Online detection of low-frequency functional connectivity

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ABSTRACT

Synchronized oscillations in resting state timecourses have been detected in recent fMRI studies. These oscillations are low frequency in nature (< 0.08 Hz), and seem to be a property of symmetric cortices. These fluctuations are important as a potential signal of interest, which could indicate connectivity between functionally related areas of the brain. It has also been shown that the synchronized oscillations decrease in some spontaneous pathological states (such as cocaine injection). Thus, detection of these functional connectivity patterns may help to serve as a gauge of normal brain activity. Currently, functional connectivity detection is applied only in offline post-processing analysis. Online detection methods have been applied to detect task activation in functional MRI. This allows real-time analysis of fMRI results, and could be important in detecting short-term changes in functional states. In this work, we develop an online algorithm to detect low frequency resting state functional connectivity in real time. This will extend connectivity analysis to allow online detection of changes in "resting state" brain networks.

Keywords: magnetic resonance imaging, functional imaging, functional connectivity, online analysis

1. INTRODUCTION

Recent studies in functional MRI have shown slowly varying fluctuations that are temporally correlated between functionally related areas. These low-frequency oscillations (<0.1 Hz) seem to be a general property of symmetric cortices, and have been shown to exist in the motor, auditory, visual, and sensorimotor systems, among others[1-3]. Thus, these fluctuations agree with the concept of functional connectivity: a descriptive measure of spatio-temporal correlations between spatially distinct regions of cerebral cortex. Several recent studies have shown decreased low-frequency correlations for patients in pathological states (such as multiple sclerosis[5], or cocaine use[6]. Accordingly, low-frequency functional connectivity may be important as a potential indicator of regular neuronal activity within the brain.

The use of investigator-defined regions of interest (ROIs) or "seed clusters" has been the primary analysis method used in functional connectivity studies[1-3,6,7]. This analysis method first uses a task activation scan to identify a functional region of interest (ROI). The corresponding timecourses in low-pass-filtered resting-state data are then averaged together to form a low-frequency reference waveform. This waveform is then cross-correlated with all other low-pass filtered resting state data to form functional connectivity maps. This standard functional connectivity analysis is implemented as an offline procedure.

Recently, however, there have been online, real-time approaches to analyzing functional MRI data. These include using cumulative correlation[8], sliding-window correlations with reference vector optimization9, online GLM analysis[10], and combined methods to collect behavioral, physiological and MRI data while performing near real-time statistical analysis[11]. So far, these online approaches have dealt with block or event-related task activation data, where the reference vector used for statistical analysis is known (or at least estimated) before the experiment. This is less useful in the case of functional connectivity, where the timecourse of the ROI is not known *a priori*. By applying an online method based on the standard offline approach, the reference timecourse can be estimated in real-time, and thus allow dynamic estimation of the functional connectivity patterns.

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In this work, we applied online analysis to detecting functional connectivity. A study involving both activation and resting-state data was analyzed using an online algorithm, and compared to the results using the standard offline approach. We demonstrate that the online analysis method allows dynamic detection of functional connectivity. This expands functional MRI studies to investigate in functionally connected resting-state networks in real-time.

2. METHODOLOGY

2.1. Online Algorithm

All online calculations were performed in the Siemens Image Calculation Environment (ICE). This allows access in real-time to online image reconstruction and display at the scanner, with no additional data transfer necessary. This helps to minimize the overall computational time required for the calculation of each final online image.

The online approach being presented uses a task activation scan to acquire the functional ROI (in this case in the motor cortex), then uses the defined ROI in a resting-state scan to form the online functional connectivity maps (see Figure 1). The nominal task reference paradigm is first defined at the beginning of the task scan. The task activation scan is performed, and then the activation data is correlated with the task reference to create task correlation maps. The block of four pixels in the correlation maps having the highest average task correlation coefficient is identified for each slice, and used to give the location of the ROI in the resting state data.

For the resting state data scan, a 10-point moving average of the data is used to low-pass filter the data. This removes the effect of the respiration and cardiac fluctuations, and confines the frequency spectrum of the BOLD (blood oxygenation level dependent) hemodynamic response (which has an upper bound of roughly ~0.1 Hz). The current estimate of the ROI reference waveform is then formed from the average of the current values of the low-pass filtered ROI voxels. The current values of the filtered data and the reference waveform are used to calculate cumulative correlation coefficient values for all voxels, using the following equations for the correlation coefficient:

$$r = \frac{\sum xy - N\overline{xy}}{\sqrt{(\sum x^2 - N\overline{x}^2)(\sum y^2 - N\overline{y}^2)}} \quad (1)$$

where x is the voxel values, y is the reference waveform values, and N is the current length of both vectors. This is computationally efficient, since it only requires the update of the cumulative sums for x,y, x^2, y^2, and the xy product, with minimal processing and storage requirements.

The current correlation maps for all slices are displayed at each timepoint. Alternatively, the current correlation threshold corresponding to a particular alpha level can be calculated, based on the current degrees of freedom, and used to display the current statistically significant voxels. The online analysis was performed for each resting-state data set, with results saved for comparison to the offline approach.

2.2. Data Acquisition

A series of functional MRI experiments were performed on a 3.0 T Siemens Trio scanner (Siemens, Tubengin, Germany) using an echo-planar pulse sequence. The sequence acquired 280 images, with pulse sequence parameters were TR/TE/FA/FOV of 750 ms/34 ms /50°/22 cm. Five 5 mm thick axial slices were acquired in each TR, with an in-plane resolution of 3.44 mm x 3.44 mm. Structural scans were acquired at the end of each session using a T1-weighted sequence, co-localized to the slices scanned in the functional sequences.

Two subjects were studied, with a task activation data set and a resting state set acquired for each subject. A sequential finger-tapping motor paradigm (21 seconds fixation, 21 seconds task, 5 repeats) was implemented for the activation data. Paradigm cues were presented to the subject in Presentation (Neurobehavorial Systems, Albany, CA) connected to a back projection screen. Resting state data was acquired while the subjects were inactive (lying still, with fixation cross being presented), and matched to the duration of the activation data (210 seconds total). The respiratory and cardiac rhythms of the subjects were recorded during all runs, using an Invivo physiological monitoring unit connected to a PC data acquisition board. In-house MATLAB code sampled the physiological rhythms at a sampling rate of 200 Hz, triggered off the start of the MRI scans by a TTL pulse output by the scanner.

2.3. Data Analysis

The moving average of the resting state data was first compared to the corresponding offline low-pass filtered data set. The frequency content of the moving average reference vector was also compared to that of the external physiological recordings to verify that these noise sources did not contaminate the low-frequency functional connectivity maps by aliasing into the frequency band of interest[12].

The online algorithm was then implemented. Task correlation maps and the reference ROI location and timecourse were generated and saved, for comparison of functional regions and examination of task performance. The online resting-state functional connectivity correlation maps were generated online and then stored, for comparison using the standard offline analysis method.

Standard offline functional connectivity maps were generated by first low-pass filtering the original resting state, using a rect filter with a cutoff frequency of 0.08 Hz. The reference waveform was formed using the saved task ROI, and was used to form functional connectivity maps with the low-pass filtered data.

3. RESULTS

The comparison of the low-frequency reference vector formed using the online 10-pt moving average and the offline low-pass filter shows good agreement between the major features of the two timecourses (Figure 2, upper) (correlation coefficient of 0.98) indicating that using the moving average reference to form the functional connectivity correlation maps will capture most of the same spatio-temporal patterns as using the offline low-pass filter timecourse. Furthermore, the frequency spectrum of the transformed moving average reference is seen to primarily lie under the 0.1 Hz cutoff for functional connectivity, and not to overlap the spectrum of the primary harmonic of the downsampled respiratory and cardiac signals of the subject (Figure 2, lower).

Motor task results from the task activation reference scan are shown in Figure 3 for a typical subject. Activity is seen bilaterally in the motor cortex, and well as in the supplemental motor region. The resulting reference ROI and timecourse for a typical slice are displayed.

Figure 4 shows a set of online functional connectivity maps during the resting-state scan. Significant correlation between the contralateral and ipsilateral motor cortices are evident, as well as the supplemental motor area, throughout the scan, even though there is no overt task. This is in agreement with previous functional connectivity studies[1-3,7,13,14]. Changes in the functional connectivity maps also indicate a possible dynamic nature to the network involved.

Comparison of the functional activity was done between the conditions of task activation, online moving average functional connectivity maps, and offline low-pass filtered functional connectivity maps. Results for a typical subject are shown in Figure 5. The bilateral activation seen in the task results are seen in the resting-state connectivity maps, for both the offline and online approaches. Again, the moving average matches the low-pass filter well, giving very similar results.

4. CONCLUSIONS

This work extended low frequency connectivity analysis to analyzing brain networks in an online manner, allowing near real-time assessment of functional networks, even with the subjects at rest. Comparison of the functional connectivity results showed good agreement between the online moving average online analysis and the offline low-pass filter analysis. Significant activity was seen in the resting-state in the motor-related functional network, and was similar to that seen in a bilateral motor task.

The design considerations for the online algorithm have been seen to work well. A minimal sliding window width combined with short MR acquisition time results in minimal lag between the current image and the cumulative correlation map display (in this case, the delay was 3.75 seconds). This allows for near real-time detection of changes in the “resting state” brain, and extends its utility for investigating time-dependent pathological states (e.g. epilepsy, pharmacological studies).

Future work will investigate: the interaction of the scan TR and the moving average window size, to try to minimize the display lag for a given scan; incorporating anatomy instead of function to define ROIs in order to reduce or eliminate the reference scan; an online GLM to remove the effects of baseline drift and physiology, and the use of model-free analysis methods in order to monitor multiple functional networks at one time while avoiding user bias.

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REFERENCES

1. B. Biswal, F. Yetkin, V. Haughton, and J. Hyde, "Functional connectivity in the motor cortex of resting human brain using echo-planar MRI," Magn. Reson. Med. **34**, pp. 537-541, 1995.
2. M.J. Lowe, B. Mock, and J.A. Sorenson, "Functional connectivity in single and multislice echoplanar imaging using resting state fluctuations," Neuroimage **7**, pp.119-132, 1998.
3. D. Cordes, V. Haughton, K. Arfanakis, G. Wendt, P. Turski, C Moritz, M. Quigley, and M.E. Meyerand, "Mapping functionally related regions of brain with functional connectivity MR imaging," Am J Neuroradiol **21**, pp. 1636-1644, 2000.
4. M.J. Lowe, M.D. Phillips, D. Mattson, M. Dzemidzic, and V.P. Matthews, "Multiple sclerosis: Low-frequency temporal blood oxygen level-dependent fluctuations indicate reduced functional connectivity-initial results," Radiol **224**, pp.184-192, 2002.
5. S.J. Li, B. Biswal, Z. Li, R. Risinger, C. Rainey, J. Cho, B. Salmeron, and E. Stein, "Cocaine administration decreases functional connectivity in human primary visual and motor cortex as detected by functional MRI," Magn Reson Med **43**, pp. 45-51, 2000.
6. M. Hampson, B.S. Peterson, P. Skudlarski, J.C. Gatenby, and J.C. Gore, "Detection of functional connectivity using temporal correlations in MR images," Hum Brain Map **15**, pp. 247-262, 2002.
7. S.J. Peltier, and D.C. Noll, "T2* dependence of low frequency functional connectivity," Neuroimage **16**, pp. 985-992, 2002.
8. R.W. Cox, A. Jesmanowicz, and J.S. Hyde, "Real-time functional magnetic resonance imaging," Magn Reson Med **33**, pp. 230–236, 1995.
9. D. Gembris, J.G. Taylor, S. Schor, W. Frings, D. Suter, and S. Posse, "Functional magnetic resonance imaging in real time (FIRE): sliding-window correlation analysis and reference-vector optimization," Magn Reson Med **43**, pp.259 –268, 2000.
10. C. Smyser, T.J.Grabowski, R.J. Frank, J.W. Haller, and L. Bolinger, "Real-time multiple linear regression for fMRI supported by time-aware acquisition and processing," Magn Reson Med **45**, pp. 289 –298, 2001.
11. J.T. Voyvodic, "Real-time fMRI paradigm control, physiology, and behavior combined with near real-time statistical analysis," NeuroImage 10, pp. 91–106, 1999.J. Hyde, and B. Biswal. Functionally related correlation in the noise. In Functional MRI (C.T. Moonen, P.A. Bandettini, Eds.), pp. 263-275. Springer-Verlag, Berlin, 2000.
12. T.E. Lund, L.G. Hanson. Physiological noise reduction in fMRI using vessel time-series as covariates in a general linear model, in "Proc., ISMRM, 9th Annual Meeting, Glasgow, 2001", p. 22.
13. J. Hyde, B. Biswal. Functionally related correlation in the noise. In Functional MRI (C.T. Moonen, P.A. Bandettini, Eds.), pp. 263-275. Springer-Verlag, Berlin, 2000.
14. J. Xiong, L. Parsons, J. Gao, and P. Fox, "Interregional connectivity to primary motor cortex revealed using MRI resting state images," Human Brain Map **8**, pp. 151-156, 1999.

Scan routine	**Task reference scan**	**Online connectivity scan**
Initialization	• Define task reference vector	• Read in motor ROI • Initialize online variables

Online	• Collect task MR images	• Update moving average of data
		• Update ref vector
		    • Update voxel vector
		    • Update cumulative correlation values
		• Display current correlation map

Offline	• Correlate image data with task reference vector • Select motor ROI • Save ROI, correlation map	• Save all online maps

Figure 1. Layout of the implemented online algorithm for dynamic detection of functional connectivity.

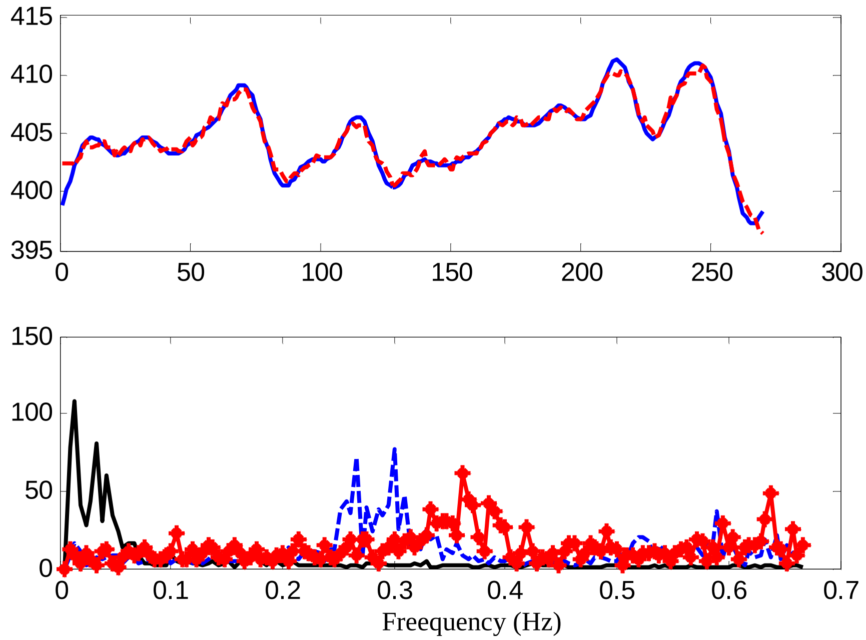

Figure 2. (Upper) Comparison of the low-freqeuency ROI reference waveform using the standard offline low-pass filter (solid) and the online 10 pt moving average (dashed).
(Lower) Magnitude frequency spectrum of the moving average reference waveform (solid), respiration waveform (dashed) and cardiac waveform (dash-dot). Physiological signals were downsampled from the acquired 200 to match the sampling rate of the MR scan (1.33 Hz).

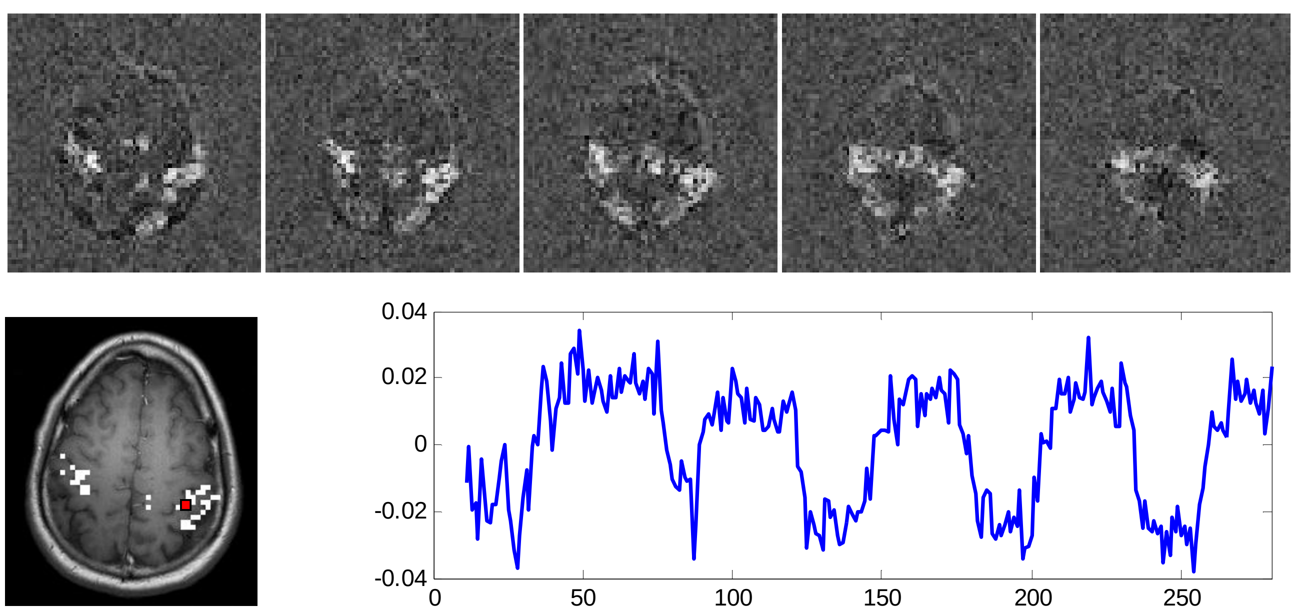

Figure 3. (Upper) Task activation correlation maps for a typical subject, across all five slices.
(Lower) The task activation of the second slice overlaid on the anatomical image (thresh), and the ROI region (box) and corresponding normalized timecourse.

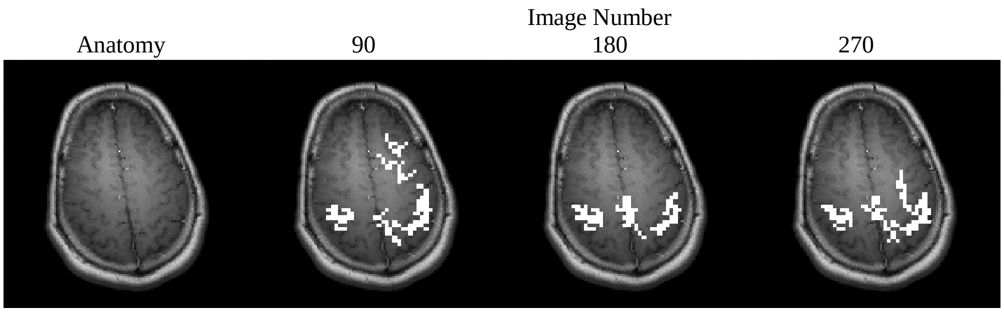

Figure 4. Low frequency resting state functional connectivity maps using the online algorithm, formed by cumulative correlation with the motor cortex ROI for a typical subject. Maps are thresholded at (p<.0005, relative to last image), and contiguity > 10 voxels for viewing purposes.

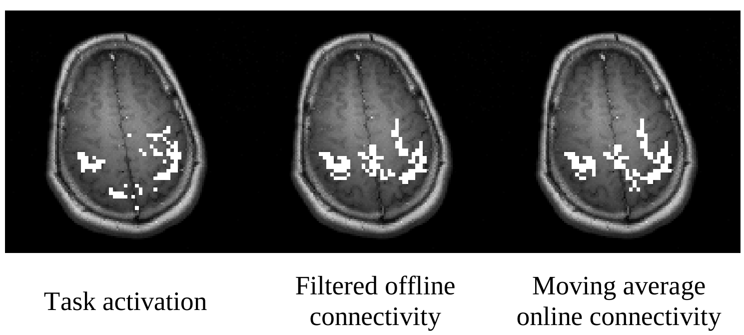

Figure 5. Task activation map (r>0.65) compared with the offline and online connectivity results (r>.55) in a typical slice.