Magnetic susceptibility alterations in mouse brains with prenatal alcohol exposure: a preliminary study

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TARGET AUDIENCE: Anyone interested in magnetic susceptibility imaging, brain development, and fetal alcohol spectrum disorder (FASD).

PURPOSE: Fetal alcohol spectrum disorder (FASD) is often used as an umbrella term that encompasses all of the various diagnoses related to prenatal alcohol exposure. The primary effects of prenatal alcohol exposure are on the brain development and the cognitive and behavioral deficits that ensue. Extensive structural abnormalities have been reported in brains of humans and animal models with prenatal alcohol exposure. Diffusion tensor imaging (DTI) studies have demonstrated that prenatal alcohol exposure has a profound impact on white matter development. Recently, magnetic susceptibility imaging was shown to have excellent sensitivity to brain white matter abnormalities in genetically altered models and other mouse models of dysmyelination or demyelination. This technique provides a new way, fundamentally different from DTI in physical and biological principles, to study brain white matter [1,2]. In this abstract, we reported our preliminary results of assessing the impact of prenatal alcohol exposure to mouse brains using magnetic susceptibility imaging

METHODS: Two groups of C57BL/6J mice (postnatal day 80) were characterized: an ethanol group (n = 3) and a control group (n = 3). In the ethanol group, pregnant dams were treated with high doses of ethanol on gestational day 7. Treatment entailed twice daily intraperitoneal injections of 2.8-2.9 g/kg ethanol administered 4 hours apart [3]. The resulting blood ethanol concentrations approach 350-420 mg/dl which models acute high ethanol intake mimicking human alcohol consumption. In the control group, ethanol was replaced with saline. Brains were perfused with ProHance then scanned at 9.4 T using a 3D spoiled-gradient-recalled (SPGR) sequence. The scan parameters were: matrix size = 512x256x256, FOV = 22x11x11 mm^3, FA = 90º, TE = 4.432 ms, TR = 50 ms. Diffusion tensor images (DTI) were acquired using a diffusion-weighted 3D spin-echo sequence with the same spatial resolution. The images were down-sampled to 60 micron isotropic spatial resolution to ensure sufficient SNR. Magnetic susceptibility was obtained using the LSQR method [4].

Two major white matter fiber bundles, including anterior commissure and corpus callosum, were automatically segmented using DTI studio. Magnetic susceptibility values of these two selected fiber structures were analyzed following Eq. [1], which describes the variations of susceptibility (χ) of white matter fibers bundles as a function of fibers angle (α) with respect to the main magnetic field [5].

$$\chi = \Delta\chi_{max} \sin^2\alpha + \chi_0 \qquad [1]$$

In Eq. [1], χ_0 is a baseline isotropic susceptibility; $\Delta\chi_{max}$ denotes the maximum susceptibility variations (or susceptibility anisotropy) for white matter fiber when imaged at different directions. By plotting magnetic susceptibility of different voxels within white matter fibers against $\sin^2\alpha$, $\Delta\chi_{max}$ was estimated with a least-square fitting.

RESULTS: Fig. 1 showed the variation of magnetic susceptibility with respect to the fiber orientation, for the fiber structure of anterior commissure and corpus callosum. In both structures, magnetic susceptibility decreases monotonously as the fiber angle increases following a sine-squared relationship [2]. For this particular example of one ethanol mouse and one control mouse, the maximum susceptibility variations, $\Delta\chi_{max}$, was estimated at -0.016 and -0.13 ppm for the ethanol and control mouse, respectively, for the anterior commissure. For the corpus callosum, $\Delta\chi_{max}$ was estimated at -0.027 and -0.046 ppm for the ethanol and control mouse, respectively. Fig. 2 showed the statistical comparison of the $\Delta\chi_{max}$ between ethanol and control groups in the two ROIs. A significant decrease ($p < 0.01$) in the absolute value of $\Delta\chi_{max}$ was observed for the ethanol group compared to that of the control group in both anterior commissure and corpus callosum.

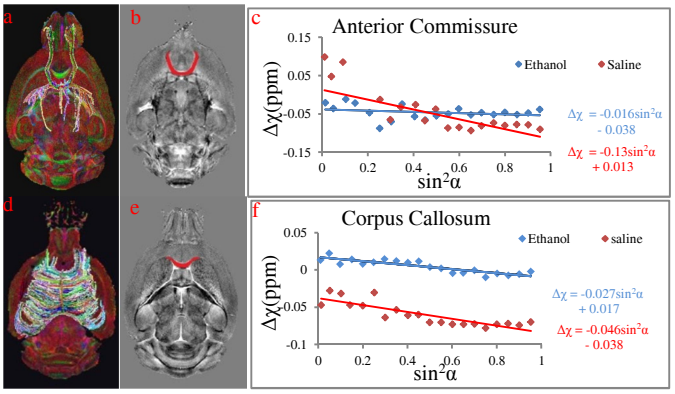

Fig. 1: Orientation dependence of magnetic susceptibility in two selected ROIs of the anterior commissure (a-c) and the corpus callosum (d-f) for an ethanol mouse and a control mouse. ROIs were segmented based on DTI tractography (a,d) and overlaid on corresponding susceptibility maps (b,e). Magnetic susceptibility increases monotonously as the fiber angle decreases following a sine-squared relationship (c,f).

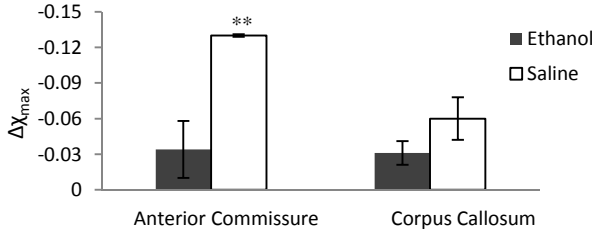

Fig.2: Susceptibility anisotropy, $|\Delta\chi_{max}|$, is significantly reduced in ethanol exposed mice compared with control mice. ** P<0.01.

DISCUSSION AND CONCLUSION: We found that the orientation dependence of magnetic susceptibility was significantly decreased in ethanol exposed brains compared to their age-matched controls, in two main white matter regions, the anterior commissure and the corpus callosum. Magnetic susceptibility reflects the distribution of a number of potential physiologically important elements including myelin, iron, chemical exchange and macromolecules [1]. A recent theoretical study suggested that $\Delta\chi_{max}$ is linearly proportional to the myelin contents of the white matter. Assuming this is true, the observed decrease of $\Delta\chi_{max}$ in the ethanol group may be interpreted as loss of myelination due to prenatal alcohol exposure. It has also been reported that the prenatal alcohol exposure will result in a disproportionate decrease in white matter and gray matter volumes [6]. In addition, alcohol can cause impaired white matter structural integrity, in particular a permanent reduction in the relative thickness of myelin sheath. Corpus callosum was regarded as the most vulnerable structure affected by the detrimental effects of prenatal alcohol exposure [7]. Previous DTI studies also reported a decrease in fractional anisotropy in the anterior commissure and the corpus callosum [8]. To conclude, our preliminary results show that prenatal alcohol exposure results in a reduced anisotropy of magnetic susceptibility, which likely reflects the abnormal white matter development caused by prenatal alcohol exposure.

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