Disrupted developmental organization of brain connectivity in fetuses with corpus callosum agenesis: an in utero study

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Target audience

Developmental biologists, neuroradiologists, fetal MRI specialists, computer scientists

Purpose

Corpus callosum agenesis (CCA) is an axon-guidance disorder characterized by missing interhemispheric connectivity and abnormal intra-hemispheric fiber structures.[1] Our purpose was to use *in utero* MRI techniques to describe the altered organization of structural connections in the fetal acallosal brain and to characterize the course of development of aberrant connectivity during the late second and third trimester of gestation.

Methods

Fetuses with isolated corpus callosum agenesis with or without associated malformations were enrolled (n=20). Diffusion tensor magnetic resonance imaging was performed on a 1.5 T scanner using a sensitivity encoding (SENSE) cardiac coil with five elements wrapped around the mother's abdomen, utilizing single-shot gradient-recalled echo-planar imaging. The sequence parameters were the following. TR: 1745 ms, TE: 90 ms, acquisition matrix: 112*77 resampled to 256*256, voxel size: 0.94*0.94 mm, slice thickness 3.3 mm. B-factor was 700 s/mm^2, 16 gradient directions were used. Using a fetal atlas, 90 regions of interest (ROIs) were matched to the brains (mean DWI image) using non-rigid deformations; and ROI-to-ROI deterministic fiber connectivity was done using the Camino software package (UCL, UK). Preprocessing of fetal DTI images included motion correction, b-matrix reorientation and bias field correction. Connection matrices consisted of ROI size-corrected streamline counts. Connectomes were compared to gestational age-matched (weeks 21-34., n=20) normally developing fetuses by utilizing permuted network-based statistics (NBS), [2] we formulated a general linear model to compare differences between CCA and normal connectivity, controlling for gestational age.

Results

Whole-brain tractography results are demonstrated in **Figure 1.** We confirmed the missing interhemispheric connectivity, while excessive intra-hemispheric connectivity was found in CCA. Gradually increasing connectivity strength and tract diffusion anisotropy during gestation were dominant in antero-posteriorly running paramedian and antero-laterally running aberrant pathways, and in short-range connections in the temporoparietal regions. In fetuses with associated abnormalities, more diffuse reduction of cortico-cortical and cortico-subcortical connectivity was observed than in cases with isolated callosal agenesis (**Figure 1/A,B**)

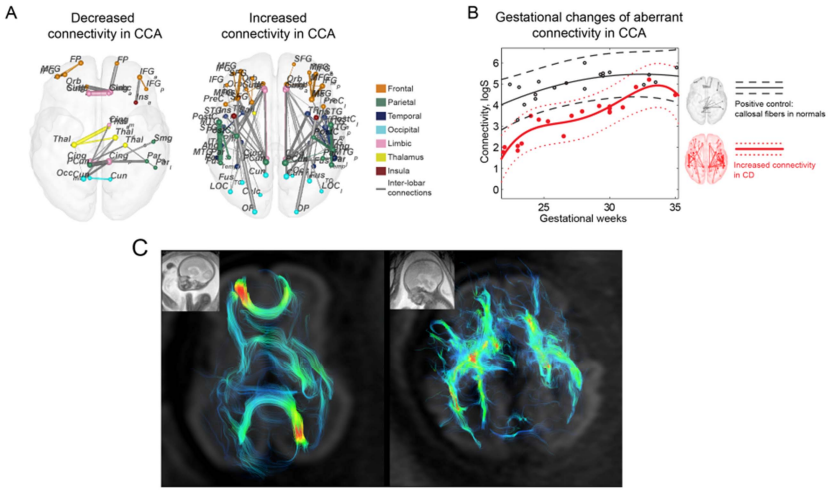

Figure 1. Malformed connections in fetuses with corpus callosum agenesis. (A): group level differences in the connectome, (B) gestational course of brain connectivity in the corpus callosum (healthy) and the aberrant pathways, (C) whole-brain tractography in a normally developing and CCA fetus.

Discussion

Our early experimental window is of particular importance, as, during infanthood and adolescence, white matter structure develops rapidly, and these physiological changes presumably affect the phenotype of acallosal brains. Acallosal fetal brains show a globally altered connectivity structure. Besides the previously described Probst and sigmoid bundles and compensatory pathways through the anterior and posterior commissures[3], we revealed a prenatally malformed macroconnectome and disrupted developmental trajectory.

Conclusion

In corpus callosum agenesis, abnormal excessive or exuberant pathways are already present during at early stages of fetal brain development in the majority of cerebral white matter.

References

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