Decreased Magnetic Susceptibility in Mouse Brains with Prenatal Alcohol Exposure

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TARGET AUDIENCE: Anyone interested in Quantitative Susceptibility Mapping (QSM), brain development, and fetal alcohol spectrum disorder (FASD).

PURPOSE:

Fatal alcohol spectrum disorder (FASD) refers to a range of permanent birth defects caused by prenatal alcohol exposure. Prenatal alcohol exposure can result in long-term cognitive and behavioral deficits. Studies by autopsy and conventional structure MRI indicate the midline structures in brain are more vulnerable to prenatal alcohol exposure. Structural MRI and Diffusion tensor imaging (DTI) have shown that abnormalities in brain white matter especially the corpus callosum are very common in FASD. Quantitative susceptibility mapping (QSM) is a novel technique that measures tissue's magnetic property. Magnetic property is affected by tissues' microstructure and molecular composition including demyelination in white matter [1]. This study was designed to assess the impact of prenatal alcohol exposure to mouse brain development using QSM and DTI and demonstrate the efficacy of QSM for assessing FASD.

METHODS:

Two groups of C57BL/6J mice (postnatal day 45) were characterized: an ethanol group (n = 7) and a control group (n = 7). In the ethanol group, pregnant dams were treated with high doses of ethanol on gestational day 7. In the control group, ethanol was replaced with Ringer's solution. The treatment was employed as described in Godin et al [2]. 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. DTI data 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 of both DTI and SPGR. Magnetic susceptibility was obtained using the LSQR method [3]. All native images were spatially registered to a standard-space template [4] with FMRIB's Nonlinear Image Registration Tool (FNIRT) based on the magnitude images (Fig.1). The ROI masks in the template including anterior commissure (AC), corpus callosum (CC), and hippocampal commissure (HC) were extracted using Matlab R2010a and transformed back to the original images including susceptibility images and DTI fractional anisotropy (FA) maps. The FA and susceptibility values in the ROIs were computed using Matlab R2010a. Magnetic susceptibility anisotropy of these three 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].

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

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.2 compared the susceptibility maps between ethanol and control groups in three slices that include AC, CC and HC (arrows). The control mice exhibited higher susceptibility contrast between gray and white matter. In the ethanol group, however, the susceptibility contrast was found significantly reduced in all ROIs. In contrast, Fig.3 showed no significant differences in the FA maps between ethanol and control groups for all three ROIs. As illustrated explicitly in Fig.4, there was a significantly decreased susceptibility contrast between gray and white matter in the ethanol group. Significant differences (P<0.05) were observed in all three ROIs. In contrast, the fractional anisotropy in the ethanol group only slightly decreased compared with the control group (Fig. 5). However, unlike the susceptibility value, FA value showed no significant difference (P>0.05) between the two groups (Table.1). Fig. 6 showed the statistical comparison of the $\Delta\chi_{max}$ between ethanol and control groups in the three ROIs. A significant decrease ($p < 0.05$) in susceptibility anisotropy (i.e. the absolute value of $\Delta\chi_{max}$) was observed for the ethanol group compared to that of the control group in the hippocampal commissure, and no significant differences were observed in other two ROIs (Table.1).

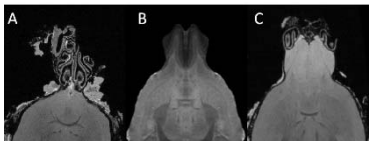

Fig.1. Native images were registered to a template with FNIRT. A. An example of native magnitude image; B. The standard-space template; C. average image (n=7) after registration.

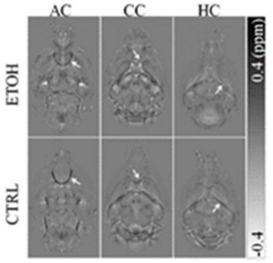

Fig.2. QSM of ROIs in the ethanol group and the control group.

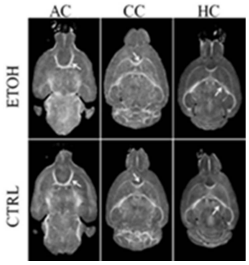

Fig.3. FA maps of ROIs in the ethanol group and the control group.

		AC	CC	HC
Susceptibility (ppm)	ETOH	-0.04±0.01	-0.02±0.01	-0.03±0.01
	CTRL	-0.07±0.02	-0.03±0.01	-0.04±0.02
	P- value	<0.001**	0.03*	0.03*
FA value	ETOH	0.56±0.04	0.52±0.05	0.57±0.04
	CTRL	0.58±0.11	0.53±0.06	0.58±0.06
	P- value	0.3	0.4	0.4
$\Delta\chi_{max}$	ETOH	-0.91±0.56	-0.54±0.29	-0.89±0.47
	CTRL	-1.11±0.84	-0.51±0.28	-1.38±0.48
	P- value	0.3	0.4	0.05*

Table.1The average value of FA and susceptibility and $\Delta\chi_{max}$ of brain regions in the ethanol group and the control group. Note: n=7. **p<0.001; *p≤0.05

DISCUSSION AND CONCLUSION:

In this study, we confirmed that prenatal alcohol exposure can affect brain white matter integrity using QSM. More interestingly, our results demonstrated that QSM is sensitive and effective for detecting brain white matter abnormalities in FASD. These abnormalities mostly likely is due to changes in myelin of the white matter. Magnetic susceptibility reflects the distribution of a number of physiologically important elements in general and myelin specifically in white matter [6]. It is now known that demyelination results in reduced susceptibility contrast in deep white matter. A recent theoretical study suggested that susceptibility anisotropy is linearly proportional to the myelin contents of the white matter. In this study, we found significant reduction of susceptibility in all three ROIs in the ethanol group compared to the control group (P<0.05) and $\Delta\chi_{max}$ deceased significantly in hippocampal commissure. This reduced contrast and anisotropy indicates demyelination in midline white matter caused by prenatal alchohol exposure. It also suggests QSM may be even more sensitive than DTI in examining changes due to prenatal alcohol exposure. To conclude, this work has provided evidences of demyelination within midline deep white matter in FASD. Although this is preclinical study, the technique QSM is readily translatable to human brain.

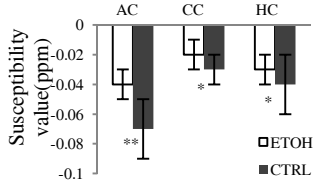

Fig.4 Quantitative comparison between the ethanol group and the control group in susceptibility value (n=7).

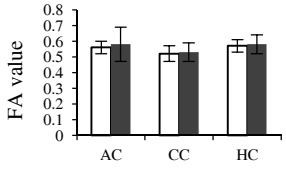

Fig.5 Comparison between the ethanol group and the control group in FA (n=7)

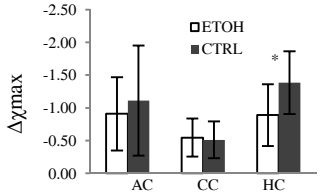

Fig.6 Comparison of $\Delta\chi_{max}$ between the ethanol group and the control group (n=7).

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