

Analysis of indirect effects: d-TGA status was the independent variable, neurocognitive outcome was the dependent variable, and the graph metrics were the mediating variables (the same covariates were included) in a statistical mediation model [4]. Bootstrapping (25,000 iterations, resampling with replacement) was used to test for statistical significance. P-values were computed using bias-corrected and accelerated confidence intervals [4, 5]. The false discovery rate (FDR) method [6-8] was used to control for false positives at $q < 0.05$. Similar analyses were conducted on the cohort of d-TGA patients, with perioperative variables the independent variable.

Results and Discussion

d-TGA adolescents exhibited increased modularity (p = 0.012) and small-worldness (p = 0.026), and lower global efficiency at a trend level (p = 0.06). Poorer performance across a wide variety of cognitive domains was mediated by decreased global efficiency, and increased modularity and small-worldness (Figure 1). Improved performance across a wide variety of cognitive domains was mediated by increased global efficiency, and decreased modularity and small-worldness (Figure 2) in d-TGA patients with longer cooling duration during the arterial switch operation (ASO).

Our findings that adolescents with d-TGA display lower network integration and higher segregation, and that these topological differences mediate poorer neurocognitive outcomes, raise the possibility that network topology may be a potent biomarker for neurocognitive outcomes in children with complex CHD. Accordingly, if applied as an early outcome measure (for example, at age 2), structural network topology may not only distinguish among populations, but also predict later neurodevelopmental outcomes. Additionally, these same network topology differences mediate improved neurocognitive outcome in d-TGA patients with longer cooling duration during the ASO. These results indicate the neuroprotective effects of therapeutic hypothermia applied in this population, and indicate the possibility of ameliorating the neurocognitive effect of d-TGA with appropriation interventions.

Conclusion

Differences in global structural network topology were found between d-TGA adolescents and TD controls which mediated worse neurocognitive outcome in d-TGA patients. However, these effects were ameliorated by the use of a longer duration of therapeutic hypothermia during the ASO.

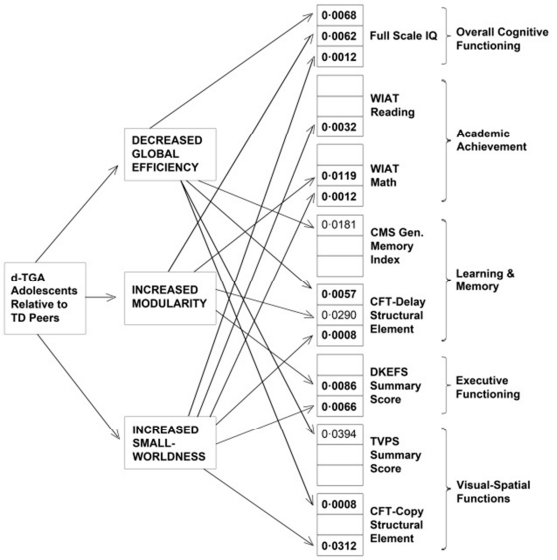

Figure 1. Structural network topology mediates neurocognitive deficits in d-TGA adolescents. Lower efficiency (less network integration) and increased modularity and small-worldness (more network segregration) mediate neurocognitive deficits in d-TGA adolescents compared to TD peers. Values above represent significant p-values for the mediation. p-values in **BOLD** are significant with correction for multiple comparisons (FDR < 0.05), whereas p-values in regular type are only nominally significant (p < 0.05, uncorrected.)

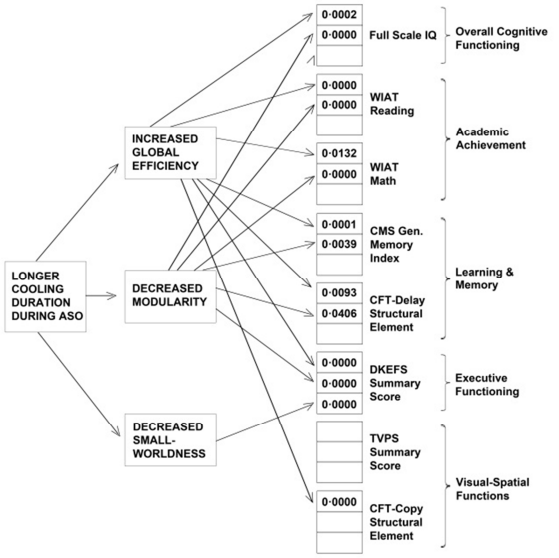

Figure 2. Structural network topology mediates better neurocognitive outcomes in d-TGA patients with longer cooling duration during the ASO. Within the d-TGA group, increased efficiency and decreased modularity and small-worldness mediate improved neurocognitive performance in d-TGA adolescents with longer cooling duration during the ASO. p-values in BOLD are significant with correction for multiple comparisons (FDR < 0.05), whereas p-values in regular type are only nominally significant (p < 0.05, uncorrected).

References

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