Reduced Connectivity in 7-year-old Preterm Brain Networks Relates to Adverse Perinatal Events, Cognitive and Motor Impairment

Deanne Thompson[1,2], Jian Chen[1], Richard Beare[1], Christopher Adamson[1], Zohra Ahmadzai[1], Claire Kelly[1], Terrie Inder[3], Lex Doyle[1,4], Marc Seal[1], and Peter Anderson[1,5]

[1]Murdoch Childrens Research Institute, Parkville, Victoria, Australia, [2]Florey Institute of Neuroscience and Mental Health, Parkville, Victoria, Australia, [3]Brigham and Women's Hospital, Massachusettes, United States, [4]Royal Women's Hospital, Parkville, Victoria, Australia, [5]Paediatrics, University of Melbourne, Parkville, Victoria, Australia

Target audience: Researchers and clinicians interested in the application of structural connectivity to pediatric populations.

Purpose: Very preterm (VP) infants <32 weeks' gestational age (GA) are born during a sensitive time of brain development and often suffer brain abnormalities related to adverse perinatal events. VP children are also at risk of cognitive and motor impairments. Difficulties VP children face may be due in part to altered white matter connections in the brain, however the impact of prematurity on structural connectivity is not yet understood. The aims of this study were to use structural connectivity to (1) identify brain networks associated with perinatal insults in VP children, and (2) identify networks that differ between VP children with or without cognitive and motor impairments.

Methods: Subjects & Scanning: 107 VP (<30 week's GA &/or <1250g) children from the Victorian Infant Brain Study cohort were scanned with magnetic resonance imaging (MRI) at 7 years' corrected age with a 3T Siemens scanner: T_1 weighted (TR= 1900ms, TE= 2.27ms, 0.8mm^3 isotropic voxels); and echo-planar diffusion-weighted images with 45 gradient directions and *b*-value 3000 s/mm^2 (TR= 7400 ms, TE= 106 ms, 2.3 mm^3 isotropic voxels) were acquired. Perinatal data were collected for GA, birth-weight standard deviation score, infection and qualitative brain abnormality assessed on term-equivalent MRI[1]. 7 Year Outcomes: At 7 years corrected age, VP children underwent the following tests: Full-scale IQ from the Wechsler Abbreviated Scale of Intelligence (WASI); Academic skills (reading and maths) from the Wide Range Achievement Test 4 (WRAT4); Attention using Score! subtest of Test of Everyday Attention for Children (TEACh); General language ability using Core Language scale from Clinical Evaluation of Language Fundamentals (CELF-IV); Working Memory using Backward Digit Recall subtext from Working Memory Test Battery for Children (WMTB-C); Visual perception using Visual Closure subtest of the Test of Visual Perceptual Skills (TVPS-3); Motor functioning using the Movement Assessment Battery for Children (MABC2). Impairment was defined as < 1SD from the mean standard score. The non-impaired comparison group was defined as a subset of VP children who were not impaired on any task (n=37). Structural Connectivity: White matter connectivity graphs were created, where nodes consisted of the 66 cortical and 14 subcortical regions from Freesurfer performed on T1 scans[2]. Edges were streamline counts, normalized by streamline length and average size of end nodes. Streamlines were created using probabilistic tractography with diffusion directions resolved using constrained spherical deconvolution[3]. Connectivity matrices were thresholded to a density of 30%. Significant edges between groups were detected for each pair of brain regions and combined into a sub-graph of the original graph. Network based statistics (NBS)[4] was conducted within the sub-graph to define a set of connected components. Significance of each component was tested using permutations (n=5000). For each permutation, subjects were randomly reallocated into a group, significant connections were generated and connected components found. If the new component was larger than the original, it was considered significant. Effects of age at assessment and intracranial volume were removed by linear regression prior to the statistical analysis of edge strength.

Results: Lower GA in VP children was associated with reduced connectivity within a network involving the left posterior aspect of superior temporal sulcus, left caudal anterior cingulate gyrus and left putamen [threshold (T)=2.5, p=0.096] (Figure 1a). Children who had perinatal infection had lower edge strength between the following nodes: left rostral middle frontal gyrus, right caudal middle frontal gyrus, and right pars opercularis (T=2.25, p=0.054) (Figure 1b). Children with neonatal brain abnormality had less connectivity within a network involving the left lateral occipital cortex, left pericalcarine cortex, left cuneus cortex, right precuneus cortex, right supramarginal gyrus, left and right thalamus, and left putamen (T=2.5, p=0.013) (Figure 1c). VP children with impaired IQ had a large network of 33 nodes with weaker connecting edge strengths, including bilateral paracentral, pars opercularis, posterior cingulate, precuneus, rostral middle frontal, superior frontal, supramarginal and caudate, left pars orbitalis, and right postcentral, caudal middle frontal, cuneus, fusiform, inferior parietal, inferior temporal, lateral occipital, middle temporal, pars triangularis, posterior aspect of superior temporal sulcus, precentral, superior parietal, superior temporal, temporal pole, thalamus, and hippocampus (T=2.25, p=0.051) (Figure 1d). Children with motor impairment had reduced connectivity within a network of nodes consisting the right inferior parietal, inferior temporal, middle temporal, precuneus, and superior temporal (T=3.0, p=0.052) (Figure 1e).

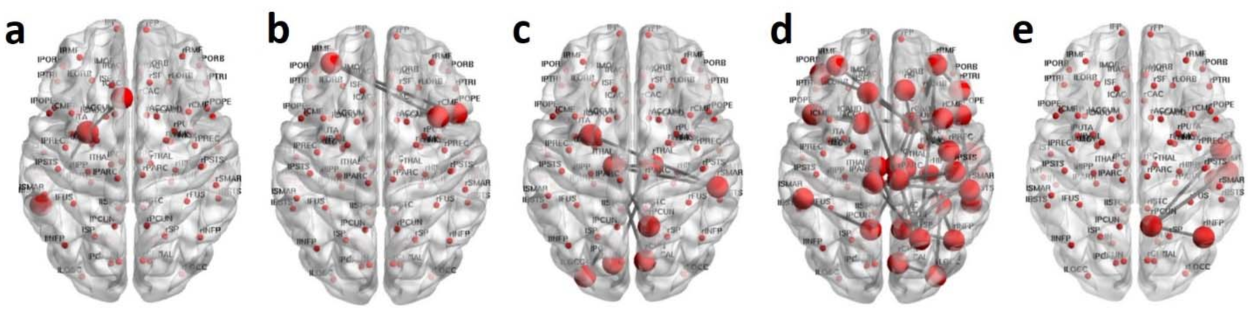

Figure 1. *Connectivity networks with reduced edge strength associated with (a) lower gestational age, (b) perinatal infection, (c) qualitative brain abnormality at term, (d) impaired IQ, and (e) impaired motor outcomes.*

Discussion. VP children born at lower GA had reduced connectivity within a network connecting left temporal, cingulate and putamen regions. Those with perinatal infection had connectivity reductions within a network involving frontal gyri at 7 years of age. Brain abnormality at term-equivalent age was associated with reduced connectivity within the occipital and parietal lobes, thalamus and putamen. This suggests that adverse perinatal events have a lasting negative impact on white matter connectivity in the brain, at 7 years of age. Impaired IQ was associated with reduced connectivity within a diffuse network. VP children with motor impairment had reduced connectivity in regions within the right parietal and temporal lobes.

Conclusion. Brain network analysis may be useful to identify at-risk VP children for surveillance. This study highlights the importance of prevention or intervention following perinatal infection or brain abnormality, and increases our understanding of the neurological mechanisms and brain networks underlying impairments common to VP children. Further study is required to examine whether structural connectivity catches up in adolescence.

References. [1] Kidokoro, et al. New MR imaging assessment tool to define brain abnormalities in very preterm infants at term. Am J Neuroradiol 2013. 34: 2208-14. [2] Desikan et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. 2006 *Neuroimage*, *31*: 968-980. [3] Tournier et al. Robust determination of the fibre orientation distribution in diffusion MRI: non-negativity constrained super-resolved spherical deconvolution. 2007. 35: 1459-72. [4] Zalesky, et al. Network-based statistic: Identifying differences in brain networks. *Neuroimage* 2010. 53: 1197-1207.