Hierarchical Clustering to Measure Connectivity in fMRI Resting-State Data

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Abstract

Temporal coherence of low frequency oscillations characterizes the mammalian brain, even when no explicit cognitive tasks are performed. Functional connectivity MR imaging is used to map regions of the resting brain showing synchronous, regional and slow fluctuations in cerebral blood flow and oxygenation. We use a hierarchical clustering method to detect similarities of low-frequency fluctuations and describe one measure of correlations in the low frequency range for classification of resting-state fMRI data. For all cortical regions studied and clusters obtained, we quantify the degree of contamination of functional connectivity maps by the respiratory and cardiac cycle.

Introduction

In functional connectivity MR imaging [1-3], functionally related regions of the brain are identified by measuring the temporal correlation of spontaneous low frequency fluctuations in their MR signals while the subject is in a "resting" state. While the feasibility of resting-state fMRI has been demonstrated in several papers, functional connectivity is incompletely characterized with the standard "seed voxel" method. To reduce reader bias, functional connectivity data should be analyzed by means of a model independent method.

In the present work we applied a hierarchical clustering algorithm to find clusters whose voxel members have high cross correlation coefficients that indicate low frequency synchronous fluctuations in the fMRI signal. We use the synchrony to infer functional connectivity. This method does not require prior knowledge of cluster centers or the number of clusters present in the data. Our approach represents a first attempt to define an appropriate distance measure for analyzing resting-state data to partition all possible cross-correlation coefficients from multi-slice data into meaningful patterns of functional connectivity. Furthermore, this approach permits an evaluation of the effects of hardware (i.e. gradient) instabilities and magnitudes of motion-induced correlations on connectivity data.

Theory

A hierarchical clustering algorithm based on the single link method was used. As an appropriate similarity measure to group voxels into clusters for functional connectivity, we specified a new distance measure, which is based on the correlation coefficient of EPI-time series restricted to very-low frequencies (<0.1 Hz). In order to accomplish this, the spectral decomposition of all correlations between two voxels in the brain must be computed. The spectral decomposition of the correlation coefficient "$cc_f(q,q')$" has the property that the sum over all frequencies will yield the correlation coefficient between voxels q and q':

$$cc(q,q') = \sum_f cc_f(q,q') \tag{1}$$

where

$$cc_f(q,q') = \frac{N(\mathrm{Re}(\omega_n)\mathrm{Re}(\lambda_n) + \mathrm{Im}(\omega_n)\mathrm{Im}(\lambda_n))}{D} \tag{2}$$

labels the Fourier component (with frequency f) of the correlation coefficient between voxel q and voxel q'. The term D represents the product of the norm of the time courses for voxels q and q'. As a relevant distance measure $d(q,q')$ for the clustering between voxel q and voxel q' we propose

$$d(q,q') = 1 - \sum_{f=0}^{0.1Hz} cc_f(q,q') \,. \tag{3}$$

The value of this distance measure ranges between 0 and 1 (for positive correlations), and it decreases as the very low frequency contributions in the correlation coefficient increase.

Methods

Four normal male volunteers, ranging in age from 20-25 years and claiming to be in good health, participated in this study. Each subject was instructed before the scanning session to be as motionless as possible during the EPI acquisitions, to keep his eyes closed and refrain from any cognitive exercise. MR scanning was performed in a commercial 1.5 T LX scanner (General Electric, Waukesha) equipped with high-speed gradients and a standard birdcage head coil. Standard anatomical whole brain images were acquired. Six resting-state gradient-recalled EPI scans (epibold) were performed in the coronal plane with parameters: 4 slices, 64x64 matrix, TR/TE 400ms/50ms, flip angle 50 deg, FOV 24 cm, slice thickness 7 mm, 2mm gap, 1300 time frames, BW +/-62.5 kHz. The locations of the slices were chosen for each resting-state scan differently, so that auditory cortex, motor cortex and visual cortex were included. The high sampling rate was selected to be able to resolve cardiac oscillations. At a TR of 400ms, the Nyquist frequency is given by 1/2TR=1.25 Hz. Therefore, oscillations that are below this frequency will not alias. Both respiratory and cardiac rates were recorded using a flexible respiratory belt and a pulse oximeter. Aliasing of the cardiac rate was eliminated by the choice of a TR of 400 ms. The EPI scan duration was 8 min 40 sec.

In addition, four different phantoms (GE QA phantom, water melon, customized brain-like phantom, formaldehyde fixed human brain (post-autopsy)) were scanned with identical EPI parameters to assess hardware (gradient) instabilities.

Results and Discussion

Artifacts resembling motion were present in all phantom data due to hardware instabilities. For the customized brain phantom linear and angular displacements were required to register the data. The linear displacement in the I-S direction is the dominant artifact. The scanner drift is present during the entire scan and has a constant slope of 0.067mm/min. A slope of similar magnitude has also been found in human data. Clustering of the registered phantom data produced two clusters corresponding to small correlation coefficients.

For human studies most of the major clusters (that contained more than 4 voxels) gave reproducible patterns in the sensorimotor cortex, thalamus, primary visual cortex, fusiform gyrus, primary auditory cortex and Broca's area. As typical examples, Fig.1 shows readily identifiable patterns in one subject. All clusters were obtained by considering only frequency contributions less than 0.1 Hz (after Gram-Schmidt orthogonalization with the major motion functions from the registration). These patterns could be obtained in several different resting-state scans and the cluster locations were stable and reliable. Besides these patterns, other non-stationary patterns could be found. These patterns were obtained in a particular resting-state data set and could not be reproduced in other data sets of the same subject. However, analysis of possible motion contribution for these clusters gave insignificant numbers and does not provide a sufficient explanation.The role of cardiac and respiratory frequencies in the clusters was analyzed by computing the integral of the average differential correlation coefficient from 0 to frequency f for all clusters. If respiratory and cardiac effects contaminate voxels in specific clusters, a step-like increase in the slope at the respiratory range (0.2-0.3 Hz) and cardiac range (0.9 to 1.0 Hz) would occur. This is in general not the case.

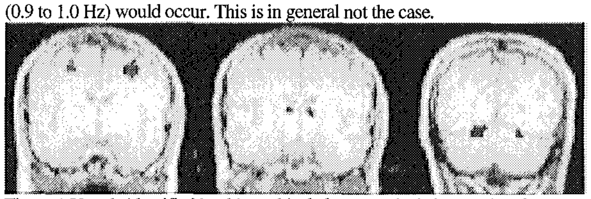

Figure 1:Voxels identified by hierarchical cluster analysis in a resting data set in the sensorimotor cortex (left), thalamus (middle) and fusiform gyrus (right).

Conclusion

The present study demonstrates that physiologically predictable patterns of correlations in low-frequency oscillations can be found in resting-state fMRI data by a hierarchical clustering methodology. A requirement for measuring connectivity with the method has been described. The method is "data-driven", meaning that the data themselves determine the natural divisions in the data set for functional connectivity. The approach is more powerful than the "seed-voxel" method in resting-state data analysis where the user selects a group of voxels and probes for all possible neuronal connections via cross correlation to the seed voxels. We have shown that most clusters are not contaminated by respiratory or cardiac noise sources and are characterized only by large correlations of low frequency components. Furthermore, we investigated the contribution of motion artifacts from scanner instabilities as well as subject motion on functional connectivity maps and illustrated a method to eliminate or reduce artifacts from resting-state data sets.

References

1. Biswal B, et al. MRM 1995; 34: 537-541 (1995).
2. Lowe MJ, et al. Neuroimage; 7: 119-132 (1998).
3. Xiong J, et al. Human Brain Mapping; 8:151-156 (1999).