Disrupted Resting State Brain Connectivity in Fetal Complex Congenital Heart Disease

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INRODUCTION: The last trimester of brain development in fetuses with complex congenital heart disease (CHD) is abnormal, with structural and metabolic abnormalities documented [1]. While resting state networks (RSN) are well characterized in preterm neonates, very little is known about the development of RSN in fetuses with complex CHD. Importantly, *in utero* healthy fetal brain RSN has been characterized through the use of resting BOLD and Independent Component Analysis (ICA) [2]. In this 3T parallel transmission fetal MR study, we use ICA analysis with resting BOLD of Fetal CHD patients to test two hypotheses: (1) there is disruption of fetal resting state networks compared to healthy controls; (2) the degree of disruption of fetal resting network within the complex CHD group is related to the degree of presumed fetal cerebral oxygenation saturation.

METHODS: A total of 17 pregnant women prospectively recruited over a 4 month period, with 13 studies meeting quality control for analysis including (n=9) having healthy fetuses in the control group (GA 26-39 weeks, mean GA = 32 wk) and four having fetuses diagnosed with CHD (GA 32-35 wk, mean GA=32.25 wk) ***[n=4; of these Transposition of the Great Arteries (n=1), Hypoplastic Left Heart Syndrome (n=1), Truncus Arteriosus (n=1), and Coarctation of the Aorta (n=1)],*** were included in this analysis. All received abdominal-pelvic single shot BOLD scans with parallel transmission on 3T Skyra (Siemens AG, Erlangen, Germany) using standard body coil (Siemens) with the following sequence parameters: FOV=256mm, TE/TR = 32/2200 ms with an in-plane resolution of 4x4 mm^2 and slice thickness of 4mm with 4mm space. At each TR interval 32 slices were acquired. Repeat scans were conducted during the session to acquire an image series with minimal or absent fetal movement. The fetal brain was manually extracted using the first TR of the image series, and the brain only binary mask applied to the successive TR's to generate a brain only series. Each successive TR was manually check for integrity of the extracted brain, and any volume with discrepancies due to motion artifacts were excluded. Finally all were corrected for motion and registered, and both single ICA and Tensor-ICA analysis were conducted on these post-hoc brain-only BOLD images using multivariate decomposition tools from FMRIB FSL (MELODIC) [3, 4].

RESULTS: Results from the single ICA analysis are presented in Figure 1. The component series for each patient was scrutinized for activation patterns similar to previously characterized networks. The healthy fetal controls all showed well-delineated bilateral hemispheric activations in the posterior (parietal-occipital) (1A) and frontal areas (1B), as well as unilateral hemispheric activations (auditory and sensorimotor). In the complex CHD group, there was variation and disruption of the presence of these resting state networks that correlated with the degree of predicted cerebral oxygenation (based on fetal cardiac physiology). For example, the coarctation case (best predicted cerebral oxygenation) showed normal RSN similar to fetal healthy controls (1C, 1D). In contrast, the TGA cases (worst predicted cerebral oxygenation) show no visible normal RSN (1H). In addition, a greater number of "deactivations" (BLUE) was noted in complex CHD cases that had relatively poorer predicted cerebral oxygenation.

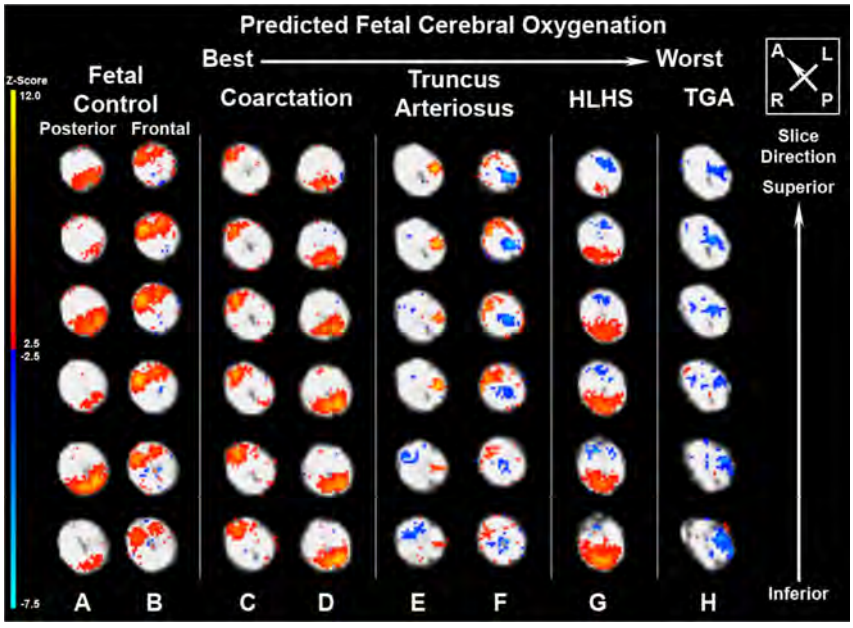

Figure1: Results of the single ICA analysis. Note frontal and posterior RSNs in healthy controls (A, B); CHD results presented from best **predicted fetal cerebral oxygenation** (C, D - Coarcation) to worst (H - TGA). Note the diagonal orientation.

CONCLUSION: This is one of the first reports of resting-state brain network characterization in fetal complex congenital heart disease. Our preliminary results provide evidence of disruption of the development of normal resting network in the frontal and posterior regions of the brain in complex CHD fetal cases compared to healthy fetal controls. We also note that the patterns and direction of activations associated with RSN was correlated with the degree of predicted cerebral oxygenation associated with the CHD lesion subtype. Further evaluation in a larger dataset and correlation with neurodevelopment outcomes is warranted.

REFERENCE: [1] Limperopoulos, C., et al. *Circulation* 2010; 121.1:26-33. [2] Ferrazzi, G., et al. *NeuroImage* 2014; 101:555-568. [3] Beckmann, C.F., et al. *Phil. Trans. RSB: Biological Sciences* 2005; 360.145:1001-1013. [4] Beckmann, C.F. & S.M. Smith. *IEEE Transactions* 2004; 23.2: 137-152.