Objective Differentiation of Pure Speech Delay from Global Developmental Delay in Young Children: DWI Tractography-Based Connectome Study

JEONG-WON JEONG[1,2], Senthil Sundaram[1,2], Diane C. Chugani[1,2], and Harry T. Chugani[1,2]

[1]*Pediatrics and Neurology, Wayne State University, Detroit, Michigan, United States,* [2]*Translational Imaging Laboratory, Children's Hospital of Michigan, Detroit, Michigan, United States*

Targeted audience: Clinical researchers using diffusion tensor imaging for developmental neurological disorders. **Purpose**: Pure speech and language delay is a common condition, which according to some estimates, affects 5-8 % of the population. Speech delay (SD) may be not only an isolated condition but can be part of a broader condition such as global developmental delay (GD)[1]. Thus, it is important to differentiate SD from GD as early as possible in order to provide appropriately focused/targeted interventions to minimize learning difficulties. The present study investigates whether diffusion weighted imaging (DWI) tractography based-connectome analysis can be used to detect the regions of interest affected by GD and SD in order to develop an effective imaging biomarker to differentiate GD from SD in young children. **Methods:** 8 children with pure SD (age: 34.5±13.5, 8 boys), 6 children with GD (age: 36.8±14.1, 5 boys) and 5 children with typical development (TD, age: 48.5±20.5, 4 boys) underwent a 3T diffusion weighted MRI with eight channel head coil at TR = 12,500ms, TE = 88.7ms, FOV = 24cm, 128x128 acquisition matrix (nominal resolution = 1.89mm), contiguous 3mm thickness in order to cover entire axial slices of whole brain using 55 isotropic gradient directions with b= 1000s/mm^2, one b=0 acquisition, and number of excitations (NEX)=1. For each subject, an independent component analysis with ball and stick model (ICA+BSM)[2] was applied for whole brain tractography. A total of 116 cortical regions of interest were generated by fitting a deformable template of automated anatomical labeling atlas (AAL, http://www.gin.cnrs.fr/spip.php), resulting in two 116×116 connectivity matrices in which the elements quantify the pair-wise connectivity scores (i.e., fiber numbers connecting any two given cortical regions which were normalized by the corresponding tract mean lengths). Brain Connectivity Toolbox (BCT, https://sites.google.com/site/bctnet) was utilized to assess the following network metrics at individual region: strength (the number of the shortest paths), efficiency (the measure of global integration), cluster coefficient (the measure of local aggregation), and betweeness (the measure of centrality)[3]. Under two null hypotheses: TD > GD and TD > SD, non-parametric Mann-Whitney-Wilcoxon tests corrected for ages were applied between unpaired samples of individual network metrics to obtain two functional networks consisting of multiple pair-wise pathways that are significantly decreased in GD and SD group, respectively. Finally, Receiver operating characteristic (ROC) curve analysis was utilized to assess the accuracy of the individual network metric to differentiate SD from GD.

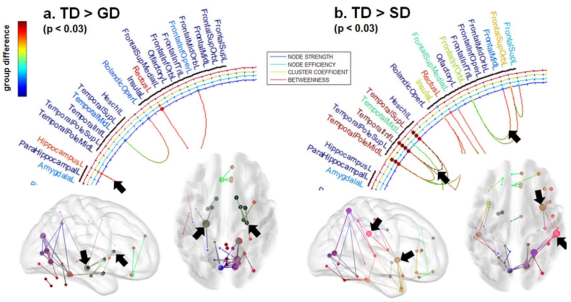

Figure 1. Regions of interest showing significantly changed network metrics in two group comparisons: (a) TD > GD (b) TD > SD. In 2-D connectogram, the color of anatomical label scales the p-value of group difference. Similarly, the color of each circle represents the p-value of individual metric. 3-D connectogram shows individual pair-wise pathways having significant group difference in nodal strength (i.e., the greater radius of sphere, the greater group difference). In both 2-D and 3-D connectograms, block arrows indicate hypocampal network and fronto-temporal language network whose nodal strengths are significantly reduced in GD and SD, respectively, compared with TD.

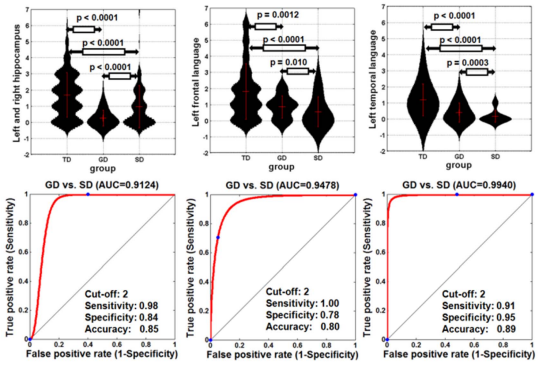

Figure 2. (1st row) Violin plots showing probability density functions of nodal strengths (black) measured from bilateral hippocampus (left), left frontal language region (superior frontal gyrus/insular, middle), and left temporal language region(superior temporal gyrus, right) of each group. To estimate the probability density function of individual group, the values of nodal strength were calculated by applying three discrete thresholds (5, 7, 10) to single connectivity matrix. Vertical red lines show mean±one standard deviation of each function. (2nd row) ROC curves to differentiate SD from GD using the nodal strength obtained from bilateral hippocampus (left), left frontal language region (middle), and left temporal language region(right).

Results: Compared with TD, GD had more significantly *reduced* node strength, efficiency and cluster coefficient bilaterally in hippocampus than the SD (**Fig. 1a**). Meanwhile, compared with TD, SD had more significantly *reduced* node strength, efficiency, cluster coefficient and betweeness in left fronto-temporal network consisting of superior frontal gyrus, insular, and superior temporal gyrus (i.e., a part of arcuate fasciculus) than the GD (**Fig. 1b**). As shown in **Fig. 2**, the subsequent ROC curve analysis revealed that the nodal strengths of those regions have significant group-differences between SD and GD (p-value < 0.01). Interestingly, the cut-off value of nodal strength (=2) could provide an excellent test (i.e., area under curve (AUC) > 0.9) to differentiate SD from GD, yielding high accuracy of 0.91 (bilateral hypocampus), 0.95 (left frontal language), and 0.99 (left temporal language). **Discussion and Conclusion**: The present study found that the nodal strengths of cognitive/language networks are differentially reduced between children with SD and GD. These different alterations may be effective imaging biomarkers underlying the neurocognitive and behavioral features commonly identified in these children. Further studies are required to establish the relevance of these findings for the severity of behavioral and cognitive deficit.

References: 1. Gopal SP, Tiwari VN, Veenstra AL, et al. Sensitive diffusion tensor imaging quantification method to identify language pathway abnormalities in children with developmental delay. J Pediatr, 2012;160:147-15. 2. Jeong JW, Asano E, Yeh FC, et al. Independent component analysis tractography combined with a ball-stick model to isolate intra-voxel crossing fibers of the corticospinal tracts in clinical diffusion MRI. Magn Reson Med. 2013;70:441–53. 4. Zalesky A, Fornito A, Bullmore ET. Network-based statistic: identifying differences in brain networks. Neuroimage, 2010;53:1197-207.