The End-Tidal CO2 Response Function in Resting-State BOLD fMRI

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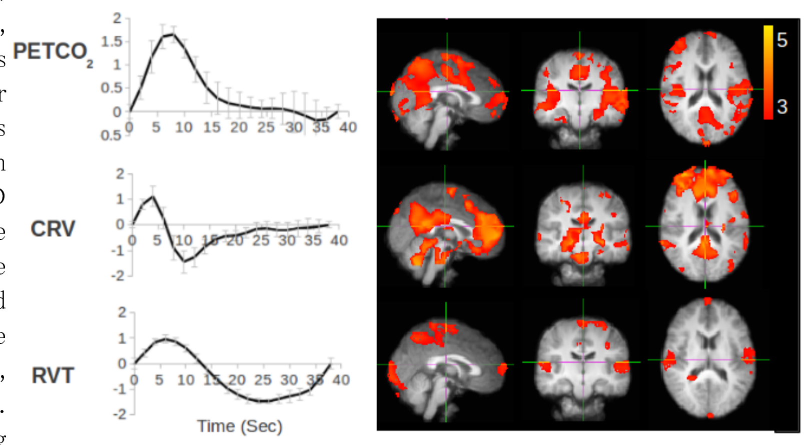
Introduction: End-tidal CO_2 ($PETCO_2$) fluctuations constitute a source of physiological noise in the BOLD fMRI signal [1]. $PETCO_2$ has been associated with respiration volume per unit time (RVT) variations [2], however the BOLD signal variations explained by the two variables are not identical [2]. Therefore, accounting for the RVT variation in the BOLD signal does not eliminate the $PETCO_2$ effect, making it essential to study the relationship between $PETCO_2$ and the BOLD signal. Previous studies either relied on cross-correlation [1,2] or assumed a standard gamma shaped hemodynamic response [1]. The objective of this study is to estimate the hemodynamic response of the resting-state BOLD signal to $PETCO_2$. To avoid possible confounding effects of other physiological variables, we simultaneously estimate the response function to $PETCO_2$ as well as cardiac and respiration variations. Knowledge about the hemodynamic responses of BOLD signal to $PETCO_2$ allows us to better characterize its effect on resting-state fMRI.

Method: 8 healthy subjects (5 male, age between 22 and 36) were scanned using a Siemens TIM Trio 3 T MRI scanner. Resting-state fMRI images were acquired using GRE_EPI sequence (TR/TE = 2000/30 ms, flip angle = 90, 26 slices, ~3.44x3.44x4.6mm^3, 360 volumes). Initial processing includes motion correction, brain extraction, spatial smoothing (10mm FWHM), high-pass filtering (0.01Hz) and regression of six motion parameters. The cardiac signal was recorded using a finger pulse oximeter. Respiratory and $PETCO_2$ signals were recorded with a respiration belt around the abdomen and a mask connected gas analysis modules, respectively (BioPac, Goleta, USA). Time-locked heart-beat and respiration artifacts were removed from fMRI data using RETROICOR [3]. The cardiac rate variation (CRV) was estimated from the time interval between consecutive R waveforms [4]. RVT was calculated as the breathing depth (difference between maximum and minimum) divided by its period [5]. $PETCO_2$ was calculated by finding the exhaled CO_2 peak in each breath. All physiological signals were re-sampled to 0.5 Hz (the sampling rate of fMRI data). Voxel-wise brain responses functions to the three physiological signals were simultaneously estimated using a linear Gaussian model as explained in [4]. Each subject's responses were estimated as the first component of principle component analysis (PCA) implemented on responses of all of the brain voxels. Group average response is then calculated as the average of the responses across eight subjects. PETCO2, CRV, and RVT signals of each individual are convolved with the corresponding estimated responses and then used as regressors to generate maps of the brain regions show significant correlation with the physiological signals.

Results: Group-average response functions to $PETCO_2$, CRV and RVT is shown on the left side of the figure, where error bars represent standard error across subjects. Estimated CRV and RVT responses are similar to those reported before [4,5]. $PETCO_2$ response shows a peak at around 9 seconds, which is in accordance with previously reported delay between $PETCO_2$ and BOLD signal [1,2]. Also, the shape of the $PETCO_2$ response function is dinstict from that of RVT. Group-average spatial maps of PETCO2, CRV, and RVT-associated BOLD signal changes are shown on the right side of the figure. In accordance with previous studies [1,2,4,5], significant contributions are mostly in the grey matter. These regions however are disjoint, potentially indicating different mechanism of interaction between BOLD and the three physiological signals. There is some overlap, however, between the regions most affected by RVT and by $PETCO_2$ fluctuations.



Conclusion: We simultaneously estimated brain response function to three major physiological variables; $PETCO_2$, CRV, and RVT variations. To our knowledge this is the first attempt to determine the BOLD response function to resting-state fluctuations in $PETCO_2$. This work permits more accurate investigations of the relationship between $PETCO_2$ and resting-state fMRI. In addition, simultaneous estimation of responses to $PETCO_2$, RVT and CRV would permit investigations of possible interactions among these three physiological responses.

References: [1] Wise R, et al., Neuroimage 21 (2004) 1652 - 1664. [2] Chang C, Glover GH., Neuroimage 47 (2009) 1381 - 1393. [3] Glover GH, et al., Magn Reson Med. 44(1) (2000) 162 - 167. [4] Chang C, et al., Neuroimage 44 (2009) 857 - 869. [5] Birn RM, et al., Neuroimage 40 (2008) 644 - 654