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ESTIMATING FUNCTION FROM STRUCTURE IN EPILEPTICS USING GRAPH DIFFUSION MODEL

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ABSTRACT

The relationship between anatomic and resting state functional connectivity (FC) of large-scale brain networks has been of interest and has been investigated in a number of articles. In a recent article we introduced a graph diffusion model which predicts the functional network from the structural network in healthy brains. In this work we apply the graph diffusion model to two types of epilepsy, medial temporal sclerosis epilepsy (TLE-MTS), and MRI-normal temporal lobe epilepsy (TLE-no). We show that it is possible to estimate function from structure in non-healthy brains. We conclude that TLE-MTS on average requires a higher graph diffusion depth to estimate FC than both the healthy or the TLE-no groups. This suggests that an overly strong FC/SC relationship might be a sign of poor brain condition.

Index Terms— epilepsy, graph diffusion, networks, functional network, structural network

1. INTRODUCTION

Epilepsy is one of the most prevalent neurological disorders. The estimated prevalence of epilepsy is 7.1 for every per 1,000 are epileptic people [1]. The most common types of temporal lobe epilepsy (TLE) are medial temporal sclerosis epilepsy (TLE-MTS) and MRI-normal temporal lobe epilepsy (TLE-no). TLE-MTS is specified by its stereotyped focus and pattern of neuronal damage, characterized by a pattern of neuronal loss in the hippocampus and an electro-clinical syndrome. TLE-no has normal-appearing hippocampus on MRI and its epileptogenic area in the temporal lobe is more widespread, and less well defined, often including both hippocampus and neocortical regions. In both types neuronal loss spreads appear to follow white matter connections [2] which are the basis of structural connectivity brain networks. Epilepsy is known to be highly network-dependent [3, 4]. In [5] it is shown that local hubs in epileptic brains increases the likelihood of developing hyperexcitability. Epilepsy is known to alter the functional network, but it is an open question as to whether function/structure relationship in epileptics is altered relative to healthy brains.

A number of publications have revealed a tight relationship between the structural network and the resting-state functional network [6, 7, 8]. Recently models estimating the cortical resting state functional connectivity (FC) given the corresponding structural connectivity (SC) network obtained from a subject's DTI have been proposed. Linear [9] and non-linear [10] models have been introduced, with the latter showing improved estimates at the expense of a more complex model which is computationally costlier to implement.

A recent work proposes a simple first order model for estimating FC from SC via graph theory [11], where it was shown that healthy brains' FC were accurately estimated. The model exploits the fact that brain networks with relatively few nodes exhibit linear ensemble average. Briefly, we model the FC network as a graph diffusion in a symmetric normalized Laplacian matrix of SC when all of the nodes are seeded. The extent of the graph diffusion, e.g. how far in the network a seed spreads, is determined experimentally.

In this work we explore the utility of the graph diffusion model for predicting FC from SC in the cases TLE-MTS and TLE-no. The behavior of graph diffusion as a model of FC is stereotyped: its agreement with measured FC first rises and more activity diffuses into the network given by SC, peaks at diffusion depth t_{max}, and eventually falls off as all nodes become uniformly diffused (as shown in Fig 3(a-c)). For all subjects, healthy and epileptic, we predict the FC matrix given its SC matrix. We evaluate the model's accuracy for a given subject by computing the Pearson correlation R between the model-obtained network and the true FC obtained from the subject's resting-state fMRI. We conclude that on average the subjects with TLE-MTS tend to have a higher diffusion depth as well as, interestingly, a higher R between the FC and its graph diffusion estimate. TLE-no shows no distinct patterns from the healthy group. The results advance counter-intuitive effect of epilepsy on the relationship between function and structure, suggesting that network disruption in epilepsy might in fact strengthen the FC/SC relationship. To our knowledge, no previous work has attempted to obtain FC from SC in non-healthy brains.

2. METHODS

2.1. MR imaging and preprocessing

24 healthy, 9 TLE-MTS, and 16 TLE-no subjects were recruited. Subjects underwent scanning on a Siemens Allegra 3T scanner at New York University Center for Brain Imaging. All participants had a T1-weighted MRI sequence optimized for gray-white matter contrast. (TR = 2530 ms, TE = 3.25 ms, T1 = 1100 ms, flip angle = 7 deg, field of view (FOV) = 256 mm, matrix = $256 \times 256 \times 192$, voxel size = $1 \times 1.33 \times 1.33$ mm). Images were corrected for non-linear warping caused by non-uniform fields created by the gradient coils. Resting state fMRI scans included 197 contiguous echo planar imaging functional volumes for each subject (TR = 2000 ms; TE = 25 ms; flip angle = 90, 39 slices, matrix = 64×64; FOV = 192 mm; acquisition voxel size = $3 \times 3 \times 3$ mm). All participants were instructed to lie as still as possible with their eyes open for the duration of the 6 min, 38 seconds scan.

All fMRI data were preprocessed using DPARSF*A* version 2.1 [12]. The first seven time points for each subject were discarded. Standard steps in fMRI preprocessing were followed, including head motion correction, normalization across the subjects, smoothing, linear trend removal, bandpass filtering (0.01 to 0.08 Hz), and finally nuisance covariates removal, including global mean signal, cere-

brospinal fluid, and white matter signals. The time series of all voxels were averaged to 90 regions for each subject using the anatomical AAL atlas [12] (cerebellum not included). Due to the weak recovery of the left and right puttamen regions, they were excluded from the networks, thus the structural and functional networks used had a total of 88 nodes each.

2.2. Functional and structural matrices

The FC matrix elements were obtained by evaluating the Kendall rank correlation between all 88 time series.

Segmentation: For each subject, tissue probability maps (GM, WM, CSF) were obtained with the SPM New Segment module which relied on the DARTEL non-linear transformation TNative $\rightarrow$ MNI from native to MNI space [13]. The subject brain mask was computed by applying a series of morphological operations on the resulting tissue probability maps. A 96-region parcellation of each subject T1 volume was obtained by applying the inverse of the previously calculated TNative $\rightarrow$ MNI transform to the AAL 116-region GM atlas and excluding the 20 regions associated to the cerebellum. The warped atlas in subject space was masked by the thresholded subject GM mask. The intersection between the dilated GM mask and the WM mask provided the interface between WM and GM.

Connectivity: The diffusion data was fitted to the diffusion tensor with FSL [14] in order to obtain FA maps. The transform TFA $\rightarrow$ T1 between diffusion and T1 space was computed by registering FA to T1 with a non-linear deformation initialized from a linear registration (FSL FNIRT and FLIRT toolboxes respectively). The inverse transform TT1 $\rightarrow$ FA was calculated and applied to the WM/GM interface, so as to provide a seed mask for tractography, as well as to the 96-region parcellation to give the target ROIs required to obtain connectivity matrices. Whole-brain deterministic tractography was performed based on the previous seed mask and on fiber directions extracted from the diffusion profile estimated with Q-Ball ([15, 16]) as implemented in Camino [17]. The count and average length of fibers connecting each pair of regions in the parcellated volume were calculated, and provided two connectivity matrices (associated with fiber count and average length respectively).

2.3. Graph diffusion model

A simple graph diffusion model is discussed in [11]. The model estimates a subject's functional connectivity network using its structural connectivity network. Here we briefly describe it for completeness. In essence, two cortical regions R_i and R_j are connected by a fibre population with weight $c_{i,j}$. Define the connection strength of the ith node as $\delta_i = \sum_j c_{i,j}$, then we have

$$\frac{\mathrm{d}x_i(t)}{\mathrm{d}t} = \beta \left(\delta_i^{-\frac{1}{2}} \sum_j c_{i,j} \delta_j^{-\frac{1}{2}} x_j(t) - x_i(t) \right).$$

Over the entire network, the resulting graph diffusion FC estimate gFC is given simply by

$$gFC(t) = e^{-\beta \mathcal{L} t},$$

where $\mathcal{L} = I - \Delta^{-1/2} C \Delta^{-1/2}$. Matrix Δ is diagonal with $\Delta_{ii} = \delta_i$, and C is the structural connectivity matrix with elements $c_{i,j}$. Matrix $\mathcal{L}$ is simply the normalized Laplacian matrix of C. At some diffusion point t_{max} the estimated functional connectivity matrix gFC matches the true FC matrix.

Group	Healthy	TLE-MTS	TLE-no
mean t_{max}	1.700	2.071	2.001
std t_{max}	0.308	0.424	0.492
mean R	0.345	0.384	0.358
std R	0.030	0.028	0.043

Table 1. Mean and standard deviation of t_{max} (μ_t, σ_t) for all three groups. μ_t is highest for the TLE-MTS and comparable with the TLE-no group. The healthy group has the smallest (μ_t,σ_R), followed respectively by TLE-no and TLE-MTS. (μ_R,σ_R) are highest for the TLE-MTS case.

2.4. Correlation metrics used

In this work we use the Pearson correlation R as a measure of how close the true FC matrix network matrix and the related graph diffusion matrix gFC are to each other. Importantly, we *exclude* the diagonal elements of both matrices in the Pearson computation, as their inclusion appears to cause an upward bias of R.

3. RESULTS

We refer to the mean and standard deviation of t_{max} achieved by a given group as (μ_t, σ_t) and similarly for R, with (μ_R, σ_R). The healthy group of subjects has the smallest (μ_R,μ_t) for all groups, with a mean diffusion depth $\mu_t = 1.700$, and $\mu_R = 0.345$. The TLE-MTS group reveals on average the highest μ_t and μ_R of all three groups, with $\mu_R = 0.384$ and $\mu_t = 2.071$. TLE-no group has a mean diffusion depth μ_t of 2.001, with associated mean R of 0.358. The large standard deviation $\sigma_t = 0.492$ of the TLE-no group appears to be due to a heterogeneity of the TLE-no's cortical atrophy patterns with focus in the temporal lobe. The statistics are summarized in Fig 1 and Table 1. The mean FC and SC matrices of all groups are given in Fig 2. Plots of the corresponding R vs t for all three groups are given in Fig 3(a-c). Fig 3(d) gives the scatter plot of R vs t_{max} for all groups. The cluster of the healthy subjects ('+') tends to have smaller t_{max} and R on average. The MTS group of epileptics exhibits both higher R and t_{max} than the healthy and TLE-no groups. The TLE-no group appears to be distributed over a range of R and t_{max}, also reflecting the relatively large associated σ_t and σ_R for the group in Fig 1.

The t-statistics of the TLE-MTS group's Pearson correlation R is 3.502 with $p = 0.003$. The diffusion depth t_{max} for the same group has t-stats 2.858 and $p = 0.007$. In the TLE-no case we obtain t_{max} t-statistics of 2.384 with $p = 0.044$. The t-statistics of

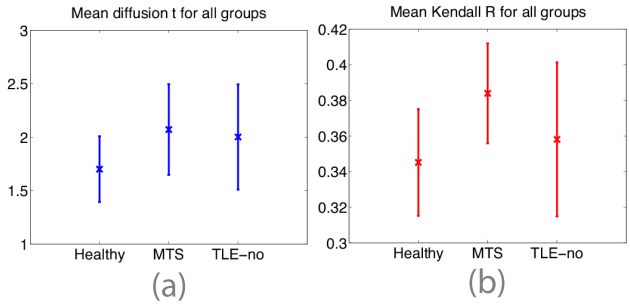

Fig. 1. Mean and standard deviation for R and t_{max} for all three groups.

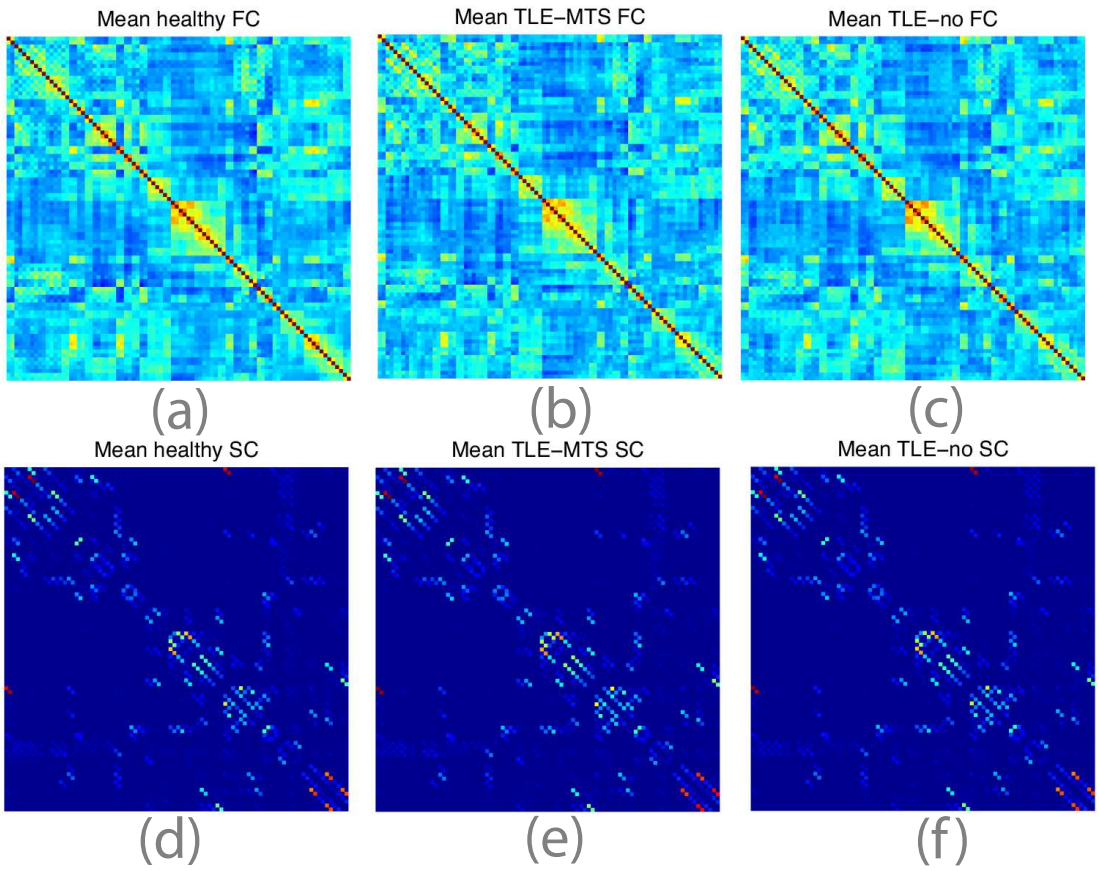

Fig. 2. Mean FC (a-c) and SC (d-f) matrices for all subjects. From left to right, healthy, TLE-MTS, and TLE-no groups.

R is not as significant (1.119, $p = 0.27$). The diffusion depth t_{max} for both epileptic groups is statistically significant. All p values are corrected for multiple comparisons.

4. DISCUSSION

In this work we propose a graph diffusion model borrowed from earlier work on image processing [18] and later applied to estimating functional network given the underlying structural network. The model possesses only one degree of freedom, the diffusion depth t, yet it is able to capture the resting-state FC network estimated from the SC network. While other articles have published similar models [9, 10], the graph diffusion model is significantly simpler to implement while at the same time yielding comparable or better estimates as shown in [11]. The model is extended to epileptic brains, considering both TLE-MTS and TLE-no types of epilepsy. In both cases the model predicts the FC network arising from the SC of an epileptic brain. We conclude that on average the subjects with TLE-MTS tend to have a higher diffusion depth t_{max} as well as, interestingly, a higher R between the FC and its graph diffusion estimate. TLE-no shows no distinct patterns from the healthy group. Taking the t-statistics of both epilepsy groups compared with the healthy group, the t_{max} estimate is significant for both TLE-MTS and TLE-no groups.

Our results show an intriguing and counter-intuitive effect of epilepsy on the SC-FC relationship – the FC of diseased groups are on average better matched to their SC than are healthy brain! It seems that the epileptic brain takes a longer diffusion time or depth t_{max} to achieve its best correlation with FC, but when it does, it frequently exceeds the SC-FC match observed in healthy brains. This suggests that the network disruption in epilepsy in fact strengthens rather than weakens its relationship with FC, a result previously observed using fMRI data [19, 20]. This also indicates that overly strong SC-FC relationship might be a sign of poor brain health

For future work the graph diffusion model will be improved by taking into account the network's delays between nodes. Another way of improving the model is by using data with high temporal resolution. Non-linear behavior revealed in EEG data of which high temporal resolution yields improved temporal resolution of interictal events in epileptic brains.

5. CONCLUSION

In conclusion, we propose a simple model estimating a subject's resting-state functional network from the corresponding structural network via a graph diffusion. The model is simple to implement and yields promising results that will be further explored in predicting epileptic networks.

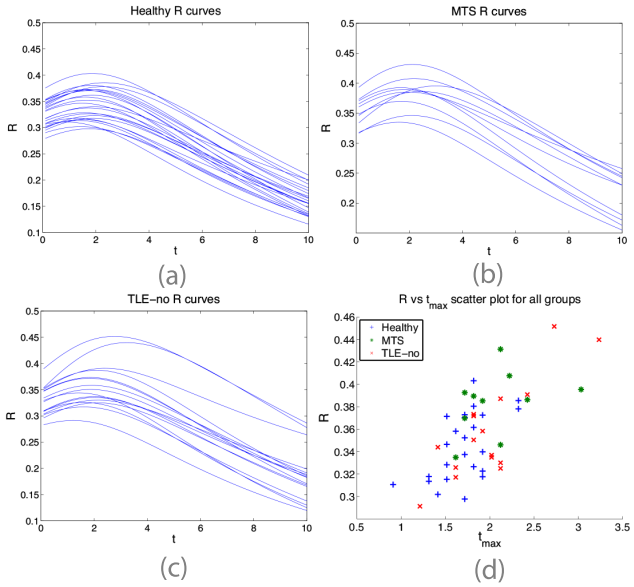

Fig. 3. R vs t plots. (a) Curves for the healthy group, $\mu_t = 1.700$. (b) TLE-MTS group, with $\mu_t = 2.071$. (c) TLE-no with $\mu_t = 2.001$. On average both epileptic groups require a higher t than the healthy group to achieve maximum R. (d) Scatter plot of R vs t_{max}. The TLE-MTS cluster ('*') tends to have higher R and t_{max} than the healthy ('+') group. The TLE-no group ('x') appears to overlap with both TLE-MTS and healthy groups.

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