Low-frequency respiration related signals in resting state fMRI: a comparison of end-tidal CO_2 and respiration volume per time

K. Murphy[1], R. K. Niazy[1,2], C. J. Evans[1], and R. G. Wise[1]

[1]Cardiff University Brain Research Imaging Centre, School of Psychology, Cardiff University, Cardiff, United Kingdom, [2]Biomedical Physics Department, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia

Introduction Functional connectivity analysis has been used to map several consistent resting state networks by exploiting coherent low-frequency fluctuations in the BOLD signal. The assumption in most of the fMRI literature is that these correlated fluctuations are neuronal in origin. Others sources of low-frequency fluctuations exist in fMRI data that are unrelated to neuronal activity. These must be removed to achieve accurate mapping of resting state networks. Fluctuations in arterial CO_2 in the range of 0-0.05Hz are related to changes in the breathed volume of air and are reflected in the BOLD signal. Two readily available surrogate measurements are end-tidal CO_2 and RVT (respiration volume over time) [1,2]. Physiological noise correction using end-tidal CO_2, a measure of the CO_2 concentration at the end of exhalation, and RVT, a measure of breathed volume over time, would be expected to remove similar components from the fMRI signal (although the measures are anti-correlated with each other). Since there is a cost in equipment, setup time and discomfort to the subjects, it is important to investigate the relationship between these measures to remove any redundancy. Accurate correction of this low-frequency noise component will increase the precision of functional connectivity analysis, improving its applicability to both healthy subject and clinical studies.

Methods *Imaging Setup:* FMRI was performed on a 3T General Electric HDx whole body MRI scanner equipped with an 8-element receive-only brain array. Single shot, full k-space gradient recalled EPI was used for all functional scans. Ten subjects underwent a resting state fMRI scan with eyes open lasting 20 minutes. Scanning parameters: TR=3s, TE=35ms, matrix=64x64, FOV/slice=20cm/3.2mm, 45 slices. Physiological signals were collected at a sample rate of 500Hz using a pulse oximeter, a respiration belt and a capnograph measuring end-tidal CO_2. *Analysis:* After images were corrected for motion using a rigid-body volume registration, low-frequency trends were removed. The RETROICOR correction technique was used to remove unwanted signal oscillations at aliased cardiac and respiration frequencies [3]. Data were time shifted to align separate slices to the same temporal origin and converted to percentage change scores. End-tidal CO_2 and RVT regressors were calculated from the physiological measurements along with time-shifted replicas ranging from a lag of 0s to 20s in 0.5s increments. Correlation coefficients across these varying lags between the end-tidal CO_2, the RVT regressors and the fMRI data were calculated. The maximum/minimum correlation value across the lags was determined for the CO_2/RVT regressor. Activation maps that include the top 20% most positively/negatively correlated voxels were calculated. For each subject, the average time lag between the CO_2/RVT regressors within the activation maps was used as the lag of the CO_2/RVT regressor to include in a GLM. Variance maps (and their associated zf-stats) for each of the regressors were calculated and transformed into standard MNI space.

Results and Discussion The end-tidal CO_2 lags the RVT regressor. The average time delay across subjects between the two regressors is 7.78s±3.44s. The anti-correlation between these measures of breathing is smaller that might be expected for the physiological relationship between ventilation and end-tidal CO_2: the largest being -0.41 (see Fig 1). The average size of correlation values in the activation maps is similar for both regressors although overlap between the CO_2 and RVT activation maps ranges from 16% to 65% suggesting that the regressors represent two spatially separated confounds. Voxels that highly correlate with the CO_2 regressor are more spatially variable across subjects than RVT related voxels indicating that artifacts relating to CO_2 are more widespread throughout the brain. Both regressors explain significant portions of variance in the time series when included together in a GLM model (see Fig 2). Variance explained by the end-tidal CO_2 regressor is more spatially widespread and of slightly higher value (average zf-stat is 3.68 vs. 3.08 in regions where the combined variance explained by CO_2 and RVT is high). The degree of variance explained by the two regressors in individual subjects is variable, with a greater role of end-tidal CO_2 in 6 subjects and a greater role of RVT in the remaining four.

Figure 1

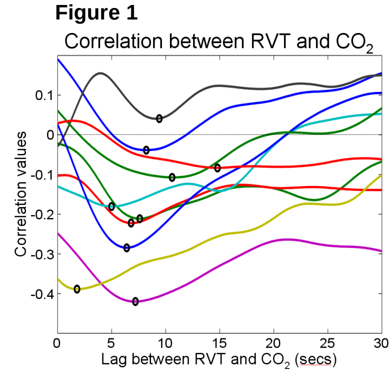
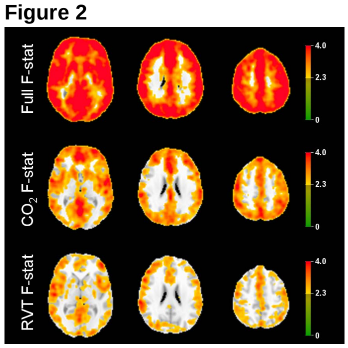


Figure 2



Conclusions A lack of similarity between the CO_2 and RVT regressors, the voxels that correlate most with them and the variance explained by them implies that each is measuring a different portion of the noise related to fluctuations in breathing and arterial CO_2. This suggests that both measurements should be collected to enable accurate clean up of low-frequency noise from resting state data.

References [1] Wise et al. (2004). NeuroImage 21:1652**;** [2] Birn et al. (2006). NeuroImage 31:1536**;** [3] Glover et al. (2000). MRM 44:162