Human brain functional connectivity in resting-state fMRI data across the range of weeks

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Abstract

Around 15 years after the invention of fMRI, Functional Connectivity, FC, in the human brain has emerged as a major issue in neuroimaging studies. The reason is that the brain regions are a complex network of functional communication that plays a key role in cognitive processes. FC is defined as the temporal correlation of neural activation across different regions of the brain. Functional connectivity of a single subject seems to be affected by their situation. The results of the other studies demonstrate that healthy brain function shows rich dynamics over the course of time. So it may be a good idea to investigate the FC network as a summary of repeatedly measured fMRI sessions over more than one time point. Few studies have been done on the coordination of neural activity over longitudinal sessions. This study evaluates the FC cross-subject averaging of a single individual repeatedly measured over 16 weeks using the My Connectome study. Resting state fMRI data were acquired in some longitudinal sessions. A variance based linear model, proposed by Fiecas et al. was employed to conduct statistical inference on FC patterns of a single human averaged across time. This model estimates the autocorrelation structure in a session-specific manner, and estimates the variance due to the heterogeneity across sessions.

Key words: Resting State fMRI, Functional Connectivity, Variance Components Mode

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Introduction

Resting state fMRI, called rs-fMRI, is a method of functional magnetic resonance imaging, of fMRI, which is used to evaluate brain activation that occurs when a subject is not performing a typical task (1). Brain activity is observed through changes in Blood Oxygen Level Dependent, BOLD, signals in the brains' voxels. Brain activity is present even in the absence of an external task, so BOLD signals will change in brain regions during a resting state.

One of the important tasks, which has received interest in recent years, is detecting of brain areas' connectivity. In general, connectivity investigates how brain regions interact with each other (2). Functional connectivity, FC, identifies regions of the brain showing similar temporal characteristics. In other words, it can be defined as the temporal correlation between spatially different brain regions. Usually, functional connectivity is determined during the resting state fMRI and it is analyzed in terms of correlation and spatial clustering based on temporal similarities in BOLD signals (3).

In fact, the statistical inference for functional connectivity are based on statistical measures of dependency among brain areas. In this way, some methods are based on temporal correlations between Regions of Interest, ROIs, or between a 'seed' region and other voxels throughout the brain (4). The other common approaches are clustering and multivariate statistical methods. Clustering approaches partition the brain into regions that exhibit similar BOLD signal characteristics over time. Multivariate methods are used for dimension reduction, such as Principal Components Analysis, PCA, and Independent Components Analysis, ICA. These methods determine spatial patterns that include most of the variability in the BOLD time-series

(5–7). In addition, there are some specific approaches such as Graphical Lasso, GLasso, and Bayesian non-parametric models (1,8,9).

It is a fact that functional connectivity changes over time (10). Therefore, it may be a good idea that the functional connectivity is considered during some sessions. So we investigated the FC network as a summary of repeatedly measured fMRI sessions over more than one time point, by averaging of a single individual repeatedly measured over 16 weeks using the My Connectome study (11).

Recently, Fiecas et al. have presented a variance-based method for comparing the FC networks between a group of patients and a group of healthy controls in a multi-subject resting-state fMRI data set (12). They introduced a variance components framework for modeling the FC networks that accounts for the autocorrelation inherent in the ROI time series of each subject and for subject heterogeneity. We have used their approach, by replacing the subjects with repeated sessions. Therefore, we have applied their model and estimated a functional connectivity pattern for a single subject based on repeated resting state fMRI acquired across some weeks.

Material and Methods

1. Statistical Inference

To perform statistical inference on the FC network, we used the proposed model by Fiecas et al. (12). We applied their approach by considering sessions instead of subjects. In this way, the model accounts for the temporal correlation in the time series within the subject, the covariance between the different pairs of ROIs within the subject, and the variability due to the sampling across sessions. Suppose data include p ROIs, across N sessions. So the number of paired ROIs are $q=p(p-1)/2$ for each session. Then the model is in the following form

$$Y_{(Nq*1)} = X_{(Nq*q)}\,\beta_{(q*1)} + \epsilon_{(Nq*1)} + \Psi_{(Nq*1)} \quad (1)$$

Where the Y=(r_11,…,r_q1,r_12,…,r_q2,…,r_1N,…,r_qN) is the vector of sample correlation coefficients stacked vertically across the sessions. The ϵ and Ψ are vectors with dimension Nq*1.

The *q* elements of vector β are the parameters of interest that capture the true FC. The model has two error terms. The first one is used to model variance and covariance related to the temporal autocorrelation in the ROI time series within the subject. The second one represents the amount of variability that can be attributed due to sampling across weeks.

Parameters estimated were obtained using the approach detailed in Fiecas et al. (12).

2. Database

We used data from the My Connectome study that consists of 89 sessions of resting state fMRI data on a single healthy human. The My Connectome project has characterized how the brain of one person changes over the course of more than one year. This data was obtained from the Open fMRI database. Its accession number is ds000031. We considered resting state fMRI data repeatedly measured over 16 weeks. The rs-fMRI acquiring was performed in 89 sessions throughout the data collection period in the production phase, using a multi-band EPI sequence (TR=1.16ms, TE=30ms), voxel size=2.4*2.4*2mm. Starting with session 27 (December 12 2012). The size of images was 2.4*2.4*2.4. Image pre-processing was carried out with the FMRIB Software Library, FSL software (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki) (13). Resting state processing included motion correction (14), removal of non-brain structures (15), spatial smoothing (5 mm FWHM), and high-pass temporal filtering.

The goal of this study was to provide comprehensive patterns of FC cross-session averaging. We specify the ROIs based on Broodman atlas including 42 ROI. Time courses for each ROI were obtained by averaging across all voxels within the ROI. Three ROIs were discarded from the analysis, because their time series had not been reached. Then we considered all the pairwise correlations between the ROI time series, 741 pairwise.

Table 1: A list of the ROIs and their numbers in analyzing process.

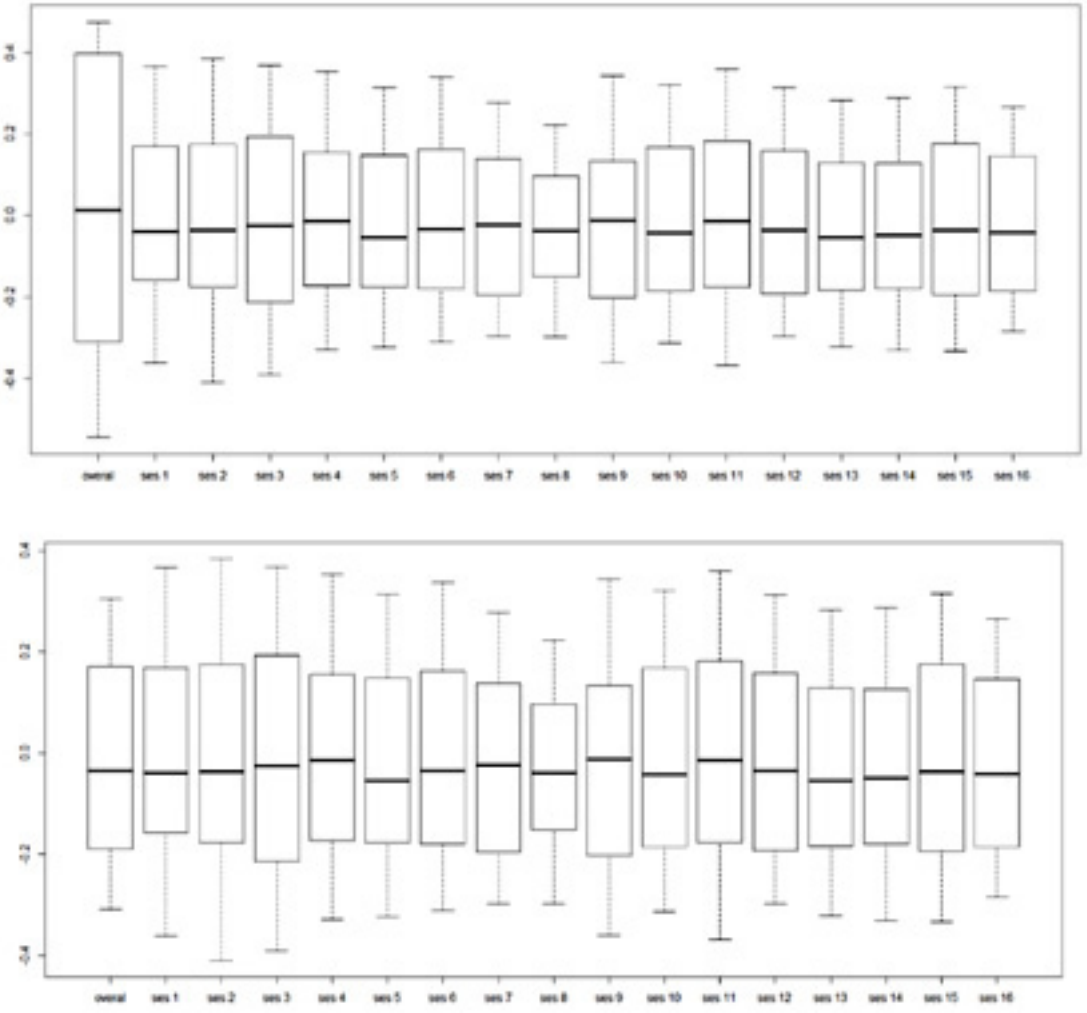
Num	Region of interest	Num	Region of interest	Num	Region of interest	Num	Region of interest
1	Brodmann area 1	11	Brodmann area 13	21	Brodmann area 27	31	Brodmann area 39
2	Brodmann area 2	12	Brodmann area 17	22	Brodmann area 28	32	Brodmann area 40
3	Brodmann area 3	13	Brodmann area 18	23	Brodmann area 29	33	Brodmann area 41
4	Brodmann area 4	14	Brodmann area 19	24	Brodmann area 30	34	Brodmann area 42
5	Brodmann area 5	15	Brodmann area 20	25	Brodmann area 31	35	Brodmann area 43
6	Brodmann area 6	16	Brodmann area 21	26	Brodmann area 32	36	Brodmann area 44
7	Brodmann area 7	17	Brodmann area 22	27	Brodmann area 33	37	Brodmann area 45
8	Brodmann area 8	18	Brodmann area 23	28	Brodmann area 35	38	Brodmann area 46
9	Brodmann area 9	19	Brodmann area 24	29	Brodmann area 36	39	Brodmann area 47
10	Brodmann area 10	20	Brodmann area 25	30	Brodmann area 37		

Results

An individual subject FC was generated using data from 16 resting state sessions for 39 ROIs following the procedure described in the previous section. A list of the 39 ROIs with their abbreviations is presented in Table 1. In Figure 1, we show the beta parameters that capture true FC estimated based on longitudinal sessions, and also the beta parameters for the FC networks in 16 sessions, individually. The overall betas have more variance related to the betas for each of the 16 sessions.

In addition, Figure 1 includes the correlations between ROIs averaged over the longitudinal sessions and the correlations among ROI for all 16 sessions. The image shows that the correlations between paired ROIs have different variation during the sessions.

Figure 1: Up: The estimated beta over sessions; Down: The correlations between ROI pairs over sessions.



Also, we have shown the beta parameters that capture true FC estimate based on longitudinal session and the beta parameters for session 1 and vice versa in Figure 2, in the upper triangle and lower triangle, respectively. In this image, we can see the difference between the estimated betas related to each of the ROI pairs in detail. FC networks for session's numbers 1, 8 and 16 also drawn vice versa in the overall FC network in Figure 2. These Results show that the FC networks are not static across the sessions.

Figure 2. Upper triangle: the estimated beta totally. Lower triangle: the estimated beta for Session 1

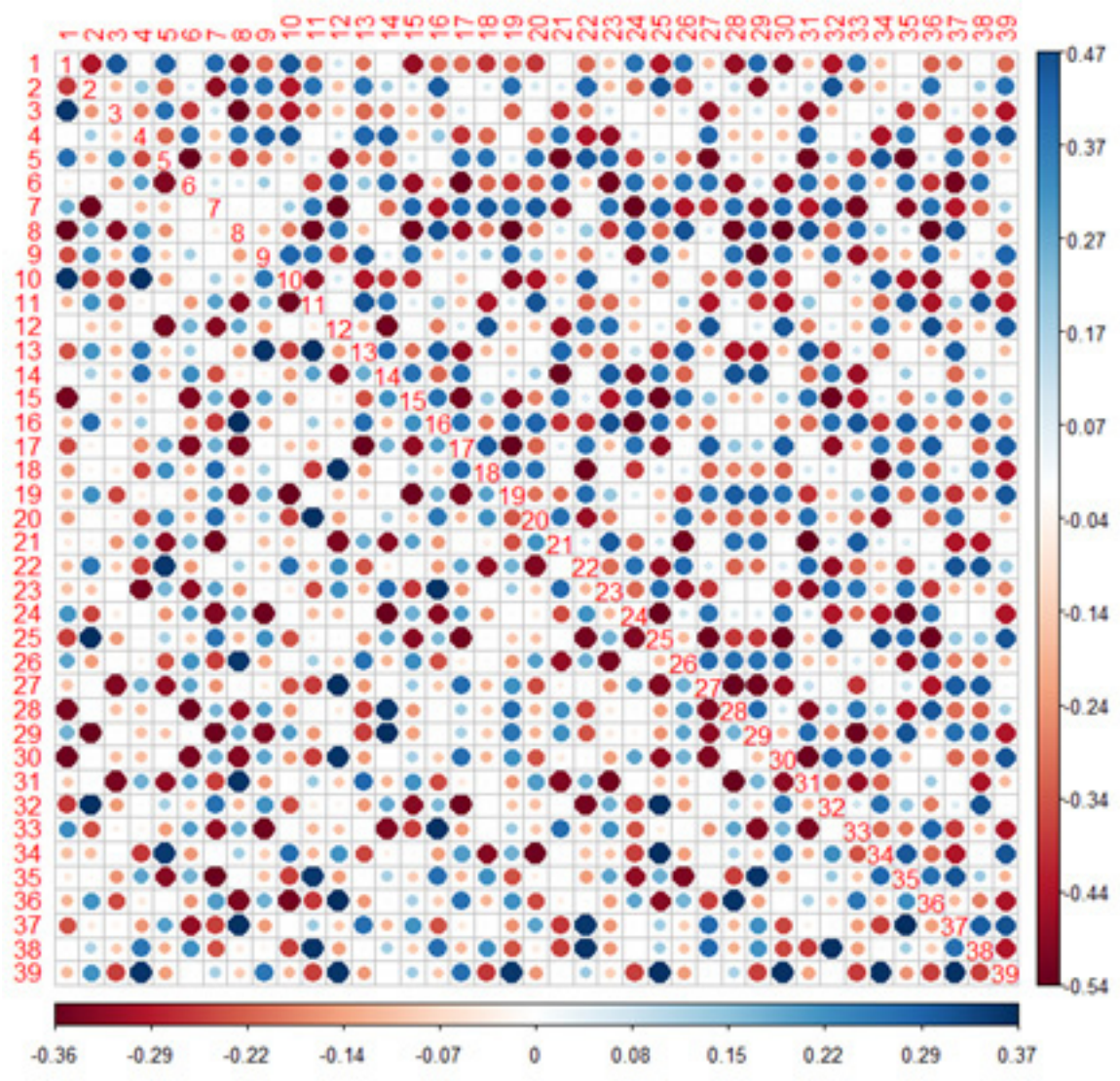
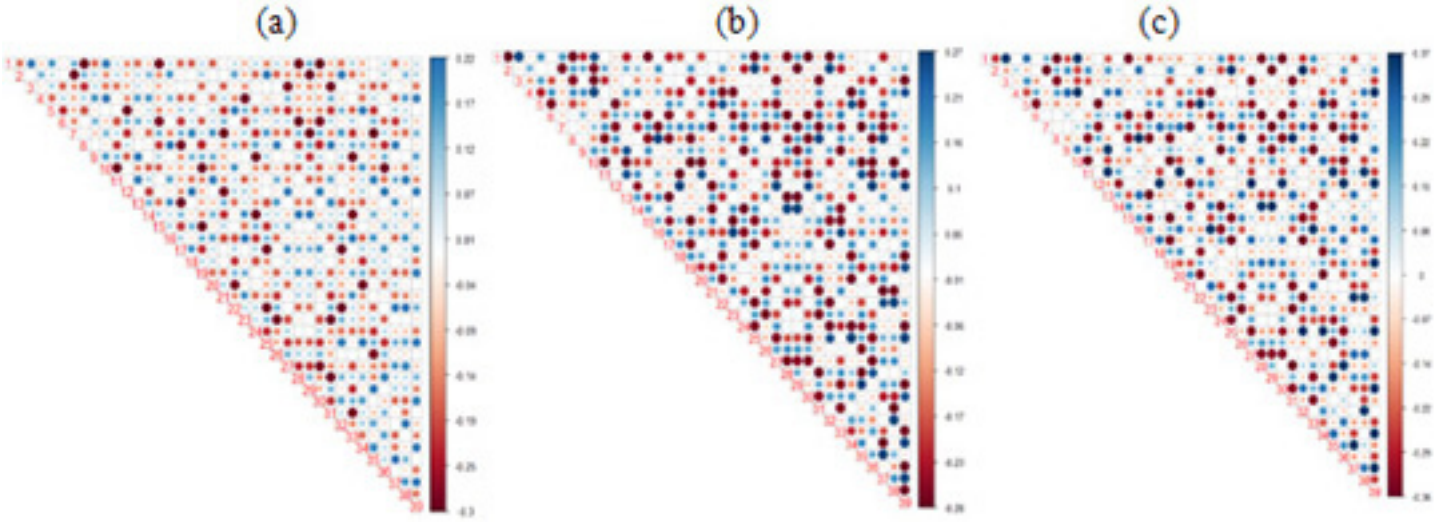


Figure 3. (a) The estimated betas for Session 1; (b) The estimated betas for Session 8; (c) The estimated betas for Session 16.



Discussion

The human brain is a network that consists of spatial regions, which are functionally linked. These regions share information with each other continually (16). Using the resting-state fMRI, we can explore the functional connections of the brain regions. Functional connectivity of rs-fMRI data is an important issue with an increasing trend of innovations in recent years. An important limitation of most rs-fMRI studies in healthy adults is reliance on functional connectivity indices calculated from an entire scan session (17). In this way, important information about within-scan temporal changes in functional connectivity may be lost.

Therefore, the present study aimed to determine the functional connectivity in a single healthy human using his repeated rs-fMRI data. The current study reveals that whole brain network properties varied within a single resting-state scan session.

Bharat et al have associated the variations of functional connectivity with the intrinsic activities of resting-state networks during a single resting state scan by comparing functional connectivity differences between the situation when a network had higher and lower intrinsic activities (18). Allen et al. have described an approach to assess whole-brain FC dynamics based on spatial independent component analysis, sliding time window correlation, and k-means clustering of windowed correlation matrices (19). There are few good review articles about dynamic FC. Hutchison et al have reviewed recent findings, methodological considerations, neural and behavioral correlates, and some directions in the emerging field of dynamic FC studies (10). In addition, Ioannides review FC results from a variety of studies, which suggest that an adequate description of brain organization requires a hierarchy of networks rather than a single one (20). Viviano et al explore the associations between dynamic functional connectivity and age differences, metabolic risk, and cognitive performance in healthy adults (21). Hutchison et al showed that the Resting-state networks have Dynamic FC in awake humans and anesthetized macaques. Their results illustrated that resting-state functional connectivity is not static (22). Marusak et al have explored the Dynamic FC of neurocognitive networks in children in a sample of 146 youth from varied sociodemographic backgrounds. They applied the Independent component analysis, sliding time window correlation, and k-means clustering to rs-fMRI data. Their results showed six dynamic FC networks that re-occur over time (23). Bhattacharya et al have proposed a nonparametric Bayesian approach to model effective connectivity assuming a dynamic non-stationary neuronal system (24).

However a large number of ROIs is possible for the variance model, but we needed to make modifications to the proposed method to accommodate the larger number of ROIs. The reason was that the number of parameters in our model were very large compared with respect to the number of ROIs. To solve this problem we ignored the covariance terms in the between-subject covariance matrix. Because of a small number of sessions, we considered only the scaled identity structure for the between-subject covariance matrix, since by this structure the model has a small number of parameters. Using larger sample sizes, one can consider structures that are more complex.

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