FIGURE S1: The relative arrival time (rAT) maps obtained from resting state (RS) fMRI data with and without thresholding. An example rAT map from a single subject is shown in the top panel (a), while an averaged rAT map over 8 subjects is shown in the bottom panel (b). Column (i) shows rAT maps with maximum cross-correlation coefficient (MCCC) greater than 0.3. Column (ii) shows rAT maps without thresholding.

In a(i), voxels in black in the brain are those that do not pass the threshold. These voxels are most likely in the color of light blue and yellow in the unthresholded rAT map in a(ii). The same thing can be observed at the group level. A greater number of voxels in the rAT maps in b(ii) are shown in the color of light blue and yellow comparing with rAT maps in b(i). This is probably because the voxels that do not pass the threshold (i.e., MCCC<0.3) are more likely to have unreasonable large rAT (i.e., between -10 s and 10 s) due to spurious correlation.

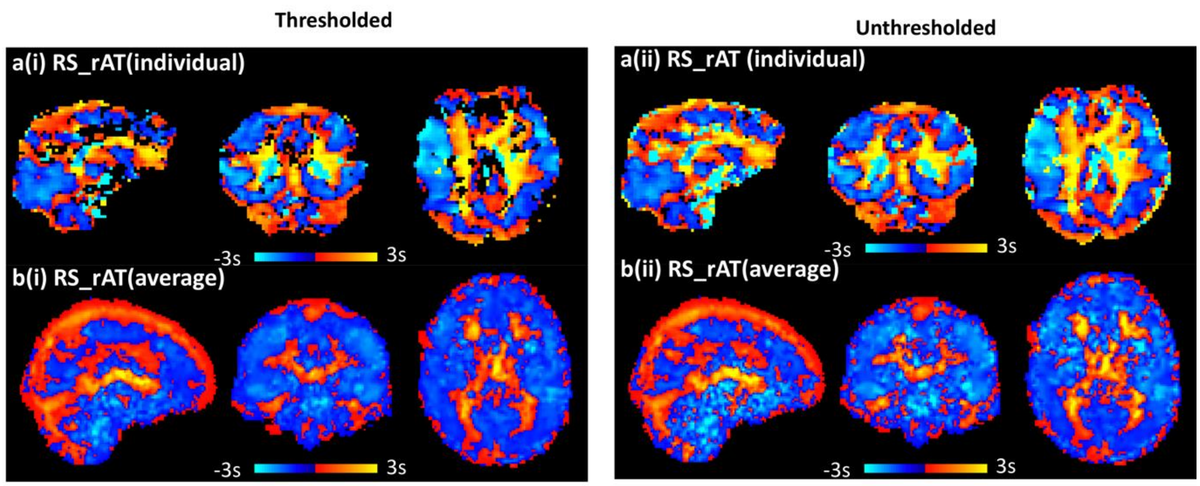


FIGURE S2: The spatial distribution of MCCC and delay times in gray matter (GM) and white matter (WM) with corresponding histograms from the RS and CO2 challenge data. The results from RS and CO2 challenge data are shown in (a-b) and (c-d), respectively. The spatial distribution of MCCCs and corresponding delay times in GM and WM are shown in the first and second columns. The corresponding histograms of MCCC and delay times are shown in the third column (GM is in blue and WM is in red).

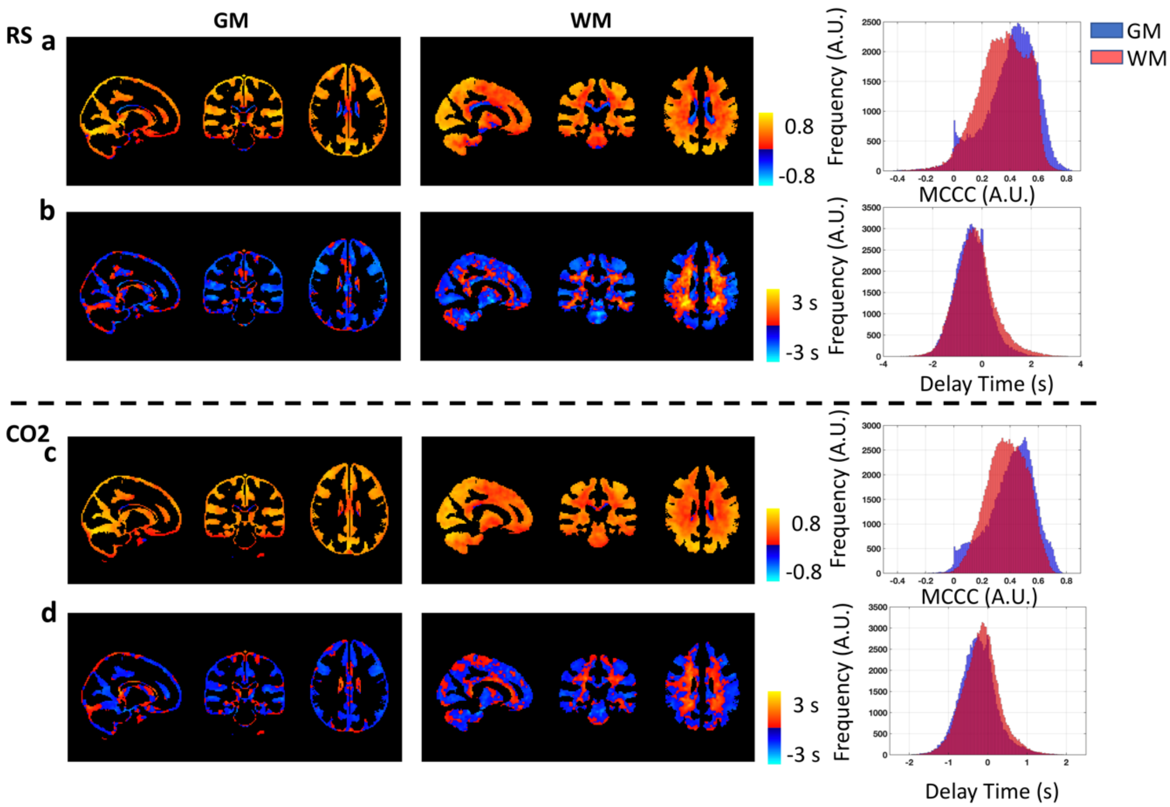


FIGURE S3: A comparison of the rAT maps from the hypercapnia and the resting-state. A paired t-test was performed on the rAT maps of the hypercapnia condition and the resting-state. The precentral gyrus in the prefrontal lobe showed a significant difference in the rAT (see left; p=0.001 (uncorrected)). The corresponding difference rAT map (CO2-RS) can be seen on the right to highlight the difference.

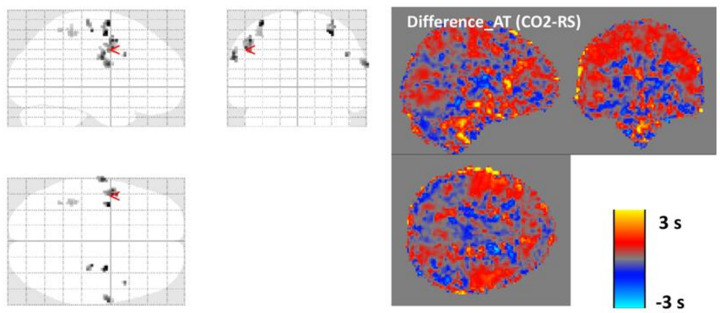


FIGURE S4: The evaluation of the spatial similarity among eight subjects. The *fslcc* from FSL software was applied to assess the similarities of the spatial pattern of eight subjects' HRF maps (registered to the standard space). Each subject was performed the spatial comparison with the other seven subjects. The mean and the standard deviation of the spatial correlation coefficients between each subject with the rest seven subjects was calculated. The results, including the correlation matrix, were shown below. Subjects 1-6 show relatively high averaged similarity correlation coefficients (0.55-0.62), while subjects 7 and 8 show relatively low values (0.51-0.53). The reason for lower similarities of subject 7,8 with other subjects was given in the limitation section.

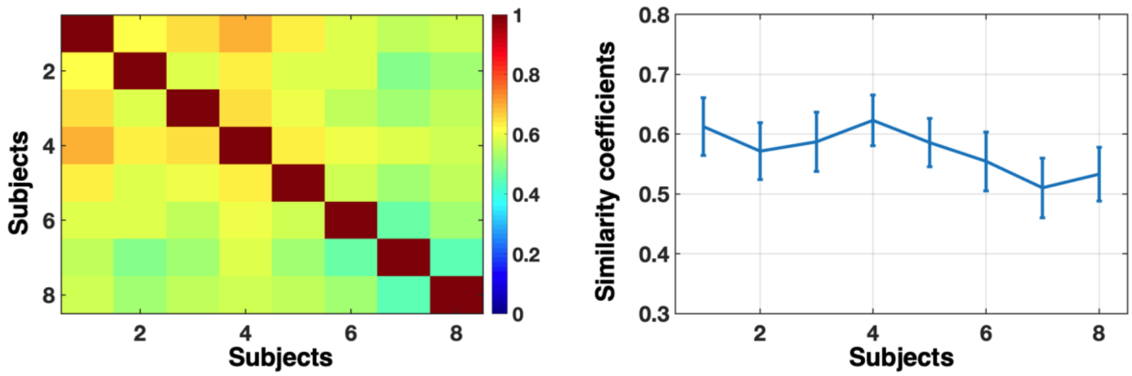


FIGURE S5: The comparison of the CVR values among three methods. Figure S5 (**a)** shows the difference maps between two of the three methods. Figure S5 (**b**) presents the R^2 contrast between two traditional methods. Figure S5 (**c**) presents the voxels that have significant differences in the CVR values between the two traditional methods under the false discovery rate (FDR) correction at 0.05. There is no significant difference under FDR correction at 0.05 between the proposed methods with the other two traditional methods. Note that the changes of the CVR do not necessarily mean the improvement of the accuracy. Higher the R^2 values indicates better the fitting between the convolved $P_{ET}CO2$ and BOLD, thus more accurate the CVR. On average, only 56% voxels have increased R^2 values with the traditional method with a fixed HRF compared to the traditional method without an HRF, while 80% voxels have increased R^2 with our proposed method compared to the traditional method without an HRF, which demonstrates that the proposed method outperformed the traditional methods in fitting the BOLD signals.

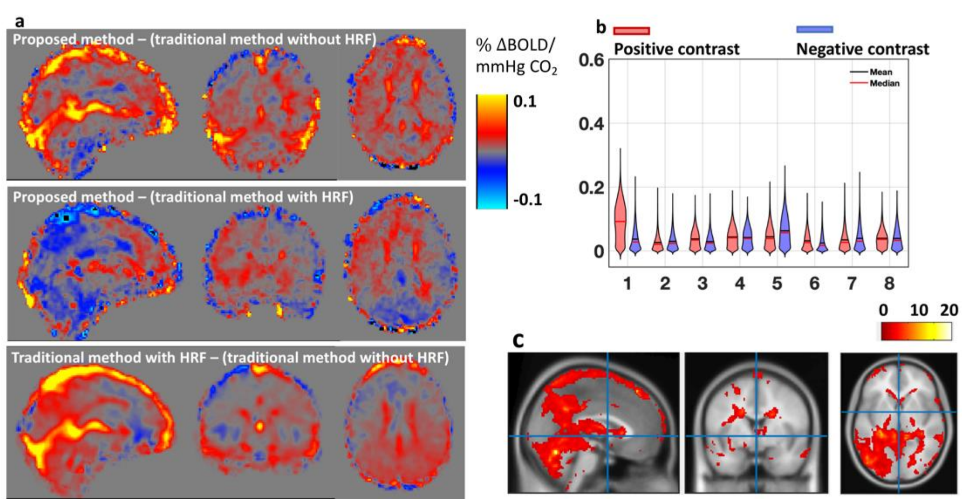


FIGURE S6: An example voxel and a simulation with increased and decreased CVR estimates. The increase of the CVR value is not necessarily related to the increase of the R^2 values. There are voxels that have decreased CVR values with increased R^2 values (An example voxel is shown). The R^2 value changed from 0.67 to 0.79, while the CVR value changed from 0.27 to 0.26. We also did a simulation to mimic these scenarios: increased R^2 leads to 1) increased CVR value and 2) decreased CVR value. The black curve is the $P_{ET}CO2$, while the red curves are the BOLD signal 1 and BOLD signal 2. To simplify the case, we assume that the estimated HRF is perfect in the way that the generated convolved $P_{ET}CO2$ is the same as the corresponding BOLD signal. The corresponding scatter plots showing these two cases are in the second row. The R^2 values increase in both cases (R^2=1) with the CVR value increased in BOLD 1 and the CVR decreased in BOLD 2. In both cases, the change of the $P_{ET}CO2$ and the convolved $P_{ET}CO2$ were maintained at 10 mmHg. However, the undershoot feature of the BOLD signal 2 lowers the convolved $P_{ET}CO2$ at 40 mmHg, which makes the CVR value decreases. Therefore, it is possible to have CVR value decreases with an increase of R^2 value, which depends on the shape of the BOLD signal.

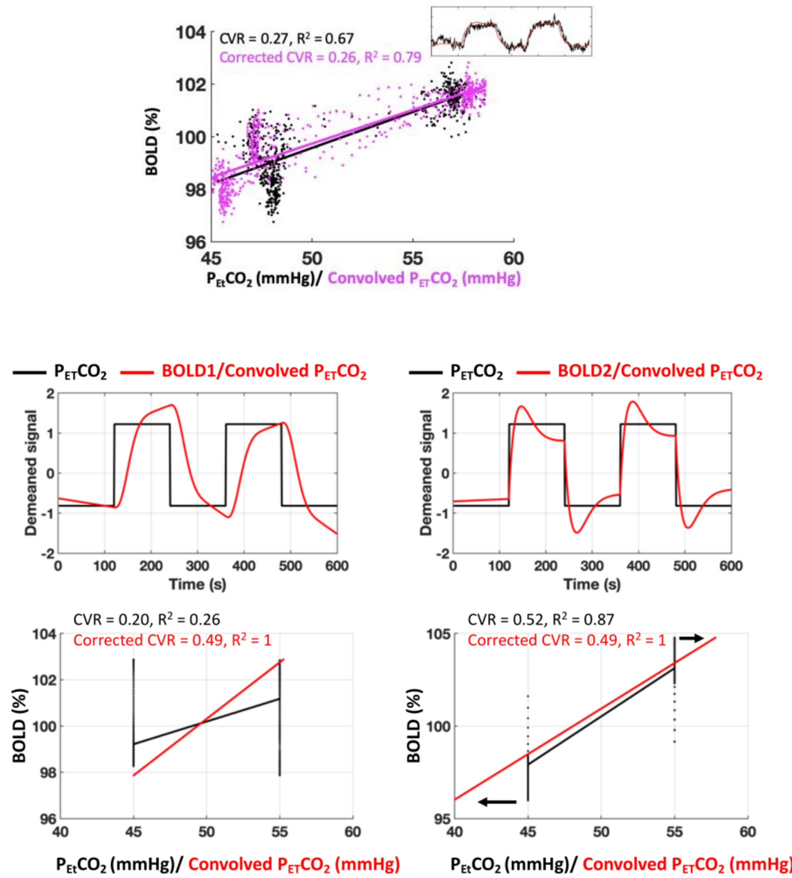


FIGURE S7: A simulation to assess the residual effect of the CO2 protocol on the delay calculation using sLFO (CO2-demodulated) signals. Though the P_{ET}CO2-related-vLFO (0.001-0.01 Hz) has been removed from the signal by subtraction, there may still be some harmonic effect or high frequency component of the boxcar stimulus left to the sLFO (CO2-demodulated). The simulation was performed in the following steps First, 1000 simulated sLFOs were created. Each combined the various frequencies (0.01~0.1Hz) with changing amplitudes (0~1). Second, the simulated BOLD was constructed by adding a P_{ET}CO2 time course (boxcar stimulus) and white noise to an sLFO created above. The sLFO was extracted from the constructed BOLD by using the same method in our approach and was compared with the original sLFO signal via cross-correlation. 95.7% of the simulations have the delay times within +1/-1 second (86.7% within +0.5/-0.5 second; 31.1% have zero delay times), and 98.7% of the simulations have

MCCCs greater than 0.3. Our results show that although the effect of the CO_2 was not fully removed in the sLFO in the hypercapnia, its effect on the resulting delay times is limited.

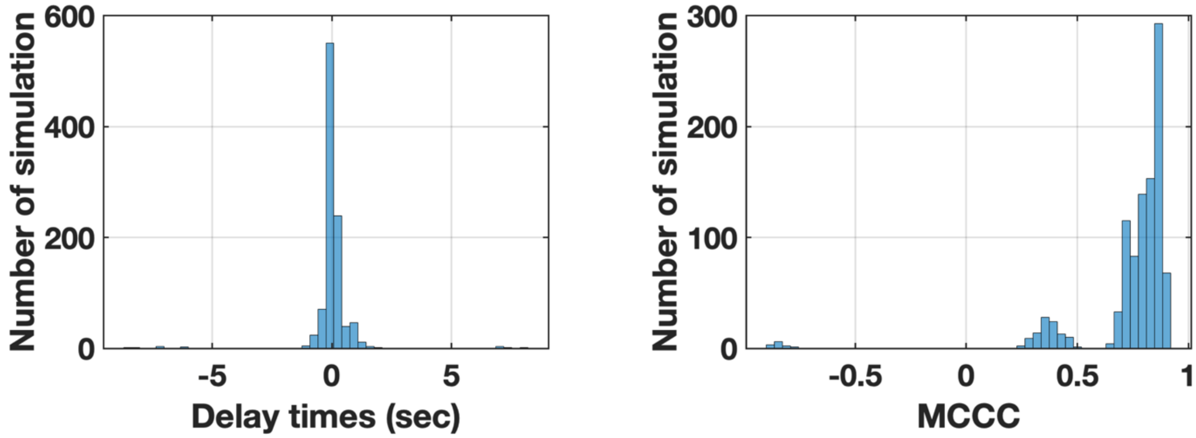


FIGURE S8: A simulation to evaluate the effect of the head motion on the delay calculation. The simulation started with two exact same BOLD signals with a time delay as 3 seconds with each other. One is defined as original BOLD and the other one is defined as shifted BOLD. The head motion was simulated as a single spike with a magnitude ranging from 0 to 5 times the standard deviation of a given BOLD signal (see left graph). The same head motion spike was added on both the original BOLD and the shifted BOLD at the same time point. The cross-correlation was performed between the sLFOs from both original BOLD and the shifted BOLD with added motion artifacts. The resulting delay times and the corresponding MCCCs were shown. The MCCC values are very high in all cases (0.939-0.998). The corresponding delay times vary from 2.6 s to 3 s, which are from 13% to 0% away from the real delay time (3 s). Based on the simulation, if the size of the motion artifact is smaller than 1.6 times the standard deviation of the given BOLD signal, the delay values will not be affected. Even with the large motion artifact (5 times the SD), the deviation is within 0.4 s. Therefore, we demonstrated that the head motion occurs instantaneously across the whole brain had limited effects on the delay time calculations.

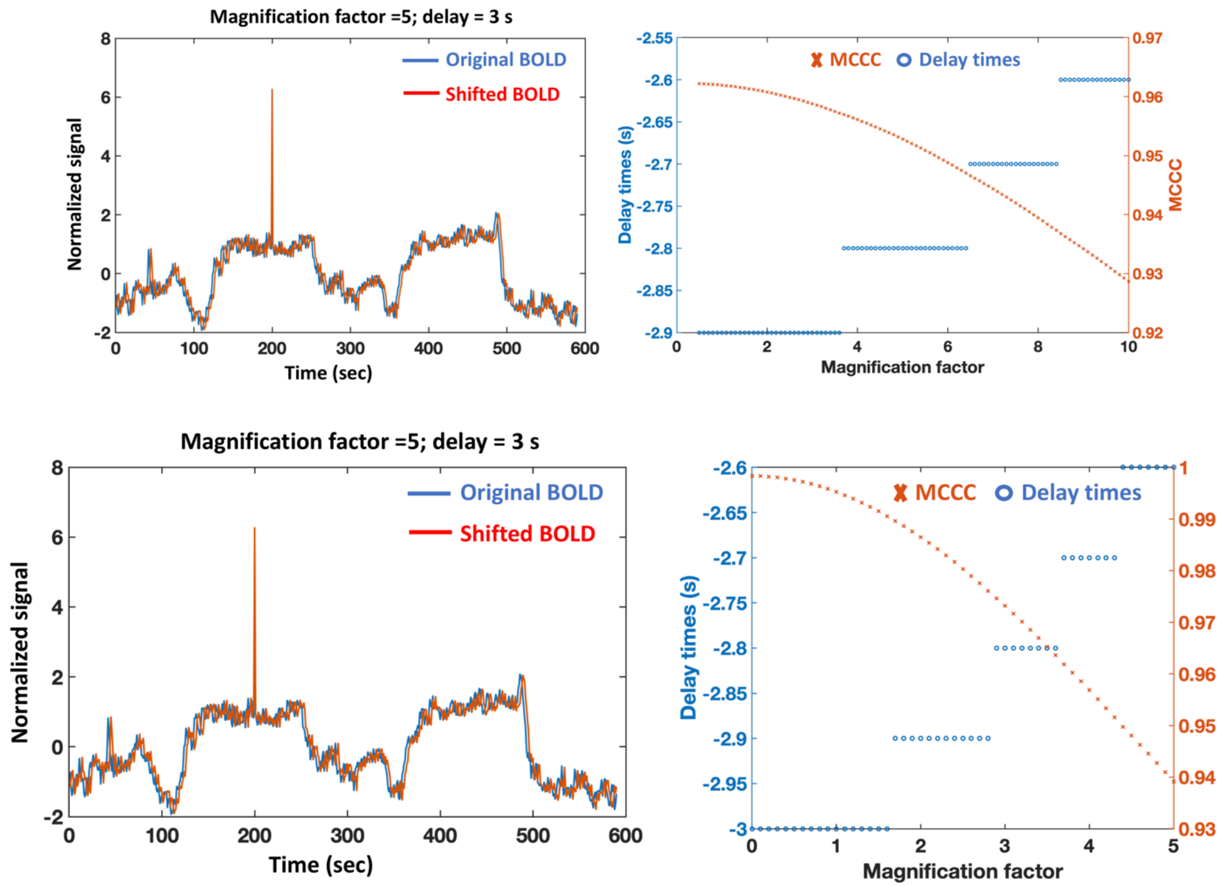
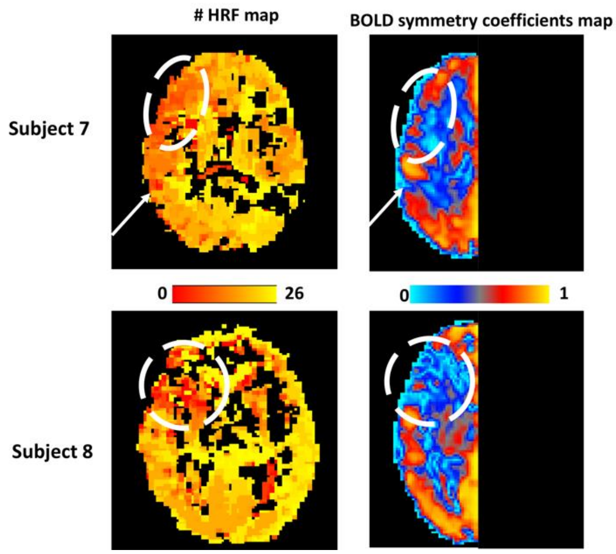


FIGURE S9: There are two reasons for the asymmetry, which are 1) the asymmetry of the BOLD and 2) the tilt of the subjects' brains during the scan (minor). A figure showing the original HRF map and the BOLD symmetrical coefficients map is given below. The symmetry of the BOLD data was assessed by acquiring the spatial correlation coefficients between symmetrical BOLD signals from the left and right hemispheres (after registration to the standard brain). The resulting coefficients map indicated the similarity of the BOLD between two hemispheres. In the HRF maps, the asymmetric areas were indicated by white circles and a white arrow (the same areas were also found in the BOLD symmetry coefficients map). We also found that the tilt of subjects' brains during the scan contributed to the HRF maps' asymmetry shown in the manuscript, even though the effect is minor.



HRF map
BOLD symmetry coefficients map
Subject 7
0
26
0
1
Subject 8