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Shorter TR Combination with Finer Atlas Positively Modulate Topological Organization of Brain Networks: A Resting State fMRI Study

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Abstract

Background: The simultaneous multislice echo planar imaging technique can shorten the repetition time (TR) of blood oxygen level-dependent acquisition and thus acquires more information. However, little is known about the influence of higher temporal resolution on functional networks. Whether the topological organization of small-world networks is modulated in the multispectra at high temporal resolution is still unclear. **Results:** The network reconstruction based on the shorter TR and the finer atlas, showed significant ($p < 0.05$, Bonferroni correction) increases in normalized clustering coefficient, small-worldness, clustering coefficient, local efficiency and global efficiency, and reductions in normalized characteristic path length and characteristic path length. **Conclusions:** The shorter TR coupled with the finer atlas can positively modulate topological characteristics of brain networks. Although five multispectra present properties of small-world networks, the properties of the network in 0.082-0.1 Hz are weaker than those in 0.01-0.082 Hz. These findings provide new insights into the topological patterns of brain networks and have implications for the study of brain connectomes and their applications in brain disease.

Keywords: *Magnetic Resonance Imaging; fMRI; Brain; Atlas; Frequency*

1 Background

The brain network of human has been proven to consist of small-world networks according to the characterization of graph theory [1, 2]. The topology of networks can be described by different measures, for example, node degree, hub, etc. Particularly, two parameters, the clustering coefficient (C_p) and the characteristic path length (L_p), are frequently adopted to investigate properties of a network. Specifically, small-world networks have both a high C_p and a short L_p , showing a good local efficiency (E_{loc}) and a high global efficiency (E_g) [3].

However, the long repetition time (TR) is a limitation of the temporal resolution of the blood oxygen level-dependent (BOLD) signal in functional magnetic resonance imaging (fMRI) studies. Typically, a 2~3 s TR may result in the signal being obscured by mixing physiological noise into the neuronal-induced BOLD fMRI signal [4]. To partially filter these undesirable signals, a higher temporal resolution may be a feasible way.

Single-shot echo planar imaging (EPI) is widely used in many fMRI studies. However, the conventional EPI sequence still needs several seconds to cover the whole brain. Recently, a simultaneous multislice (SMS) EPI technique has been proposed that can shorten TR without reduction in echo time (TE) and signal-to-noise ratio [5]. However, little is known about the influence of shorter TR on properties of the brain network.

The scale of the brain parcellation is known to have an effect on the organization of brain networks [6]. The properties of networks vary with the distinct parcellation

scales [7]. The Automated Anatomical Labeling (AAL) atlas [8] is one of the most popular brain atlases. By contrast, the parcellation containing 200 regions [9] was adopted. It remains unclear whether there is an interaction between the temporal resolution and the scale of brain parcellation.

Additionally, previous studies have indicated that brain networks exhibit various properties in distinct frequency bands [10, 11]. Particularly, the subtle temporal differences might be averaged out within the typical frequency interval [12], which might lead to information being overlooked. It is necessary to decompose the typical frequency interval into several subbands to further evaluate the organization of networks.

There are two main aims in this study. First, we inspected the effects of TR length (0.5 vs. 2 s) and the scale of brain parcellation (90 vs. 200 regions of interest (ROIs)), as well as their possible interaction, on the characteristics of brain networks. Second, we tested whether the topological organization of networks was modulated in the multispectra when the BOLD signal was acquired at a high temporal resolution.

2 Results

2.1 Single spectrum

ANOVA results showed that the main effect of brain parcellation was significant as revealed by Cp, Lp, Eloc, and Eg, as well as λ . The main effect of TR length was significant, as revealed by Eloc, γ and σ . There was no interaction effect between them. The detailed statistical results are shown in Table 1.

Table 1

2.2 Simple main effects of brain parcellation

When networks were constructed based on the AAL atlas, the results revealed that the dataset with the shorter TR possessed significantly larger γ , Cp, and Eloc (Fig. 1).

Fig.1. Network metrics for a single spectrum (0.01-0.1 Hz). All measures were represented as functions of sparsity across a range from 0.05 to 0.5 with an increment of 0.0045. TR0.5 means the repetition time is 0.5 ms, and the last digit presents the number of regions.

When networks were built based on a finer atlas, the shorter TR condition showed significant increases in γ , σ , Cp, Eloc and Eg as well as decreases in λ and Lp. The statistical comparisons of the different brain parcellation methods showed that the finer atlas condition had significant decreases in λ , Cp, Lp, and Eloc and an increase in Eg over a wide range of sparsity, in both TR conditions.

2.3 Multispectrum

The subfrequency band of 0.064-0.082 Hz was chosen as an illustration to replicate the findings from the single spectrum, as shown in Fig. 2.

Fig.2. Network metrics for a particular subspectrum (0.064-0.082 Hz).

When the AAL atlas was used, the shorter TR condition showed significant increases in γ , σ , Eloc, and Eg and decreases in λ and Lp. When the high-resolution atlas was applied, the shorter TR condition showed significant increases in γ , σ , Cp, and Eloc and decreases in Lp. In the comparison of the two different parcellation methods, the results revealed that the finer atlas presented significant reductions in λ , Lp, and increases in Cp, Eloc, Eg. These results were totally applied to the other subspectrums.

2.4 Differences between multispectra (TR = 0.5 s and 200 parcellation)

All five multispectra presented the properties of small-world networks (Fig. 3); however, their characteristics were different from those of the single spectrum. In particular, 0.082-0.1 Hz presented significant differences in all seven parameters. In the 0.01-0.046 Hz spectra, γ , σ , C_p , and E_{loc} were significantly decreased, and λ in 0.046-0.082 Hz was significantly reduced.

Fig.3. Network metrics for the multispectra at the global level.

The pairwise comparisons between the five subfrequency bands showed that the two parameters σ and E_g of 0.082-0.1 Hz were significantly smaller than those of the other four multispectra, while C_p , L_p , and E_{loc} of 0.082-0.1 Hz were larger than those of the other four multispectra. C_p of 0.01-0.028 Hz was significantly larger than that of 0.028-0.082 Hz, L_p and E_g of 0.01-0.028 Hz were significantly longer and lower than those of 0.046-0.064 Hz. E_{loc} of 0.064-0.082 Hz was significantly higher than that of 0.028-0.046 Hz.

3 Discussion

The results indicated that the shorter TR can modulate the properties of small-world networks. This was directly supported by the fact that the σ of the shorter TR conditions was significantly larger than that of the longer TR conditions. Additionally, it was found that the C_p , L_p , E_{loc} , and E_g from the shorter TR conditions were tighter, shorter, higher, and larger than those of the longer TR conditions, respectively.

Our results revealed that the organization of the network is changed as a function of the parcellation, as characterized by the significant differences in λ , C_p , L_p , E_{loc} and E_g between the two parcellation schemes. In particular, networks based on a finer parcellation exhibited different small-worldness. This was highly in accordance with a previous study [6].

Based on 90 ROIs, the significant differences between the two TR lengths existed only in the parameters of γ , C_p and E_{loc} . Based on 200 ROIs, significant differences between the two TR lengths were found in all seven parameters. Particularly, the

shorter TR coupled with the finer parcellation, might be more beneficial to the transmission of information and trend toward reinforcing the optimal balance between local specialization and global integration in a small-world model.

The topological properties of the network of 0.082-0.1 Hz were slightly weaker than those of the other four subfrequency bands. This is completely congruent with some previous reports. For example, they [10, 16] found that small-world properties were salient at lower frequencies. However, there was a counterexample [17], which reported that the highest small-worldness was located on scale 2. It was argued that this inconsistency can be accounted for by the difference in the number of time points. Limited number of time points may lose some important information.

4 Conclusion

This study first demonstrated that the BOLD signal acquired with SMS-EPI at a higher temporal resolution, coupled with the finer atlas, can positively modulate the small-world topological properties of brain networks. Although five multispectra present properties of small-world networks, the properties of the network in 0.082-0.1 Hz are weaker than those in 0.01-0.082 Hz.

5 Materials and Methods

5.1 Subjects

Twenty healthy young volunteers were recruited (aged 23-28 years, mean age=25.3 years, ten male). The exclusion criteria were (1) a history of neurological or psychiatric disorder or head injury; (2) current treatment with vasoactive or psychotropic medication; (3) any physical or intellectual disability; and (4) any contraindication to MRI. Data from one subject was discarded due to a failure to cooperate during the MRI scan.

5.2 Data acquisition

MRI scans were acquired using a MAGNETOM Verio 3T MR Scanner (Siemens, Erlangen, Germany). The resting-state fMRI (R-fMRI) data were obtained using two scanning protocols: (1) shorter TR protocol: TR, 500 ms; TE, 30 ms; flip angle (FA), 90°; 32 slices; matrix, 64*64; voxel size, 3.75*3.75*4 mm³; SMS factor, 4; (2) longer TR protocol: TR, 2000 ms; TE, 30 ms; FA, 90°; 32 slices; matrix, 64*64; voxel size, 3.75*3.75*4 mm³; SMS factor, 1. During the R-fMRI scans, subjects were instructed to hold still, keep their eyes closed.

5.3 Data Preprocessing

All images were preprocessed using the Statistical Parametric Mapping (SPM12, <http://www.fil.ion.ucl.ac.uk/spm/>) software package and Data Processing Assistant for Resting-State fMRI (DPARSF) [13]. The first 10 time points of the longer TR data and the first 20 time points of the shorter TR data were discarded. The images were then corrected for the staggered order of slice acquisition and head motion. Data from

one subject were excluded due to excess head motion (translation > 2 mm). The data were then spatially normalized to the Montreal Neurological Institute space and resampled to 3 mm isotropic voxels using the normalization parameters estimated during unified segmentation [14]. Subsequently, the images were smoothed with a Gaussian kernel of $4 \times 4 \times 4 \text{ mm}^3$ full-width at half-maximum. Temporal filtering ($0.01 \text{ Hz} < f < 0.1 \text{ Hz}$) was applied to the time series.

Since the R-fMRI signals are complex, the frequency interval (0.01-0.1 Hz) was decomposed into five equal-length spectra. The five spectra were 0.01-0.028 Hz, 0.028-0.046 Hz, 0.046-0.064 Hz, 0.064-0.082 Hz, and 0.082-0.1 Hz. Regressions of six motion parameters, white matter signals and cerebrospinal fluid signals were performed. The global signal was not regressed out. Finally, two atlases (AAL and Craddock template) were adopted to extract the BOLD time series.

5.4 Network Analysis

5.4.1 Construct the correlation matrix

The functional connectivity matrices were obtained by calculating Pearson correlation coefficients between each pair of ROIs before a Fisher's z transformation was done. Then, the matrices were put into the GRETNA toolbox [15] to compute the parameters of networks.

5.4.2 Thresholding

The measurement of sparsity was defined as a percentage of the existing number of edges divided by the maximal possible number of edges in a network. The range of

0.05 < sparsity < 0.5 with an increment of 0.0045 was employed to threshold the correlation matrices into binary matrices.

5.4.3 Network metrics

For a given binary graph G with N nodes and K edges, the C_p of the network is defined as

$$C_p = \frac{1}{N} \sum_{i \in G} C_i \quad (1)$$

where C_i is the ratio of the number of existing connections to the number of all possible connections in a subgraph. $C_i = 2 * E_i / [D_i(D_i - 1)]$, where D_i represents the degree (defined as the number of edges connected to the node) of the i th node, and E_i denotes the number of edges in the subgraph G_i (defined as a set of nodes directly connecting to the i th node). The L_p is defined as the mean of the shortest path length of all pairs of nodes in the network:

$$L_p = \frac{1}{N(N-1)} \sum_{i,j \in G} l_{ij} \quad (2)$$

where l_{ij} expresses the shortest path between node i and j . The E_{loc} can be calculated as follows:

$$E_{loc} = \frac{1}{N} \sum_{i \in G} E_{loc}(i) \quad (3)$$

where $E_{loc}(i)$ is the local efficiency of node i . The $E_{loc}(i)$ can be measured as

$$E_{loc}(i) = \frac{1}{N_{G_i}(N_{G_i} - 1)} \sum_{j,k \in G_i} \frac{1}{l_{jk}}, \text{ where } N_{G_i} \text{ is the number of nodes in the subgraph } G_i. \text{ The}$$

E_g of the network can be formalized as follows:

$$E_g = \frac{1}{N(N-1)} \sum_{i \neq j \in G} \frac{1}{l_{ij}} \quad (4)$$

The normalized clustering coefficient $\gamma = C_p / C_{rand}$ and normalized characteristic path length $\lambda = L_p / L_{rand}$ were also calculated, where C_{rand} and L_{rand} represent the mean of clustering coefficient and the average of characteristic path length of random networks, respectively. Two-way analysis of variance (ANOVA) and two-sample t-test were used to measure significant differences ($p < 0.05$, Bonferroni correction).

Abbreviations

TR, repetition time;
SMS, simultaneous multislice;
 γ , normalized clustering coefficient;
 λ , normalized characteristic path length;
 σ , small-worldness;
 C_p , clustering coefficient;
 L_p , characteristic path length;
Eloc, local efficiency;
Eg, global efficiency;
BOLD, blood oxygen level-dependent;
R-fMRI, resting-state functional magnetic resonance imaging;
AAL, automated anatomical labeling;

Declarations

Ethics approval and consent to participate: This study was conducted in accordance with the Declaration of Helsinki. Informed consent to participate in the study was obtained from the participants verbally and in writing. This study was

approved by the Ethical Review Board of Shanghai Fifth People's Hospital of Fudan University.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests : The authors declare that they have no competing interests.

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Authors' contributions: XZ: Conceptualization, PL: Conceptualization, JL: Methodology, ZH: Formal analysis and investigation, TQ: Data Curation, QH: Writing - original draft preparation, YZ: Writing - review and editing, QL: Funding acquisition. All authors read and approved the final manuscript.

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	The main effect of brain parcellation			The main effect of TR length			Interaction effect		
	Sparsity	F Value	<i>P</i> Value	Sparsity	F Value	<i>P</i> Value	Sparsity	F Value	<i>P</i> Value
Cp	0.05-0.095, 0.2705-0.5	7.8420- 74.3617	1.6201×10 ⁻¹² - 0.0066	/	/	/	/	/	/
Lp	0.05-0.239	7.7083- 35.6278	9.6360×10 ⁻⁸ - 0.0071	/	/	/	/	/	/
Eloc	0.05-0.212, 0.374, 0.3785, 0.3875-0.5	7.9918- 149.1590	8.2742×10 ⁻¹⁹ - 0.0062	0.0635, 0.0086, 0.095, 0.1085, 0.1175-0.1535, 0.176, 0.1895-0.1985	7.7136-11.1360	0.0014-0.0071	/	/	/
Eg	0.05-0.2615	7.9212- 55.2858	2.3183×10 ⁻¹⁰ - 0.0064	/	/	/	/	/	/
γ	/	/	/	0.455-0.5	7.6964-8.6072	0.0046-0.0071	/	/	/
λ	0.05-0.257	8.0123- 20.9622	2.0513×10 ⁻⁵ - 0.0061	/	/	/	/	/	/
σ	/	/	/	0.4595-0.5	7.9814-8.4051	0.0050-0.0062	/	/	/

Figures

Figure 1

Network metrics for a single spectrum (0.01-0.1 Hz). All measures were represented as functions of sparsity across a range from 0.05 to 0.5 with an increment of 0.0045. TR0.5 means the repetition time is 0.5 ms, and the last digit presents the number of regions.

Figure 2

Network metrics for a particular subspectrum (0.064-0.082 Hz).

Figure 3

Network metrics for the multispectra at the global level.