A Multi-Scale Whole-Brain Optimized Diffusion Tensor Imaging of Dyslexics at 3.0T

K. M. Hasan[1], J. M. Fletcher[2], L. Ewing-Cobbs[3], A. Sankar[1], T. J. Eluvathingal[1], L. A. Kramer[1], M. Ashtari[4], J. Juranek[5], S. Sarkari[5], and A. C. Papanicolaou[5]

[1]Diagnostic and Interventional Imaging, University of Texas Medical School, Houston, Texas, United States, [2]Psychology, University of Houston, Houston, Texas, United States, [3]Pediatrics, UTHSC, Houston, Texas, United States, [4]Psychiatry, University of Minnesota, Minneapolis, Minnesota, United States, [5]Neurosurgery, UTHSC, Houston, Texas, United States

Introduction: Dyslexia is a reading disorder that affects 5-10 % of school-age children **[1]**. Despite numerous neuroimaging investigations in adult and child dyslexic populations, conclusive evidence identifying the underlying neural substrates of dyslexia remains to be elucidated **[2].** Although converging lines of evidence from PET, MEG, MRS functional and anatomical MRI studies have implicated the left hemispheric language circuits in this developmental disorder, a reliable and sensitive surrogate marker of brain structure-function relationships, including structural integrity, has not yet been reported in the current literature for dyslexia **[3-5**]. In this study we adopted an optimized diffusion tensor imaging approach to investigate both macro and microstructural aspects of dyslexia **[6-7].**

Methods: *Subjects*: We included children in the age range 9-15 years. 10 dyslexics patients ($\mu\pm\sigma$= 12.4±1.8 years; 8 males, 2 left-handed) and 16 ($\mu\pm\sigma$ =11.6 ±1.6 years; 9 males, 4 left-handed) healthy pediatric age-matched (p=0.3) were included after subject assent and parental consent**.** *Psychometric and Behavioral Testing*: The behavioral testing focused on several measures of reading skills **[8]** including selected tests from the Woodcock Johnson Achievement Tests – Word Attack and Letter Word ID, a measure of word reading fluency- the Test of Word Reading Efficiency, the Comprehensive Test of Phonological Processing. Children also completed the Edinburgh Handedness Inventory and the Wechsler Abbreviated Scale of Intelligence. Children were referred for a DTI scan if their Basic Reading Skills composite score was under the 20th percentile. *Conventional and DT MRI Acquisition*: Data were using a Philips 3.0 T Intera system using a SENSE receive head coil. The MRI protocol included conventional MRI (dual echo FSE, phase-sensitive, FLAIR & 3D anatomical) in addition to a matching prescription of DT-MRI. The DTI data were acquired using a single-shot spin-echo diffusion sensitized EPI sequence with the balanced *Icosa21* encoding scheme **[9-10],** b=1000 sec mm^{-2}, T_R/T_E = 6100/84 msec. To reduce EPI related image artifacts, we used a SENSE acceleration factor R=2. The slice thickness was 3.0 mm with 44 contiguous axial slices covering the entire brain; FOV=24 cm, k-space acquisition matrix 112x128 and an image matrix after zero-filling of 256x256. The number of b~0 magnitude image averages was 8; in addition each diffusion encoding was repeated twice and magnitude averaged to enhance the signal-to-noise ratio. The total DTI acquisition time was approximately 7 minutes and resulted in SNR-independent DTI-metric reproducible results. *Data Processing and Whole-Brain Tissue Segmentation*: Diffusion-weighted data were distortion corrected using the mutual information maximization approach. All data sets were masked to remove non-brain tissues; the gray matter (GMv), white matter (WMv) and cerebrospinal fluid volumes (CSFv) were extracted using a validated and automated DTI-based segmentation procedure that used a large pool of DTI data acquired on controls **[9].** In addition, the DTI-segmentation method was combined with the Witelson's seven midsagittal corpus callosum subdivisions **[10]** (CC1=rostrum, CC2=genu, CC3=anterior midbody, CC4=midbody, CC5=posterior midbody, CC6=isthmus, CC7=splenium). *ROI Analysis:* The regions-of-interest represented 50 "normally appearing" white and gray matter structures that included the corpus callosum, bilateral caudate, putamen, posterior limb of the internal capsule (plIC), corticospinal tract, and forceps minor and major. The procedure was done by trained raters and used anatomical landmarks from the conventional MRI sets (sagittal phase-sensitive inversion recovery). The ROI placement procedure was supervised by a radiologist and used a sophisticated system that fused DTI maps with conventional MRI **[10].** *Arcuate fasciculus Fiber Tracking*. We have used a brute force and multiple ROI tracking method and the FACT algorithm [**DTIStudio**, **11**] to obtain the DTI metrics from the two segments of the arcuate fasciculus bilaterally [**12,13**].The transverse diffusivity was defined as the mean of the minor and medium eigenvalues. The transverse diffusivity was defined as the mean of the minor (third) and medium (second) eigenvalues (($\lambda_t = (\lambda_2 + \lambda_3)/2$) **[14].** Statistical group comparisons were made using ANOVA. Age and reading score correlations with DTI-derived whole-brain, regional and fiber track DTI-metrics were computed sing the Pearson and Spearman correlation coefficient, respectively.

Results. Figure 1.A summarizes the comparisons between the dyslexic and control groups using DTI-derived whole-brain ICV=WMv+GMv+CSFv=cerebral + cerebellar volumes. Dyslexics in this small population show significantly smaller ICV (p<0.0001), GMv (p<0.0001), WMv (p=0.003), while CSF volume was comparable (p=0.55). The GM and WM to ICV fractions (GMf & WMf) and GM/WM ratio were not significantly different (p>0.4; **Fig 1B**) between the two age-matched groups reflecting scaling effects due to smaller brain size in dyslexics**.** The CC regional midsagittal segments in both groups showed normative area and DTI metric heterogeneity trends (e.g. sCC>gCC) (**Fig. 1.C**). Dyslexics exhibited a trend towards a decrease but did not reach the significance level (p>0.1). **Fig. 1.D** shows that the DTI related metrics in the CC regions (gCC-sCC & entire CC) indicate a trend and significant decrease in anisotropy commensurate with an increase in transverse diffusivity (**Fig. 1.D). Figure 2.a** shows that FA is reduced in posterior and anterior regions of the frontal lobe that are connected through the forceps minor and reduced anisotropy in the plIC (p<0.001)**. Fig. 2.b** shows that the reading (Word-Attack) scores in dyslexics correlated positively with the mean FA in the forceps minor fibers traversing the frontal lobe through the CC (r=0.64, p=0.04). **Fig 2.c** shows that Word-Attack scores correlated positively with the mean FA in the entire CC (r=0.66; p=0.04), while the Letter Word ID % score correlated with mean FA of the left arcuate fasciculus (AF) with a stronger trend in the fronto-temporal segment (r=0.68; p=0.03). **Discussion and Conclusions:** This is the first non-invasive report to document macro and micostructural tissue organization in the brain of dyslexics using the same entire brain data set collected using optimized high-SNR, high spatial and angular resolutions at 3.0 T under 7 minutes. The findings of reduced WMv, GMv, ICV and invariant parenchymal volume to ICV fractions are concordant with previous reports **[3-5].** The callosal areas transverse diffusivities are elevated in dyslexics reflecting possibly delayed, poor or arrested myelination **[14]**. Our DTI-based tracking observations are consistent with previous voxel based morphometry (VBM) results. Our ROI results on the pLIC may be consistent with similar early DTI reports using VBM **[6,15,16].** However, we could not detect significant correlation of reading scores with DTI-derived metrics of the pLIC. In conclusion, these preliminary results indicate that a multi-scale DTI-derived whole-brain, ROI and track metrics offer important surrogates to the understanding of the neuronal substrates of dyslexia.

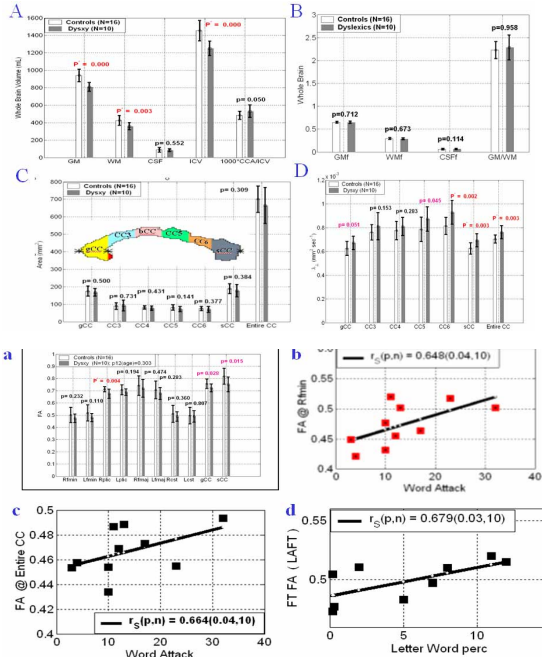

Fig. 1(A,B,C,D upper) and **Fig. 2 (a,b,c,d)** summarize the multi-scale DTI results (group comparisons and correlations)

References

[1] Shaywitz SE. Dyslexia. N Engl J Med. 1998;338(5):307-12. **[2]** Eckert M. The Neuroscientist. 2004;10(4):362-71.
[3] Schultz et al**.** Ann Neurol. 1994;35:732-42**. [4]** Casanova et al. Child. Neurol. 2004;19(4):275-81. **[5]** Eliez et al. 2000;41:637-44**.**
[6] Klingberg et al. Neuron 25:493-500. **[7]** Moseley et al. 2002;50:396-413. **[8]** Torgesen JK, Wagner RK, Rashotte CA. *Test of Word Reading Efficiency.* Austin TX: Pro- Ed, 1999. **[9]** Hasan KM et al. JMRI. 2005;21:735-43. **[10]** Hasan et al. Neuroimage 2007 (***in press***). **[11]** Xu *et al***.** Neuroimage.2002;17:1131-43**.**
[12] Jiang et al. Comput Methods Programs Biomed. 2006;81:106-16. **[13]** Catani M and ffytche DH. Brain 128; 2224-39**.**
[14] Song et al. Neuroimage 2005; 15;26:132-40. **[15]** Beaulieu et al. Neuroimage 2005;25:1266-71.**[16]** Deutsch et al. 2005.Cortex.2005;41:354-63.