

## Whole brain connectivity analysis using resting state functional MRI in pediatric TSC patients

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**Introduction:** Tuberous Sclerosis Complex (TSC) is a neurologic disorder with symptoms of epilepsy and neurological developmental delay [1]. In several studies abnormalities in white matter of TSC patients including myelination in white matter tracts have been reported [2]. However, there is limited knowledge about functional and structural connectivity in pediatric TSC patients. In this study we have used complex graph measures to investigate the impact of TSC on whole brain functional connectivity using resting state functional MRI (rsfMRI).

### Materials and Methods:

Structural MRI and rsfMRI was carried out in 22 subjects with TSC (age range 3 – 24 years, mean age 11.4), and in 18 age-matched controls on a 3T Siemens scanner. For rsfMRI, EPI sequences with TR ranging from 2400 ms to 3000 ms were used. T1-weighted MPRAGE images of each subject were automatically segmented by label fusion into 128 cortical/sub-cortical structures using IBSR datasets [3]. A series of pre-processing steps was applied to the rsfMRI data of each subject. Head motion was corrected by rigid registration of each volume to the average of all volumes, and each motion corrected volume was spatially smoothed using a 8-mm full-width half-maximum (FWHM) Gaussian kernel.

T1-weighted images and their segmentation were registered to the average of the head motion corrected rsfMRI images. Using a regression model, linear and quadratic trends, the averaged signal over the whole brain, the averaged signal over the ventricles, and the averaged signal over the deep white matter were removed [4]. Finally, the time series were band pass filtered by retaining frequencies between 0.01-0.08Hz. For each one of  $N = 114$  cortical/sub-cortical grey matter structures, the average pre-processed time signal was utilized to construct a weighted connectivity graph for each subject based on Pearson's correlation.

In this graph  $s_{ij}$  shows the correlation between regions  $i$  and  $j$ . After construction of the connectivity graph, the correlations were rescaled using

$w_{ij} = \frac{1+s_{ij}}{2}$  to assure that  $0 \leq w_{ij} \leq 1$  [5]. Finally, a series of complex network measures was used to analyze the functional connectivity networks in

TSC patients and controls. The measures were: 1- Total connection strength:  $K = \frac{1}{N} \sum_{i,j} w_{ij}$ , 2- Overall weighted clustering-coefficient:

$$C = \frac{1}{N} \sum_i \frac{\sum_{j,h} (w_{ij} w_{ih} w_{jh})^{\frac{1}{3}}}{(\sum_j w_{ij})(\sum_j w_{ij} - 1)}, \text{ 3- Overall weighted transitivity: } T = \frac{\sum_{i,j,h} (w_{ij} w_{ih} w_{jh})^{\frac{1}{3}}}{\sum_i (\sum_j w_{ij})(\sum_j w_{ij} - 1)} [6].$$

**Results:** Figure 1.(a) shows parcellation and segmentation of an axial slice through the brain based on 114 cortical and sub-cortical grey matter structures, and Figure 1.(b) shows the rescaled connectivity matrix of the same dataset. We performed a group difference analysis using Welch's t-test and a permutation test for each one of the complex network measures  $K, C$ , and  $T$ . For the permutation test and for each one of the measures, we have used 10000 random permutations and counted the number of cases that the difference of measures between two randomly generated groups is larger than the difference between controls and TSC patients. Table 1 shows the statistical analysis results using both Welch's t-test and the permutation test for 3 different measures.

**Table 1.** Statistical group difference analysis showing p-values for three different complex network measures using both t-test and permutation test.

	t-test	permutation test
Total connection strength	0.0606	0.0613
Overall weighted clustering-coefficient	<b>0.0202</b>	<b>0.0175</b>
Overall weighted transitivity	<b>0.0126</b>	<b>0.0111</b>

**Discussion and Conclusion:** We have performed resting state functional connectivity group analysis of pediatric TSC patients and controls. The statistical analysis using both t-test and permutation test shows a significant difference between network segregation. Both of the complex network measures show reduced long range functional connectivity in TSC patients compared to normal controls. This finding is consistent with previously reported observations of deficits in major white matter tracts in tuberous sclerosis [7].

### Bibliography:

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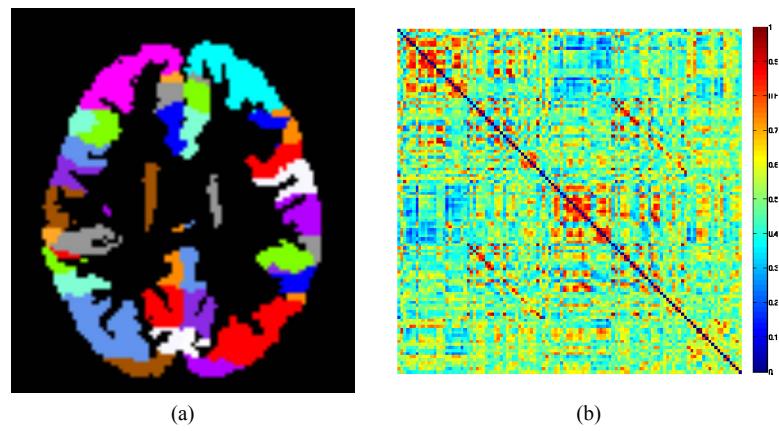


Figure 1.(a) shows parcellation and segmentation of an axial slice based on 114 cortical and sub-cortical grey matter structures and Figure 1.(b) shows the rescaled connectivity matrix of the same dataset.