Longitudinal Changes in Diffusion Properties in the White Matter Pathways in Patients with Tuberous Sclerosis Complex

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TARGET AUDIENCE: Neuroradiologists and neuroscientists interested in brain development and pathology of tuberous sclerosis complex.

PURPOSE: Tuberous sclerosis complex (TSC) is a multisystem congenital disorder often linked to one of two genetic mutations. Neuropathological findings include subependymal nodules, subependymal giant cell astrocytomas, cortical tubers, and changes in the white matter adjacent to the tubers. Clinically, many patients with TSC have disabling neurologic conditions, including epilepsy, mental retardation or autism (Crino et al., 2006). To date, two studies that have looked at diffusion characteristics of entire white matter tracts in TSC patients, the geniculocalcarine tract (Krishnan et al., 2010) and the corpus callosum (Peters et al., 2012) and no studies that have looked at evolution of diffusion properties in white matter pathways in individual TSC subjects over time. Given that multiple factors are involved in the TSC pathology and the relationships among the factors in the TSC pathology is still under debate, cross-sectional studies can miss important predictors for TSC progression. The goal of this study was to provide exploratory data on the relationship between common pathologies in TSC and pattern of longitudinal diffusion changes in projection, association and commissural fibers using diffusion tractography.

METHODS

Table 1: Demographic Data

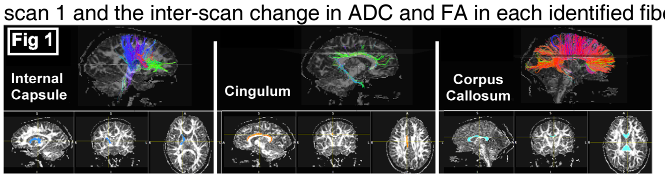
Age	1st Scan: 2.0-17.5yr	2nd Scan: 3.0-18.6yr
Gender	Male: 10 (58.8%)	Female: 7 (41.2%)
Seizure Disorder	Yes: 10 (58.8%)	No: 7 (41.2%)
Autism	Yes: 5 (29.4%)	No: 13 (70.6%)

***<u>Imaging</u>*:** We performed T1-weighted MPRAGE imaging and a 3D diffusion-weighted spin-echo echo-planar imaging. Thirty diffusion-weighted (b = 1,000 sec/mm2) and five non diffusion-weighted (b = 0 sec/mm2) measurements were acquired at a 3T Siemens MR system with TR/ TE = 10 sec/88 msec; ∂/Δ= 12.0/24.2 ms; field of view = 22 cm; spatial resolution 2x2x2mm, iPAT= 2. Characteristics of the patient population are shown in **Table 1**.

<u>Diffusion Data Reconstruction for Tractography:</u>

Diffusion Toolkit and TrackVis (http://trackvis.org) were used to reconstruct and visualize tractography pathways. We used a HARDI reconstruction algorithm (Tuch et al., 2003) with a streamline approach (Mori et al., 1999). Trajectories were propagated by consistently pursuing the orientation vector of least curvature. We terminated tracking when the angle between two consecutive orientation vectors was greater than the given threshold (45°). The color-coding of tractography pathways is based on a standard RGB code applied to the vector between the end-points of each fiber.

***<u>Tract Delineation</u>*:** A coordinate-based tractography atlas (Catani & Thiebaut de Schotten, 2008) was used to guide ROI placement in order to delineate the internal capsule/corona radiata, the cingulum, and the corpus callosum on the MRI datasets for each subjects at first scan (**Fig 1**). These ROIs were then co-registered using FLIRT to each subject's second scan. We identified and calculated the apparent diffusion coefficient (ADC) and the mean fractional anisotropy (FA) for the right and left internal capsule (RIC/LIC), right and left cingulum (RCing/LCing) and the corpus callosum (CC). We investigated changes in these measurements over time for each subject as well as for the group as a whole. The outcomes included ADC and FA at scan 1 and the inter-scan change in ADC and FA in each identified fiber pathway.



***<u>Statistical Analysis</u>*:**

We used IBM SPSS Statistics software (version 19, SPSS Inc., Chicago, IL) for all statistical analysis. All p-values were 2-sided and significance was set at $p \leq 0.05$. The Shapiro-Wilk test of normality was performed on all variables.

RESULTS and DISCUSSION

Table 2: Correlation of Mean ADC and Mean FA at Scans 1 & 2 and Inter-Scan Change with Age at Scan 1

		ADC		FA	
		Pearson Correlation	p-value	Pearson Correlation	p-value
Right Internal Capsule	Scan 1	-0.624	**0.007**	0.480	**0.051**
	Scan 2	-0.534	**0.019**	0.486	**0.035**
	Inter-scan Change	0.458	0.064	-0.112	0.659
Left Internal Capsule	Scan 1	-0.557	**0.020**	0.472	**0.056**
	Scan 2	-0.490	**0.033**	0.582	**0.009**
	Inter-scan Change	0.1	0.701	-0.032	0.904
Right Cingulum	Scan 1	-0.473	**0.055**	0.447	0.072
	Scan 2	-0.282	0.273	0.498	**0.048**
	Inter-scan Change	0.423	0.091	-0.076	0.770
Left Cingulum	Scan 1	-0.505	**0.039**	0.534	**0.027**
	Scan 2	-0.451	0.069	0.542	**0.025**
	Inter-scan Change	0.012	0.963	-0.201	0.439
Corpus Callosum	Scan 1	-0.343	0.178	0.258	0.317
	Scan 2	-0.143	0.585	0.224	0.387
	Inter-scan Change	0.447	0.072	-0.128	0.623

Table 3: Simple Linear Regression for Predictors of ADC & FA at Scan 1

		ADC		FA	
		β value	p-value	β value	p-value
RIC	Age	-0.624	**0.007**	0.480	**0.051**
	Seizure	0.408	0.104	-0.243	0.348
	Autism	0.447	0.072	-0.249	0.335
LIC	Age	-0.557	**0.020**	0.472	**0.056**
	Seizure	0.212	0.413	-0.226	0.383
	Autism	0.366	0.148	-0.287	0.264
RCing	Age	-0.473	**0.055**	0.447	0.072
	Seizure	0.294	0.252	-0.455	0.067
	Autism	0.271	0.292	-0.404	0.108
LCing	Age	-0.505	**0.039**	0.534	**0.027**
	Seizure	0.420	0.093	-0.398	0.114
	Autism	0.186	0.474	-0.277	0.282
CC	Age	-0.145	0.578	0.258	0.317
	Seizure	0.417	0.096	-0.233	0.368
	Autism	0.481	**0.050**	-0.416	0.096

The 4 independent variables tested were (a) Age at scan 1; (b) gender; (c) history of seizures; and (d) diagnosis of ASD. The significant results are highlighted above.

Table 4: Multiple Linear Regression Model Predicting Mean Change in ADC or FA between Scan 1 and 2

		ADC		FA	
		β value	p-value	β value	p-value
RIC	Seizure	0.135	0.525	-0.072	0.739
	Gender	-0.284	0.130	0.130	0.536
LIC	Seizure	0.498	**0.022**	-0.295	0.153
	Gender	-0.516	**0.014**	0.337	0.092
RCing	Seizure	0.239	0.353	-0.380	0.109
	Gender	-0.472	**0.042**	0.327	0.122
LCing	Seizure	0.318	0.277	-0.309	0.179
	Gender	-0.706	**0.002**	0.064	0.769
CC	Seizure	0.156	0.520	-0.301	0.138
	Gender	-0.414	**0.048**	0.523	**0.003**

For each white matter structure, the 4 independent variables tested were (a) Age at scan 1; (b) gender; (c) history of seizures; and (d) diagnosis of ASD while accounting for mean ADC/FA at Scan 1. Of note, for the following: RIC ADC & FA, LIC FA, RCing ADC & FA, and CC ADC & FA, the mean ADC or FA value at scan 1 was a significant predictor of the mean change in ADC or FA respectively. Of note, separate models were run accounting for time elapsed between scans, but this was never a significant predictor of mean change in ADC or FA so the variable was removed from the model.

<u>Age:</u> Our results showed moderately negative correlations between age and ADC and moderately positive correlations between age and FA in the IC and Cing, not all of which reached statistical significance. There was no correlations between age and ADC or FA in the CC. This result is consistent with general trends seen in diffusion characteristics during childhood (Moon et al., 2011). Moreover, simple linear regression showed that age is a significant predictor of ADC and FA in the RIC and LCing and of ADC but not FA in the LIC, with a trend toward significance in the Rcing. There was no correlation of age with FA or ADC n the CC. These findings suggest that the pattern of white matter maturation is similar in TSC patients as in the normal population.

Moderately positive but non-significant correlations emerged between age and mean inter-scan changes in ADC for the RIC, RCing, and CC but not for left-sided structures. This suggested a preference in changes of the microstucture, reflected by changes in ADC/FA, in right-sided structures in this population.

<u>Gender:</u> Males had a significantly lower inter-scan change in ADC in the LIC and L Cing than females, and a significantly greater inter-scan change in FA of the CC than females. Gender emerged as a significant predictor for ADC and FA in the CC, and for ADC in the LIC, R Cing and LCing, controlling for baseline scan values.

<u>Autism (ASD):</u> A significant difference between patients with and without a diagnosis of ASD was observed for the ADC value of the CC at Scan 1. Simple linear regression analyses showed ASD was a significant predictor for ADC in the CC. These CC findings are consistent with those of Peters et al. (2012), but it is interesting that the effects of ASD on ADC and FA were observed in the other white matter tracts. This finding suggests a stronger link between ASD and TSC-related microstructural changes in the CC than in other structures.

<u>Seizures:</u> A significant difference between patients with and without a history of seizure was observed at Scan 2 for the ADC values of the LIC, CC, and L Cing and the FA values of the R&LCing. Seizure history emerged as a significant predictor of the LIC ADC adjusting for baseline ADC at scan 1.