Preliminary Evidence of Abnormalities in the Prefrontal Cortex of 10 Weeks Old Ts65Dn Mouse Model of Down Syndrome Using DKI-Cerebral Microenvironment Modeling.

Xingju Nie[1], Edward S Hui[1], Jens H. Jensen[1], Joseph A. Helpern[1,2], Ann-Charlotte E. Granholm-Bentley[2], Heather A. Boger[2], and Maria F Falangola[1,2]

[1]*Radiology and Radiological Science, Center for Biomedical Imaging, Medical University of South Carolina, Charleston, SC, United States,* [2]*Neurosciences, Medical University of South Carolina, Charleston, SC, United States*

TARGET AUDIENCE: For those interested in diffusion MRI and animal models of neurodegeneration.

PURPOSE: Down syndrome (DS) is the most common genetic cause for cognitive impairment in humans. Mouse models of DS have been used to study the morphological abnormalities and the mechanisms underlying DS-associated cognitive disabilities. The Ts65Dn mouse model is widely studied[1], developing neuropathology and cognitive impairment with age similar to that seen in the brain of DS subjects[2,3]. These mice exhibit abnormal development and maturation of the brain, with progressive alterations in the frontal cortex, associated with reduced brain derived neurotrophic factor (BDNF) levels and changes in dendritic structure and abnormal synaptic plasticity[3,4,5]. Despite the fact that these mouse models have been well characterized cognitively and morphologically, little has been published using in vivo neuroimaging[6]. Diffusional kurtosis imaging (DKI) is a diffusion MRI technique that extends diffusion tensor imaging (DTI) by quantifying the non-Gaussian behavior of water diffusion, contributing additional information beyond that provided by DTI[7]. Recently, a cerebral microenvironment modeling (CMM) method has been proposed for relating DKI data to specific tissue characteristics of the entire brain parenchyma. The model, which generalizes a previously proposed method[8], idealizes neural tissue as consisting of two non-exchanging compartments, a non-Gaussian confined- (CC) and Gaussian open- (OC) compartment. The CC represents water confined in neurites (i.e. axons and dendrites) that are idealized as infinitely long, narrow cylinders. The OC represents all other water that yields a detectable signal. The non-Gaussianity of the CC stems from a distribution of neurite orientations. CMM yields several quantitative measure of brain tissue for the characterization of neurite cytoarchitecture. In this study we investigate the morphological abnormalities in the prefrontal cortex of 10 weeks old Ts65Dn mice using CMM.

METHODS: Ten week old male mice, Ts65Dn (TS, n = 8) and normosomic mice (NS, littermates, n = 8) were studied. All in vivo MRI experiments were performed on a 7T Bruker MR system. A 2-shot SE-EPI sequence was used for DKI acquisition. Sequence parameters were: TR/TE=3750/32.6 ms, δ/Δ=5/18 ms, slice thickness=0.6 mm, 15 slices with no gap, data matrix=128×128, image resolution=156×156 μm2, 2 averages, 64 gradient directions and 4 b-values for each gradient direction (0.5, 1, 1.5 and 2 ms/μm^2). Total acquisition time was approximately 65 minutes. Mean kurtosis (MK), axial ($K_{//}$) and radial ($K_{\perp}$) kurtosis, mean (MD), axial ($D_{//}$) and radial ($D_{\perp}$) diffusivity, fractional anisotropy (FA), as well as CMM metrics (density (f), diffusivity (D_{CC}), diffusional kurtosis (K_{CC}) and fractional anisotropy (FA_{CC}) of the CC were derived from the DKI data set using an in-house post-processing software[9]. A region of interest (ROI) at the level of the prefrontal cortex was manually drawn in the b=0 image, using ImageJ (http://rsb.info.nih.gov/). Two-tailed t-test was performed to assess differences in the ROI measurements between the two groups; $p < 0.05$ was considered as statistically significant.

RESULTS: Table 1 shows the group means, standard deviations and p-values for all the diffusion metrics. Among the diffusion metrics, only diffusional kurtosis (K_{CC}) and fractional anisotropy (FA_{CC}) of the confined compartment (CC) showed statistical differences, with increased K_{CC} and decreased FA_{CC} in the prefrontal cortex of the TS mice compared to NS (Figure. 1).

Table 1: Group mean, standard deviation and p-values for the DKI CMM measurements in the prefrontal cortex

Groups	MK	$K_{//}$	$K_{\perp}$	MD	$D_{//}$	$D_{\perp}$	FA	f	D_{CC}	K_{CC}	FA_{CC}
NS	0.58 ± 0.06	0.60 ± 0.04	0.60 ± 0.08	0.75 ± 0.02	0.87 ± 0.02	0.69 ± 0.02	0.18 ± 0.01	0.25 ± 0.02	0.60 ± 0.04	1.82 ± 0.20	0.55 ± 0.09
TS	0.62 ± 0.05	0.63 ± 0.05	0.64 ± 0.05	0.76 ± 0.02	0.88 ± 0.03	0.70 ± 0.02	0.18 ± 0.01	0.26 ± 0.02	0.62 ± 0.04	2.03 ± 0.07	0.46 ± 0.04
t-test (p value)	0.20	0.19	0.15	0.43	0.45	0.45	0.49	0.21	0.36	**0.02**	**0.02**

Diffusivities units: μm^2/ms; f, K_{CC} and FA_{CC}: dimensionless

DISCUSSION & CONCLUSION: The K_{CC} and FA_{CC} changes in the prefrontal cortex of TS mice may represent less coherence in neurite orientations for this region, probably related to morphological changes such as abnormal cortical lamination and dendritic and synaptic abnormalities previously reported in this model[10]. For example, TS mice have significant alterations in both brain shape and volume[11], with an overall smaller brain, thinner cerebral cortex with smaller, less branched and less spinous dendrites as compared to controls[10]. However, the interpretation of the changes in K_{CC} and FA_{CC} can only be inferred here and future morphological correlation studies are necessary. This study is the first application of the new CMM method in an animal model of neurodegeneration, demonstrating that CMM parameters are sensitive indicators of changes in the complexity of the neurite architecture of grey matter, and maybe an early biomarker for abnormal brain development and maturation. We stress that this is a pilot project, and these results should be confirmed in a future study with a larger sample size and using a longitudinal design.

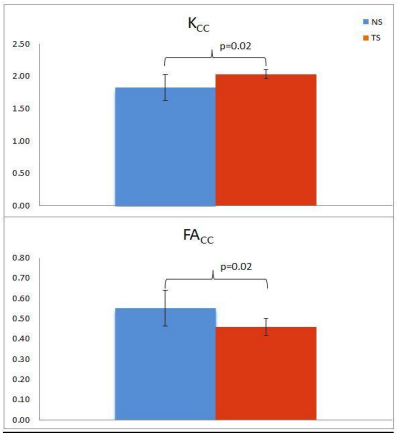

Figure 1: Diffusional kurtosis (K_{CC}) and fractional anisotropy (FA_{CC}) (dimensionless units) of the confined compartment (CC) in the prefrontal cortex of TS and NS mice. Error bars are standard deviation.

REFERENCES: **1**. Davisson, MT, et al. (1990) Prog. Clin. Biol. Res. 360, 263–280; **2.** Sérégaza Z, et al. (2006) Behav Genet. 36(3):387-404; **3.** Hunter CL, et al. (2003) Behav Brain Res. 138(2):121-31; **4.** Bimonte-Nelson HA, et al. (2003) Behav Brain Res.139(1-2):47-57. **5**. Lockrow J, et al. (2009) Exp Neurol 216, 278-289; **6.** Chen Y, et al. (2009) Neurobiol Aging. 30(9):1453-65; **7.** Jensen JH & Helpern JA. (2010) NMR Biomed. 23(7):698-710. **8.** Fieremans et al. (2011) Neuroimage.;58(1):177-188. **9.** Tabesh A, et al. (2011) Magn Reson Med, 65(3):823-36. **10**. Dierssen, M et al. (2003) Cereb Cortex. 13(7):758-64. **11**. Aldridge K et al. (2007)Am J Med Genet A. 143A(10):1060-70.

ACKNOWLEDGMENTS: This study was supported by NIH 5R03EB009711-2 (MFF). The authors would like also to thank the Sie Foundation and a bridge fund from the MUSC College of Medicine.