Reduced cortical connectivity in excised rat brain with thyroid hormone deficiency

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Introduction: Thyroid hormone (TH) deficiencies have been shown to affect the developmental process of myelination in rat brains[1]. Thyroid hormone deficiencies induce various neurological symptoms, such as cognitive deficits, sensory loss, and motor impairments. The neurological symptoms related to TH deficiencies are also associated with changes in brain structure, which result from the reduction of white matter volume[1]. The thyroid-hormone deficiency (TD) model is ideal for the study of connectivity since the structural changes in the brain are due to changes in white matter (WM) volumes, which in turn could possibly lead to a decrease in the strength of connectivity measures and changes in network connectivity. In order to study the effects of thyroid disruption in rat cortical networks, we acquired diffusion-weighted data and performed tractography on *ex vivo* rat brains and performed graph theory analysis of node degree and node strength over the entire brain network.

Methods: *Animals Treatment*; Experiments were performed at the University of South Florida (USF, St. Petersburg, FL) with the approval of the USF Institutional Animal Care and Use Committee (IACUC) permit #R3486. Offspring of rat dams were randomly selected and assigned for group treatments. The groups are control rats (n = 5) and rats treated with 10 ppm 6-propyl-2thiouracil (n = 4) (PTU; Sigma Aldrich Corp, St. Louis, MO). 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) with a 20 mm birdcage coil (M2M Imaging Corp., Cleveland, OH). High angular diffusion imaging (HARDI) 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. Finally, an interpolation of the original image was performed to obtain an image 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. FSL's FLIRT was used to register the Paxinos atlas regions as nodes in the diffusion weighted images. Each connection between cortical regions was assigned an edge weight, defined as Colon-Perez, et.al[4]. A total of four networks were analyzed; control brains with a total of ~70% of all possible edges (APE) between nodes, PTU brains treated with ~70% APE, control brains with ~20% APE and PTU brains treated with ~20% APE.

Results: As expected, TD brains displayed reductions in connectivity and strength of connectivity. Previous studies have shown deformities in WM and GM in rat brains with thyroid hormone deficiencies [1]. These deformities cause changes in brain structure in the form of reduced WM volumes and heterotopias (abnormal presence of GM in WM locations) in the corpus callosum. 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). The strongest and most connected nodes in normal and PTU brains were not the same, identified with marks in the plots of Fig 1 (top row networks with ~20% APE, bottom row ~70% APE). This suggests that the WM reduction observed by Powell et al. [1] is not only an global reduction of WM, but may be accompanied by a network reorganization. Possibly this can represent a "rewiring" to make up for the reduced WM volumes and heterotopias in WM tracks which may allow the rat maintain vital functions even with the effects of TD during brain development.

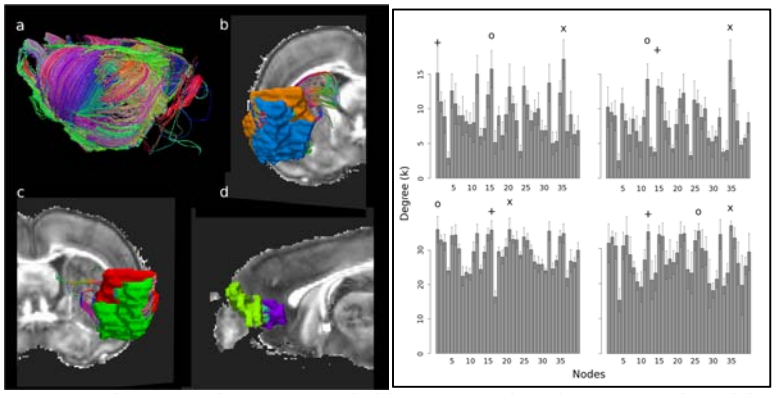

Figure 1. Rat brain network organization. Black box; (a) streamlines that connect nodes and (b-d) cortical nodes connected by streamlines. White box; degree values. Top-left plot, normal ~ 20% APE. Top-right plot, PTU ~ 20% APE. Bottom-left, normal ~70% APE. Bottom-right, PTU ~70% APE. The marks correspond to the largest degree values: (x) largest , (o) second largest, and (+) third largest . The first twenty nodes represent the right side of the brain and the latter twenty represent the left side of the brain.

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