CORRELATION BETWEEN NOISE ESTIMATES AND GRAPH THEORETICAL MEASUREMENTS ON RESTING STATE FMRI DATA

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Abstract: Graph theory applied to functional Magnetic Resonance Imaging (fMRI) analysis allows valuable and specific information of the functional network structure within the brain. Due to the sensitivity of graph theoretical measures, any noise in the data may alter these measurements, including subject head motion. However, noise in fMRI can be generated not only by head motion, but several other undesired sources, such as physiological noise or equipment errors. The amount of noise can be estimated though an outlier measurement of the time series within the voxels. This article aims to assess the impact of noise in fMRI data in Graph Theoretical Measurements (GTM), within a normal population, using two parameters; patient head motion and number of outliers in the functional data. With different threshold levels used to calculate the GTM (Global Efficiency, GE; Characteristic Path Length, CPL; Average Local Efficiency, ALE; Average Clustering Coefficient, ACC) we calculate the correlation with the two noise. We found high levels of correlation between GTM and patient motion estimation (ME) and outlier measurements (OM). However, there is a greater correlation between OM and GTM than ME and GTM. Our results demonstrated that GTM are affected by more than just head motion, but by other noise sources that can be captured by observing the outliers within the functional time series.

Keywords: fMRI, resting state, graph theoretical measures

Introduction

The analysis of complex networks is an area that is currently being extensively explored. The neural topology of the brain is a typical example of a complex network. The analysis of complex networks allows us to describe important properties of complex systems, quantifying their structural organization. The study of topological properties of the network is called graph theory. When graph theory is applied to evaluate functional magnetic resonance images (fMRI) data, the nodes are defined as the brain regions (i.e. regions of interest - ROIs) chosen a priori, and the edges are the connections (i.e. functional correlation) between the ROIs [1].

The application of graph theory in fMRI allows us to get valuable and distinct information that is not obtained by typical methods that evaluate brain connectivity [2], such as seed-based connectivity maps. Furthermore, through the use of resting state fMRI (rs-fMRI) and electroencephalography data, it was demonstrated that the human brain is organized in such a way that it embraces several small-world properties [3][4][5]. Graph theory is increasingly being applied in neuroimaging data and novel measurements are being created and tested for their potential applicability to study the human brain connectome at a structural and functional level [1][6].

Neuroimaging studies have shown that the brain topology can vary according to mental state, including neuropsychological disorders [7][8][9], age [4][10][11] and even sex [12]. Henceforward, even between healthy individuals the architecture of the neural network can be significantly distinct.

Knowing that head motion alters the fMRI signal and induces erroneous correlations [13] a study of the impact of head motion on measurements of graph theory is required. Yan et a., [15] evaluated different forms of motion estimation in rs-fMRI and found that graph theoretical measurements (GTM) vary quite substantially depending on level of head motion.

However, noise in fMRI can be generated not only by head motion [14] but several other undesired reasons, such as: thermal noise intrinsic to the patient and electronic equipment's, noise related to the imperfections of hardware, noise related to cardiac, respiratory cycle and other physiological processes.

This article aims to assess the impact of noise in fMRI data in GTM, in a normal population, using two parameters: patient head motion and number of outliers in the functional data. The latter was chosen because outlier measurements not only address motion, but also other sources of noise.

Materials and methods

Data Sample

The sample used in this work consists of a publically available dataset, the 1000 connectomes Functional Project which is part of the International Neuroimaging Data-sharing Initiative (INDI) (http://fcon_1000

.projects.nitrc.org/) [15]. A subset of one hundred and two subjects from the Peking University where used in this study, including only right handed healthy controls.

Data preprocessing

All functional data was preprocessed using AFNI [16]. Data was initially despiked, slice-time corrected, and motion corrected (explained more in depth below). Then it was spatially normalized to a standard space (MNI152), and passed through a band-pass filter (0.01 - 0.1 Hz). Additional, the average signal of white matter and cerebrospinal fluid as well as the six estimated motion parameters where used as nuisance variables in a general linear model analysis with the functional data.

Motion Estimate (ME)

Motion correction in functional data is performed using a 6-parameter rigid body affine transformation (AFNI - 3dvolreg). Specifically, using a reference image (typically the first image in the functional scan) and an optimization algorithm (linearized weighted least squares) the six motion parameters (translation: x,y,z; rotation: roll, pitch, yaw) are estimated in each functional image and used to align data in the preprocessing steps. The amount of motion in each image is calculated by:

$$Mot\ (i)_s = ((x_i - x_{i-1})^2 + (y_i - y_{i-1})^2 + (z_i - z_{i-1})^2 + (r_i - r_{i-1})^2 + (p_i - p_{i-1})^2 + (yaw_i - yaw_{i-1})^2)^{1/2} \qquad (1)$$

where *x, y* and *z* are the translation estimates and *r, p, yaw* are the rotation estimates, *i* is image, and *s* is the subject. The amount of motion of each subject within a functional scan was estimated by calculating the average of $Mot(i)_s$ across time, denoted here as motion estimate (ME) score. ME scores were correlated with GTM.

Outlier Measurement (OM)

Outliers' measurements are calculated by analyzing time series of all the voxels within the brain. For each voxel, the median ($m(v)$) and the median absolute deviation ($MAD(v)$) are calculated. Next, an acceptable intensity range for each voxel is defined by [$m(v) - a \cdot MAD(v)\ ;\ m(v) + a \cdot MAD(v)$], where $a = Q^{-1}(0.01/N) \cdot \sqrt{(\pi/2)}$, and $Q()$ is the reversed Gaussian cdf and N is the length of the time series. If a time point of a particular voxel is outside this range, it is considered an outlier. For each time point, the total amount of outliers within all the voxels is computed. Finally, the average number of outliers throughout time is defined as the outlier measurement (OM) and is compared to GTM [17].

Network Extraction

To define the nodes, a mask that divides the brain into 200 non-overlapping regions [18] was used. To define the edges, a connectivity matrix was created by calculating the pairwise functional correlation between each node-pair. Using the Brain Connectivity Toolbox [1], the following GTM were computed: characteristic path length (CPL), global efficiency (GE), average clustering coefficient (ACC), and average local efficiency (ALE).

Results

The average ME across all subjects is 0.0672 (±0.0232) and the average OM is 0.0028 (±0.0069). With a 0.2 threshold on the connectivity matrix, the resulting average GTM were: GE= 0.568 (±0.022), CPL=1.959 (±0.065), ALE=0.659 (±0.055) and ACC=0.430 (±0.051). Correlation between ME and OM and GTM (with different thresholds on the connectivity matrix and corresponding statistical p-score) are displayed in Table 1 and **Erro! Fonte de referência não encontrada.**, respectively.

Table 1. Correlation – Graph theoretical Measures and Motion Estimation

GT Measures	Threshold 0.2	0.3	0.5
GE	0.293 (p<0.005)	0.313 (p<0.001)	0.269 (p<0.01)
CPL	-0.282 (p<0.005)	-0.240 (p<0.05)	-0.040 (p>0.05)
ALE	0.293 (p<0.005)	0.290 (p<0.005)	0.286 (p<0.005)
ACC	0.261 (p<0.01)	0.286 (p<0.005)	0.286 (p<0.005)

GT – Graph Theoretical, GE – Global Efficiency, CPL – Characteristic Path Length, ALE – Average Local Efficiency and ACC – Average Clustering Coefficient.

Table 2. Correlation – Graph theoretical Measures and Outlier Measurements

GT	Threshold 0.2	0.3	0.5
GE	0.476 (p<0.001)	0.475 (p<0.001)	0.511 (p<0.001)
CPL	-0.435 (p<0.001)	-0.426 (p<0.001)	-0.151 (p>0.05)
ALE	0.375 (p<0.001)	0.365 (p<0.001)	0.397 (p<0.001)
ACC	0.369 (p<0.001)	0.333 (p<0.001)	0.347 (p<0.001)

GT – Graph Theoretical, GE – Global Efficiency, CPL – Characteristic Path Length, ALE – Average Local Efficiency and ACC – Average Clustering Coefficient.

A graphical representation of the correlation between GTM and GE are shown in **Erro! Fonte de referência não encontrada.**. Analyzing in more detail Fig. 1(b), it appears that one subject exhibit an elevated amount of OM (indicated in a red circle). The correlation between the noise estimates (ME and OM) and GTM (threshold = 0.2) were recalculated without the one subject with elevated OM. Correlation between ME and GTM are the following: GE=0.219 (p<0.05), CPL=-0.219 (p<0.05), ALE=0.240 (p<0.05) and ACC=0.203 (p<0.05). Correlation between OM and GTM without the outlier subjects are the following: GE=0.443 (p<0.001), CPL=-0.441 (p<0.001), ALE=0.377 ($p<0.001$) and ACC=0.342 ($p<0.001$). Finally, Additional analysis showed that there was a correlation of r=0.453 ($p<0.001$) between the ME and OM.

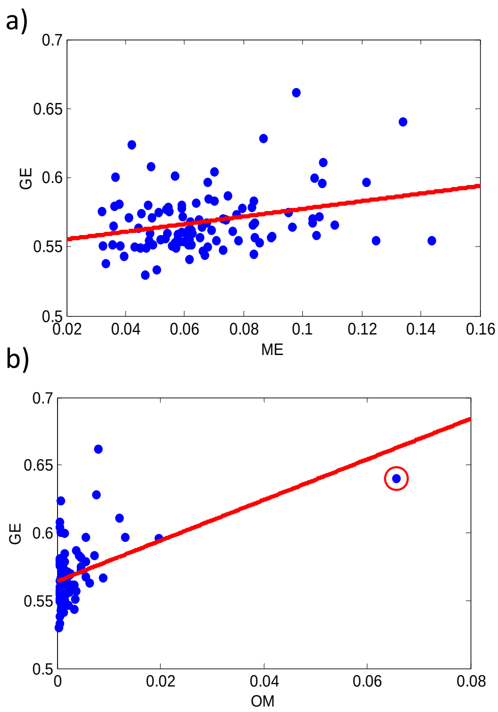

Figure 1 – Grafical representating of the correlation between (a) Global Efficiency (GE) and Motion Estimation (ME) and (b) GE and Outlier Measurement. In (b), red circles respresnt two subjects that had exessive outliers.

Discussion

The objective of this study was to evaluate the effect of two different methods to measure noise in fMRI data on graph theoretical measurements: estimation of head motion and the measurement of time series outliers. Specifically, the effect was tested with a homogeneous group of healthy controls, which underwent an rs-fMRI scan. It was expected and desired that there would be little or even no relationship between noise measurements and GTM. However, it was observed that there is in fact a high level of correlation between noise measurements (ME and OM) and GTM.

It has been shown that head motion can affect GTM [19], however, there are also other sources of noise in fMRI that are not captured by algorithms that estimate motion. Within the preprocessing steps of fMRI, algorithms attempt to remove or minimize the effect of these imperfections within the data, using motion estimation and average signals from white matter and cerebrospinal fluid (where it is expected to have no BOLD signal) as nuisance variables in a multiple regression analysis. We have performed these preprocessing steps in our study. However, it is supposed that OM is a means of measuring the effect of the all the different noise sources that may affect fMRI data.

Overall, our results indicate that the GTM are more highly correlated with OM compared to ME. This was observed for all the GTM and at different levels of threshold of the connectivity matrix (see Table 1). The correlation of GTM with OM is higher at all threshold values, when compared to the correlation of GTM with ME.

It can also be observed that there is a general decrease in correlation between the noise estimates and GTM as connectivity matrix threshold increases. With higher thresholds only the stronger connections (higher r-scores) are kept, precisely those that are not affected by noise. Also, it was observed that there is still a high level of correlation between GTM and OM, even when the one subject with elevated OM level was removed from the analysis. The removal of subjects with high level of noise or head motion from a study is usually done in fMRI studies. However, through the results in this article, this has been shown to not be sufficient since there still is a correlation between GTM and OM or ME.

Conclusion

Our results agree with the results obtained by previous study [19], where GTM are affected by head motion. However, we have extended the analysis and shown that GTM are affected by more than just head motion, by observing the outliers within the functional time series. This is indicated by the correlation score between ME and OM (r=0.453, $p<0.001$), where the correspondence between them is not perfect.

Measuring outliers in the time series within voxels is not a faultless measurement of the level of noise in functional data. However, there is still no complete and precise way to estimate noise.

Further work still needs to be done to completely understand the effects of noise in GTM. A limitation of this study is that only one group of subjects was used. Future work should be performed on datasets from several different sources. Additionally and more importantly, we need to develop techniques that reliably “clean up” functional data which used in brain topology measurements. Therefore we can reliably use GTM to understand different clinical populations or groups.

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