The role of glial fibers in human fetal connectome with high resolution diffusion tensor imaging

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Target audience: MR physicist, developmental neuroscientist, pediatric neurologist, pediatric radiologist

Purpose: The formation of human brain connectome in the fetal stage is poorly understood. Both fetal axons and transient glial fibers exist in the fetal brain and the latter are associated with the neuronal migration pathways. Fetal axons and glial fibers are both coherent and organized fibers that can be noninvasively traced with DTI. The human fetal brain cerebral wall is a laminated structure [1, 2] and can be delineated into three distinctive layers, namely, cortical plate, subplate and the inner layer, with clear DTI contrasts [3]. Based on the segmented cerebral wall layers, fetal axons and glial fibers can be differentiated by the fiber termination locations. One of the two terminals of the glial fibers is in the ventricular zone of the cerebral wall; and the other terminal could be in cortical plate, subplate or ventricular zone in the cerebral wall. On the other hand, both axonal terminals are in the cortical plate of the fetal brain cerebral wall. With few long-range association axons such as inferior or superior fronto-occipital fasciculus being apparent in early to middle fetal stage [5-6], we hypothesize that glial fibers play a vital role in the formation of human brain network. In this study, we aimed to explore the role of the glial fibers in constructing human brain connectome in the fetal stage. High resolution DTI data was acquired from *ex vivo* fetal brains at 13 weeks of gestation (wg), 15wg, 17wg and 19wg. Based on DTI tractography and cortical parcellation, brain network properties based on graph theory were measured with the connectivity contributed by glial fibers only, axons only and both glial fibers and axons.

Methods:

High resolution DTI data acquisition of fetal brain specimens from 13wg to 19wg: 4.7T Bruker scanner was used to acquire diffusion weighted images (DWI) from postmortem fetal brain specimens from 13wg to 19wg. A 3D multiple spin echo DTI sequence was used. The DWI parameters were: b-value=1000s/mm^2, resolution=0.3x0.3x0.3mm^3. High resolution DTI of one specimen at 13wg, 15wg, 17wg and 19wg, respectively, was used for connectome analysis below. *Template-free cortical parcellation for defining nodes of the network:* Due to the lack of anatomical landmarks on the cortical surface of the fetal brains, a template-free parcellation scheme [7] was applied to parcellate the cerebral wall into 56 different regions with similar size. The segmented nodes were constrained to be consistent across the hemispheres of each brain and consistent across the brains of different subjects. *DTI tractography for edge definition:* With each of the 56 parcellated nodes as seeds, deterministic tracking was performed using TrackVis. A filtering algorithm was applied to keep only those tracts connecting two different nodes. A binary 56x56 whole brain connectivity matrix was established for each subject. Note this connectivity was contributed by both the glial fibers and the axons connecting parcellated nodes. *Separating glial fiber connectivity from axonal connectivity*: The whole brain connectivity matrix was further divided into those with (a) axonal connectivity only, (b) glial fiber connectivity only and (c) combined axonal and glial fiber connectivity. Specifically, those node-node connections that had tract endpoints beginning and terminating at the cortical plate were marked as axonal connectivity and those node-node connections that had tract endpoints outside of the cortical plate were marked as glial fiber connectivity. These steps yielded three binary connectivity matrices for each subject. *Network analysis with graph theory:* Each of three binary connectivity matrices of every brain was then used for measuring network properties based on graph theory, including strength, local efficiency, global efficiency, cost efficiency and small-worldness with GRETNA toolbox [8].

Results:

DTI orientation-encoded colormap and whole brain fibers: Coronal views of the orientation-encoded DTI colormaps of 13wg, 15wg, 17wg and 19wg fetal brain are shown in the top panel of Fig. 1. The three distinctive layers of the fetal brain cerebral wall, namely the cortical plate, subplate and the inner layer [3] can be clearly observed and are marked by the yellow, orange and the green arrows, respectively. As can be observed from the bottom panel of Fig. 1, rich corticocortical fibers including both axons and glial fibers exist for fetal brains from 13wg to 19wg. Furthermore, the majority of these fibers were identified as glial fibers, not the axons based on termination locations of the fibers. *Network properties from 13wg to 19wg:* As shown in Fig.2, the network properties undergo a dramatic change during fetal brain development with monotonic increase in the strength, local and global efficiency and small-worldness. Furthermore, all these well-established network properties are contributed almost exclusively by the glial fibers. The fetal brain connectivity of axons, however, has very limited contribution to shaping the brain network during fetal brain development from 13wg to 19wg.

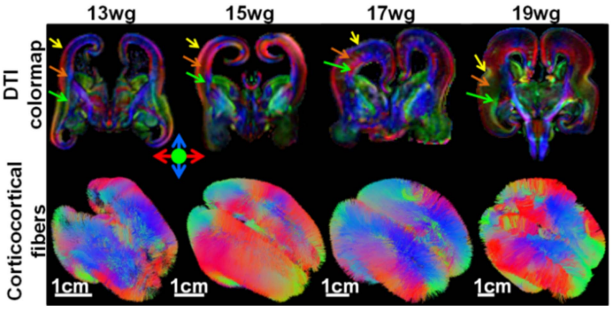

Figure 1 (left): Coronal views of orientation-encoded colormap at 13wg, 15wg, 17wg and 19wg (top panels) and 3D corticocortical fibers traced with DTI tractography (bottom panels). The cortical plate, subplate and the inner layer are denoted by the yellow, orange and green arrows, respectively, in the top panels.

Discussion and Conclusion:

In this study, we demonstrated that the glial fibers, instead of axons, contributed overwhelmingly to well-established network properties in fetal stage from 13wg to 19wg. Delineating the networks contributed by the glial fibers offers a refreshing insight into the formation of human brain connectome. Specfically, our results suggest that the network of the glial fibers precedes the network of axons and the glial fiber network constitutes the basis for the circuit formation and the axonal network development. Analysis with more specimens at each fetal time point is underway. Differentiation of glial fibers from axons based on termination locations of traced fibers from DTI will also be validated with immunohistochemisty.

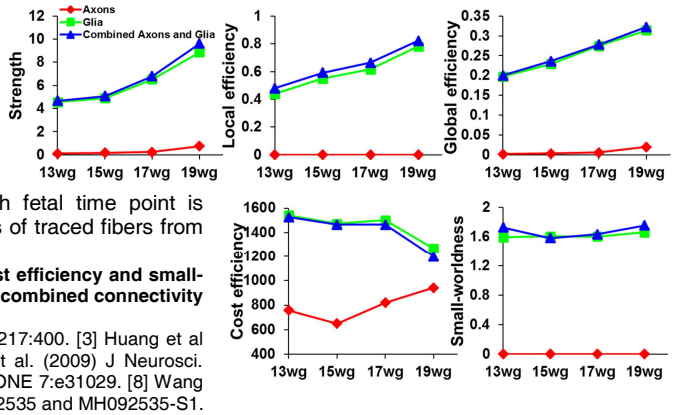

Figure 2 (right): The developmental changes of network strength, local, global and cost efficiency and small-worldness from13wg to 19wg. Network properties contributed by axonal, glial fiber and combined connectivity are shown in red, green and blue.

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