

Quantifying the effects of CO2 on the resting BOLD signal

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Introduction

Low-frequency fluctuations in the blood oxygen level-dependent (BOLD) signal are an important component of 'physiological noise' in functional MRI signals. Identification and characterization of these sources is extremely important in order to develop noise reduction strategies and hence obtain more accurate activation maps. Spontaneous low frequency fluctuations in arterial carbon dioxide (CO2) have previously been identified as an important factor in the resting BOLD signal through the use of linear regression analysis. However, it is well known that there is a strongly frequency dependent relationship between CO2 and CBF, in which CO2 effects are concentrated in the low frequency range 0-0.05Hz. We therefore hypothesize that the effects of CO2 on the resting state BOLD signal are also restricted within low frequencies and investigate the frequency-dependent effects of CO2 on the resting state BOLD signal by using wavelet cross-correlation analysis.

Methods

A total of 11 healthy subjects participated in the study. Two fMRI scans (3T, TR = 3sec), eyeopen and eyeshut were performed, with simultaneous measurements of breath-to-breath spontaneous fluctuations of end-tidal CO2 acquired. First-level regression analysis (equivalent to cross-correlation analysis) were used to determine the effect of CO2 on the fMRI signal at each image voxel, regression coefficients of which were subsequently transformed to Z statistics indicating the statistical significance of the CO2-related BOLD signal change.

Wavelet cross-correlation was defined as the cross-correlation between the wavelet coefficients of two time series for a relative time shift τ :

$$WCC_{j,n} = \frac{|R_{X,Y}(\mathbf{W}_{j,n}^X, \mathbf{W}_{j,n}^Y, \tau)|}{\sqrt{|R_{X,X}(\mathbf{W}_{j,n}^X, 0) \times R_{Y,Y}(\mathbf{W}_{j,n}^Y, 0)|}}$$

The wavelet coefficients are computed by the recently developed maximal overlap discrete wavelet packet transform using Hilbert wavelet pair filters (MODHWPT). Wavelet cross-correlation is a measure of how well correlated two time series are across different frequency bands (decomposed using Wavelets).

Results

Regional distribution of CO2-related BOLD signal fluctuations in both the eyes open and shut cases identified from the first-level linear regression analysis is shown in Figure 1. The time shift between CO2 and BOLD oscillations is then determined by cross-correlation analysis, summarized in Table 1, which illustrates the different time delay associated with eyeopen and shut cases.

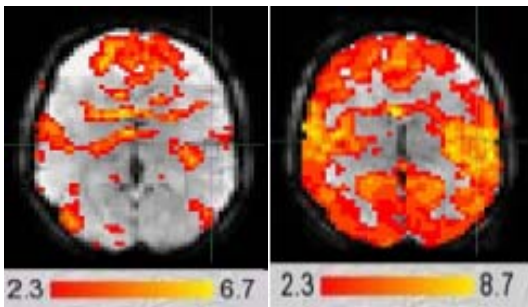


Figure 1 Z statistical map showing significant CO2 correlated BOLD signal change in (top) eyeopen and (bottom) eyeshut cases.

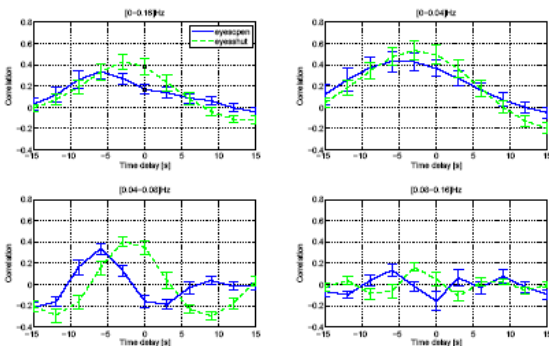


Figure 2 Cluster-averaged wavelet cross-correlation between CO2 and BOLD fluctuations across different frequency bands (cluster indicated by black square shown in Figure 1). Error bars represent standard deviation.

Condition	Maximum cross-correlation		Time shift [sec]	
	Eyeopen	Eyeshut	Eyeshut	Eyeopen
Grey matter	0.17±0.08*	0.18±0.07*	8.9±1.3 ⁺	6.7±3.0*
White matter	0.16±0.07	0.17±0.06	9.1±2.1 ⁺	7.3±3.2

Table 1 Group statistics of CO2-related BOLD fluctuations.

*P<0.05 grey vs white, +P<0.05, eyeopen vs eyeshut.

Figure 2 shows the wavelet cross-correlation results, illustrating the frequency-dependent coupling between the two oscillations. Wavelet cross-correlation values for the low frequency oscillations (0-0.04Hz, where most CO2 power is concentrated for this subject) between the two time series (top right) are significantly higher than for ordinary correlation (P < 0.01 with eyes both open and shut). The correlation curve for the other frequency band, i.e. 0.04-0.08Hz, clearly illustrates the different temporal dynamics of CO2 related BOLD response between the two conditions. Correlation for high frequencies, 0.08-0.16Hz, collapses since there is no CO2 power in that high frequency range.

Conclusion

The results demonstrate that CO2 fluctuations are an important source of low-frequency variations in resting-state BOLD fMRI data. The time delay between the CO2 and BOLD signals was found to be significantly shorter in eyeshut than in eyeopen. This difference in temporal dynamics would contribute to the observed large variability of the percentage of voxels which show significant CO2-related BOLD signal changes between the two cases, based on linear regression analysis which is equivalent to correlation at zero time shift. This illustrates the variable time shift should be carefully compensated for in such analysis. Moreover, wavelet cross-correlation was also used to assess the frequency-dependence of the CO2 -BOLD coupling, which illustrates that the effects of CO2 are concentrated in the low frequency band 0-0.08Hz.