3D proton MR spectroscopy of normal-appearing brain in Tuberous Sclerosis Complex

I. Kirov[1], S. Milla[1], J. Oved[2], O. Devinsky[3], H. Weiner[3], and O. Gonen[1]
[1]Radiology, New York University, New York, NY, United States, [2]School of Medicine, New York University, New York, United States, [3]Neurosurgery, New York University, New York, NY, United States

INTRODUCTION: Tuberous Sclerosis Complex (TSC) is a genetic disorder which leads to benign tumors (tubers) in multiple organ systems, including the brain. Approximately 90% of patients suffer from seizures, mostly starting before the age of 2 years. In cases of refractory epilepsy, electro-encephalography (EEG) is used to localize the onset region, which is then surgically removed. Traditionally, tubers are thought to comprise the main seizure loci, but some seizures may originate beyond the tuber's border[1]. Explicit evidence for this is a cohort of epileptic TSC patients with normal conventional MRI. These patients are often not considered surgical candidates and suffer the devastating sequelae of a lifetime of seizures. Non-conventional MR imaging in these patients may be a potential tool to identify abnormal brain tissue and guide the electrophysiologist/neurosurgeon to a suspected epileptogenic region. In this study, we used three-dimensional proton MR spectroscopy (^{1}H-MRS) in TSC-normal-appearing tissue to assess neuronal health, membrane turnover and glial status via their metabolic surrogates *N*-acetylaspartate (NAA), choline (Cho), creatine (Cr) and *myo*-inositol (mI).

METHODS: Twelve TSC patients (10 children, age range 2-10 years and 2 adults, age range 18-42) are currently enrolled. Recruitment is ongoing. If referred for surgery, each patient underwent a standard comprehensive pre-surgical evaluation, which included history and physical examination, video EEG monitoring, MRI scanning, and neuropsychological testing. The study was IRB-approved, and informed consent was signed by the patients and parents; assent was obtained from the children where applicable. Scans requiring anesthesia were done on a Siemens 1.5 T and all others on a Siemens 3 T. The $10_{AP}\times8_{LR}\times6_{IS}$ = 480 cc ^{1}H-MRS volume-of-interest (VOI) (**Figure 1**) was centered on the corpus callosum and excited with *TE*/*TR* = 26/1800 ms PRESS in 3 sequentially-acquired slabs each with 2nd order Hadamard-encoding in the IS direction[2]. The $16_{AP}\times16_{LR}\times 6_{IS}$ cm^3 field-of-view containing the VOI was partitioned into $1.0_{AP}\times1.0_{LR}\times 1.0_{IS}$ = 1 cm^3 voxels with $16_{AP}\times16_{LR}$ 2D chemical-shift imaging matrix, yielding 480 nominal voxels. Both region-of-interest (ROI) (**Figure 1**) and global analysis (**Figure 2**) was performed. The latter was done by frequency aligning and then summing all spectra inside the VOI to yield one global spectrum per subject[3]. This resulted in superior spectral resolution in comparison to a *single* large voxel, owing to better B_0 homogeneity across small voxels which is preserved in the sum. Metabolite signals were fitted with the SITools package[4] and absolute concentrations were obtained using phantom replacement, incorporating corrections for T_1 and T_2 differences between *in vivo* and *in vitro*.

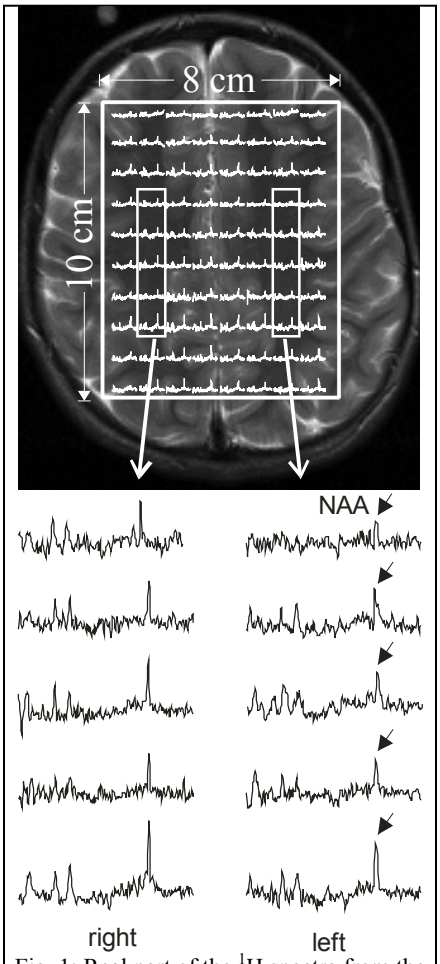
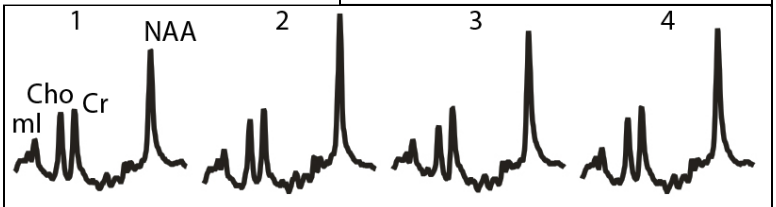


Fig. 1: Real part of the ^{1}H spectra from the right and left normal-appearing centrum semiovale. Low NAA levels (arrows) are noted in the left tract.

RESULTS: Three of the twelve patients presented with epileptic activity in the absence of MRI-defined tubers. In one case (6 year old girl) ^{1}H-MRS showed metabolic differences between the left and right hemispheres: compared to the contralateral tract, NAA levels were lower in the left centrum semiovale (**Figure 1**). Global ^{1}H-MRS of an adult tuber-free patient showed decreased NAA and increased Cho and mI compared to 3 age- and gender-matched controls (**Figure 2**).

CONCLUSION: The utility of ^{1}H-MRS to identify abnormalities in normal-appearing TSC brain is demonstrated. We hypothesize that the metabolic hemispheric differences stem from (*i*) intrinsic biochemical imbalance of the white matter itself; and/or (*ii*) abnormal cortical tissue in the compromised hemisphere whose axons comprise the centrum semiovale. The global NAA deficits in the adult patient suggest diffuse neuronal dysfunction throughout the VOI. Increased Cho and mI imply glial abnormalities such as astrogliosis and myelin breakdown.



Patient: 43F	*Control: 37F*	*Control: 38F*	*Control: 44F*
African-American	*African-American*	*Caucasian*	*Asian*
NAA: 7.3 mM	NAA: 9.2	NAA: 7.4	NAA: 9.0
Cr: 5.9 mM	Cr: 5.6	Cr: 4.9	Cr: 6.6
Cho:1.51 mM	Cho:1.2	Cho: 1.0	Cho: 1.47
mI: 4.1 mM	mI: 3.4	mI: 3.6	mI: 3.9

Fig. 2 Top: Real part of the summed ^{1}H spectra for the patient (#1) and her matched controls (#2-4). Bottom: Subject demographics and metabolic concentrations in millimoles (mM). Bold signifies values larger or lower than all the controls'.

REFERENCES: **1**. Bollo *et al*. Neurosurg. Focus 2008. **2**. Gonen *et al.* MRM 1998 **3**. Kirov *et al.* JNNP 2009 **4**. Soher *et al.* MRM 1998