Comprehensive Autoregional DTI and MTR of Asymptomatic HIV Brain

Ying Wu[1,2], Ryan Hutten[1], Yi Gao[3], Hongyan Du[3], Nadia Abbasi[1], Robert R. Edelman[1,4], and Ann Ragin[4]

[1]*Department of Radiology, NorthShore University HealthSystem, Evanston, IL, United States,* [2]*Department of Radiology, The University of Chicago Pritzker School of Medicine, Chicago, IL, United States,* [3]*Center for Clinical and Research Informatics (CCRI), NorthShore University HealthSystem, Evanston, IL, United States,* [4]*Department of Radiology, Northwestern University Feinberg School of Medicine, Chicago, IL, United States*

INTRODUCTION: Many neurological disorders are characterized by ongoing neuropathological changes that remain clinically silent for decades. More sensitive methods for detecting early, preclinical alterations would benefit interventions to slow or reverse neural injury. Magnetization Transfer (**MT**) and Diffusion Tensor Imaging (**DTI**) can be used to quantify in vivo changes in brain tissue at microscopic and macromolecular levels (*Dousset et al. 1992 and Basser et al. 1996*). However, these methods require labor-intensive, operator-dependent manual sampling to evaluate changes in regions of interest (**ROIs**). This introduces various sources of error, compromising feasibility and sensitivity for neurological studies. To overcome these limitations, we developed a fully automated, "autoregional" framework for deriving DTI and MT parameters in 3D neuroanatomic structures of interest (*Wu et al. 2010- 2012*, *Sidharthan et al. 2012 and Hutten et al. 2011*). To evaluate utility in a clinical population, the autoregional strategy was used to evaluate subjects in the Chicago early HIV infection cohort study. Brain involvement is a serious complication of HIV infection, characterized by early CNS viral invasion with indolent, asymptomatic progression that may extend decades in some patients. Therefore this cohort is ideally suited to test the sensitivity of the autoregional strategy for detecting neuropathological changes in early stages of brain injury.

METHODS AND MATERIALS: 52 HIV (46 Males, 6 Females; mean age: 33.2 ± 9.9) and 21 seronegative (16 Males, 5 Females; mean age: 31.4 ± 8.8) subjects (Table 1) were scanned using a 3 Tesla Siemens system (Siemens Verio, Germany). ***Image Aquisition:*** **1) Isotropic High Resolution MT:** obtained with a 3D FLASH sequence (TR/TE/FA= 43ms/5ms/10°, resolution = 1.0 x1.0 x1.0 mm^3). With and wthout MT saturation pulse 16 ms/ FA 20° and 1200 Hz offset from water resonance was applied. **2) DTI:** 2D SE-EPI-DTI with a b=0 reference image and 64 diffusion-weighted images has a b-value of 1000 sec/mm² were acquired (TR= 9600ms, resolution = 2.0×2.0×2.0 mm^3), bandwidth ±1325 Hz. **3) MP-RAGE T1-weighted Images:** ADNI protocol (TR/TE/TI/FA=2300ms/2.91ms/900ms/9°, resolution=1.0 x 1.0 x 1.2mm3). ***Image Analysis:*** **1) Parametric Maps:** on a Linux workstation, Magnetization transfer ratio (**MTR**) maps were constructed using custom software according to the standard equation as $(M_0-M_{SAT})/M_0$. M_{SAT} and M_0 represent voxel signal intensity with and without MT, respectively. Parametric maps of fractional anisotropy (**FA**) and mean diffusivity (**MD**) were derived using FDT (FMRIB's Diffusion Toolbox). **2) Autoregional Quantification:** DTI and MTR parametric maps were coregistered to the T1 structural image. Automated segmentation was performed on this structural scan using FreeSurfer (*Fischl et al. 2002*) for masking 3D volume of interests (**VOIs**) and used to extract mean regional MTR, FA, MD values (see Fig. 1). The VOIs used in this study include: corpus callosum, caudate, cerebral cortex, cerebral white matter, hippocampus, putamen and thalamus. For comparison, manual region of interest were conducted in the studied regions. ***Statistical Analysis:*** Group comparisons of the autoregional brain measurements, which were continuous variables, were accomplished with independent t-tests, executed with SAS (Cary, NC).

RESULTS: As shown in Table 2, significant FA reductions were identified in cerebral white matter and corpus callosum (CC); MD was significantly increased in CC in the early HIV cohort. A similar pattern was identified with MTR, with reductions in aggregate cerebral white matter, cerebral cortex and CC. No group differences were identified for caudate, putamen or thalamus with either DTI or MT.

Table 1. Chicago Early HIV Infection Cohort

Demographics	HIV n = 52	Controls n = 21	p
Age (mean years ± sd)	33.2 ± 9.9	31.4 ± 8.8	0.47
Gender (% Male)	88%	76%	0.25
Race (% White)	63%	76%	0.22
Education (% College)	75%	89%	0.07
NART-R (estimated. IQ)	106.6 ± 9.9	111.2 ± 8.6	0.07
Clinical Characteristics of the HIV Group			
Antiretroviral Therapy (% Naïve)	52%		
CD4 cell count cells/μL	548 ± 35.3		
Plasma HIV RNA (log_{10} copies/mL)	3.19 ± 0.21		

NART-R: North American Adult Reading Test

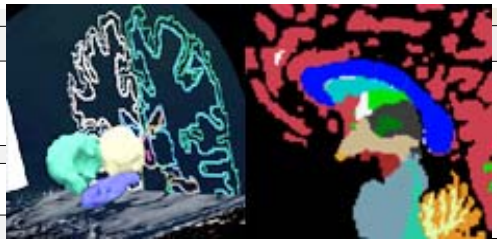

Fig. 1 the autoregional masks(color) and MTR map (grayscale)

Table 2. Autoregional Analysis of DTI and MTR Alterations

	HIV n=52	Control n=21	p	ES
Fractional Anisotropy				
Corpus Callosum	0.66 ± 0.04	0.69 ± 0.02	0.001	-0.73
Cerebral White Matter	0.45 ± 0.02	0.46 ± 0.01	0.058	-0.50
Mean Diffusivity ($x10^{-5}$)				
Corpus Callosum	84.5 ± 4.0	82.5 ± 4.1	0.054	0.50
Magnetization Transfer Ratio				
Corpus Callosum	44.35 ± 1.96	45.34 ± 1.12	0.001	-0.56
Cerebral Cortex	33.64 ± 1.54	34.15 ± 0.78	0.069	-0.38
Cerebral White Matter	41.84 ± 1.84	42.90 ± 1.00	0.003	-0.65

DISCUSSION: The autoregional framework detected both white and gray matter alterations early in HIV infection. Importantly, corpus collosum (CC) abnormalities were identified with all three MR parameters (FA, MD, MTR). Autopsy e.g. (*Wohlschlaeger et al.2009*) and in vivo imaging studies of advanced infection e.g. (*Wu, Storey et al. 2006; Wu et al. 2008*) have found callosal injury in HIV infection. With the autoregional strategy, early changes in CC were identified in a cohort infected less than one year. DTI and MT measurements derived with manual placement of small 2D ROIs were not sensitive to these changes (data not shown). Measurements derived with the fully automated autoregional approach overcome the limitations of manual ROI placement. These measurements are not biased by operator introduced variability. The autoregional strategy also affords more comprehensive measurement of 3D volumes for structures of interest and it is possible to standardize measurements across quantitative MR methods, for example, to define identical volumes for DTI and MT measurements, across settings (for multi-center studies) and across time, which is invaluable for large sample, longitudinal and comparative effectiveness studies. Quantitative DTI and MTR parameters are particularly sensitive to changes in myelination and axonal organization and may represent promising, noninvasive biomarkers for detecting preclinical brain changes (*Wu et al 2006, Wu et al 2008*).The availability of more sensitive quantitative imaging methods for detecting early alterations in the brain has considerable potential to improve neurological outcome in many CNS disorders.

REFERENCES:

{Basser PJ et al.. *JMRI* 1996} {Dousset V et al. *Radiology* 1992} {Fischl B. *Neuron* 2002} {Hutten R et al. *ismrm* 2011} {Sidharthan S et al. *J Neuroimaging* 2012 } {WohlschlaegerJ et al. Epub 2009}{Wu Y et al. *JMRI* 2010} {Wu Y et al. *JMRI* 2012} {Wu Y et al. *AJNR* 2008} {Wu Y et al. *AJNR* 2006}