Inter-regional Differences in Brain Response Delay to End-Tidal CO2 Estimated from Resting-State fMRI

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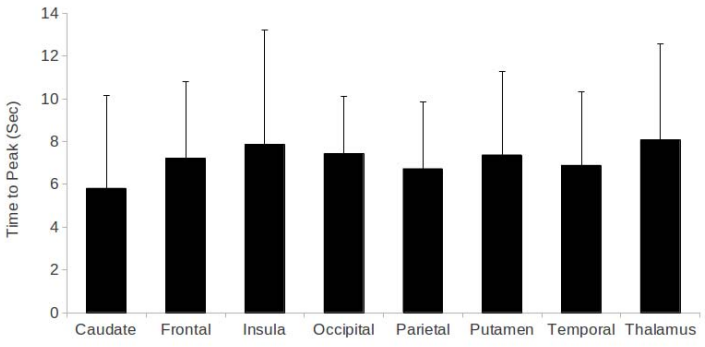
Introduction: Variations in end-tidal CO_2 ($PETCO_2$) level drive the BOLD signal due to vasodilation effect of CO_2 [1]. This effect is not homogeneous across brain regions, and different regions have exhibited different delays in their responses to CO_2 [2-4]. Delay maps are estimated from breath holding task [2,3] or cued breathing [3,4]. In addition to their clinical application, which include stroke, and arterial stenosis [5], these delay maps have been used to correct for regional differences in hemodynamic response to increase accuracy and validity of functional connectivity and causality analysis [2]. In this study, we attempt to estimate voxel-wise $PETCO_2$ response function and use the estimated responses to investigate regional variability of $PETCO_2$ effect on brain. Specifically we consider time-to-peak (TTP) of the estimated responses as an index of CO_2-associated BOLD response delay. To more accurately capture temporal variability, we used data acquisition with high temporal resolution.

Method: 6 healthy subjects (5 male, age between 22 and 36) were scanned using a Siemens TIM Trio 3 T MRI scanner. Slice-accelerated single shot GE-EPI image [6] were acquired using the simultaneous multi-slice technique (TR/TE = 323/30 ms, flip angle = 40, 15 slices, ~$3.44x3.44x6mm^3$, 2230 volumes, accelerating factor of 3). Processing steps include motion correction, brain extraction, spatial smoothing (10mm FWHM), high-pass filtering (0.01Hz), and regression of six motion parameters. Cardiac signal was recorded using a finger pulse oximeter. Respiratory and $PETCO_2$ signals were recorded with a BioPac system (BioPac, Goleta, USA). Time-locked heart-beat and respiration artifacts were removed using RETROICOR [7]. $PETCO_2$ was computed as local maxima of exhaled partial CO_2 pressure in each breath. In addition, cardiac rate variation (CRV) [8] and respiratory volume per time (RVT) [9] variation were included into the response function estimation to eliminate possible interaction between them and $PETCO_2$ response. Voxel-wise brain responses to the three physiological signals were simultaneously estimated with the linear Gaussian model explained in [8]. MNI structural atlas is used to segment grey matter into eight sub regions (caudate, insula, putamen, thalamus, frontal, occipital, parietal, temporal). $PETCO_2$ responses of all voxels inside each of the brain regions are reordered into a matrix and common response function is extracted using principle component analysis. Time to peak (TTP) of each response was computed in each sub-region.

Results: The average TTP of all sub-regions are shown in the figure, in which error bars represent standard deviation across subjects. On average, $PETCO_2$ response has delay of 6 to 9 seconds, which is in accordance with previous studies [1,2]. Subcortical regions (Insula, Putamen, Thalamus) generally have longer TTP compared to cortical regions.



Conclusion: The BOLD response delay to CO_2 can be a valuable clinical measure of vascular health [5]. Previous studies relied on breathing tasks to estimate this delay, but such methods could be uncomfortable for subjects, especially patients. In this study we demonstrate the feasibility of estimating the BOLD response function to $PETCO_2$ using resting-state data, and further estimated the CO_2-associated response delay in different brain regions. Sub-cortical regions appear to have longer TTP compare to cortical regions. Results from previous studies are not conclusive; while some are consistent with our findings [2], others reported different delay pattern [3,4]. While this work demonstrates the feasibility of estimating hemodynamic delay using resting-state fMRI data, further work is required to establish the reproducibility of these estimates as well as their sensitivity to pathology.

References: [1] Wise RG, et al., Neuroimage 21 (2004), 1652 ¨C 1664. [2] Change C, Glover GH, Neuroimage 47 (2009), 1381 ¨C 1393. [3] Bright MG, et al., Neuroimage 48 (2009), 166 ¨C 175. [4] Blockley NP, et al., Magn Reson Med 65 (2011), 1278 ¨C 1286. [5] Yezhuvath US., et al., NMR in Biomed 22 (2009) 779 “C 786 [6] Breuer FA, et al., Magn Reson Med 53(3), (2005) 684 ¨C 691. [7] Glover GH, et al., Magn Reson Med. 44(1) (2000) 162 ¨C 167. [8] Chang C, et al., Neuroimage 44 (2009) 857 ¨C 869. [9] Birn RM, et al., Neuroimage 40 (2008) 644 ¨C 654.