Cortical Connectivity in Excised Rat Brain with Thyroid Hormone Deficiency

L.M. Colon-Perez (UF, Biochemistry & Molecular Biology); E. Montie (USCB, Natural Science); M. Couret (UF, Chemistry); T. Mareci (UF, Biochemistry & Molecular Biology)

Introduction

Thyroid hormone (TH) deficiencies have been shown to affect the developmental process of myelination in rat brains[1]. TH deficiencies (TD) induce various neurological symptoms, such as cognitive deficits, sensory loss, and motor impairments. The neurological symptoms related to TD have been associated with changes in brain structure, which Powell et al. observed in the form of reduction of white matter volume[1]. The TD model is ideal for the study of connectivity in the brain as a network of connected nodes, since the structural changes could possibly lead to a decrease in measures of connectivity in brain networks.

Methods

Animal Treatment; Offspring of rat dams were randomly selected and assigned for group treatments. The groups were control rats (n = 5) and rats treated with 10 ppm 6-propyl-2thiouracil (PTU; Sigma Aldrich Corp, St. Louis, MO) (n = 4). Dosing began at gestation day 7 and continued until postnatal day 25. *MRI acquisition*; MR images were acquired at 750 MHz on a Bruker 17.6 T imaging spectrometer (Bruker Corp, Billerica, MA). High angular resolution diffusion imaging data of the entire brain was obtained using a diffusion weighted spin echo sequence with the following parameters: TR/TE = 4000/28 ms, 7 diffusion weightings with b values of 100 s/mm^2, and 64 diffusion weightings with b values of 2225 s/mm^2. The diffusion gradient directions were distributed following a scheme of electrostatic repulsion[2]. An image resolution of 190 x 190 x 190 μm^3 was acquired and interpolated to of 95 x 95 x 95 μm^3. *Network Definition*; Using a digitized Paxinos atlas[3] a total of 40 rat cortical nodes were defined. Each connection between cortical regions was assigned an edge weight, defined as Colon-Perez, et.al[4]. A threshold is applied to compare networks with all the connections obtained from tractography (~70% of all possible edges (APE) between nodes) to the networks where only the strongest connections are considered (~20% APE). A total of four networks were analyzed; control and PTU brains with ~70% APE, and control PTU brains with ~20% APE.

Results

Previous studies have shown deformities in WM and GM in rat brains with thyroid hormone deficiencies [1]. Network analysis defines hubs as nodes with a large number of connections to all other in the network and these are identified as those nodes with the largest degree values in the network. The hub nodes in normal and PTU brains were not the same (Table 1) suggesting the rat brain network is reorganized with TD accompanied by the WM reduction observed by Powell et al [1]. The node strength is a network quantity that sums the edge weights (i.e. edge strength) that connects any node to all its neighbors; hence, it quantifies the WM strength connecting any node to its neighbors. In this study the average node strength across the entire cortical network with 70% APE for controls rats was (2.75 ± 0.36) x10^{-2} compared to (2.39 ± 0.30) x10^{-2} in TD rats. Meanwhile, in 20% APE cortical network for controls rats was (2.56 ± 0.40) x10^{-2} compared to (2.11 ± 0.33) x10^{-2} in TD rats. Paired t-tests in rat brains with TD compared to controls showed significant differences ($p < 0.01$) on both network metrics (node degree and strength) at both APE's (20% and 70%). In summary, rat brains with TD displayed reduced global connectivity and strength of connectivity, implying that thyroid disruption reduces the brain connectivity by means of inhibited connectivity (reduced degree) and reductions of WM volumes (reduced node strength) in a global scale.

Controls							
70% APE				20% APE			
Side	Cortical region	Average degree	σ	Side	Cortical region	Average degree	σ
L	Anterior cingulate	36.0	1.8	L	Primary somatosensory	17.1	2.8
R	Anterior cingulate	36.0	4.7	R	Primary somatosensory	15.7	2.7
R	Primary somatosensory	35.9	2.8	R	Anterior cingulate	15.1	3.8
PTU							
70% APE				20% APE			
Side	Cortical Region	Average degree	σ	Side	Cortical Region	Average degree	σ
L	Retrosplenial	36.5	1.3	L	Retrosplenial	17.0	2.9
L	Gustatory	35.0	2.2	R	Piriform	14.3	2.2
R	Piriform	34.8	2.1	R	Retrosplenial	13.3	1.0

Table 1. Hubs (most connected) nodes in rat brain networks. Hubs in control and PTU brains differ in anatomical location but maintain similar value suggesting reorganization in the cortical network connectivity with TD.

Acknowledgements

The MRI data was acquired in the Advanced Magnetic Resonance Imaging & Spectroscopy (AMRIS) Facility at the McKnight Brain Institute of the University of Florida. This study was supported by the University Corporation of Atmospheric Research under Grant No. NA06OAR4310119 from the National Oceanic and Atmospheric Administration, US Department of Commerce. We also acknowledge the partners of this training grant: University of California Davis Wildlife Health Center, the Marine Mammal Center, and North-west Fisheries Science Center. Additional funding was provided by the National Institute of General Medical Sciences grant no. P20GM103499 and the National Institute of Neurological Diseases and Stroke grant no. R01 NS063360.

References 1. Powell, M. H. *et al. Neurotoxicology* 33, 1322–1329 (2012). 2. Jones, D. K., Horsfield, M. & Simmons, A. *Magnetic Resonance in Medicine* 42, 515–525 (1999). 3. Paxinos, G. & Watson, C. 256 (Academic Press, 1998). 4. Colon-Perez, L. M. *et al. Proc. Intl. Soc. Mag. Reson. Med* 686 (2012).