On the Spatial Distribution of Cerebrovascular Reactivity during Breath Hold and CO_2 Inhalation tasks as Assessed by Data-Driven Analysis Methods

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Introduction

Blood Oxygenation Level Dependent (BOLD) based imaging under a hypercapnic condition can be used to characterize hemodynamic impairment of cerebral vasculature[1] as well as the calibration of neuronally-induced BOLD signals in fMRI[2]. Administering acetazolamide and CO_2 inhalation (CO_2) are two standard methods for assessing Cerebrovascular Reactivity (CVR). Both methods require additional setup that may impede clinical workflow or detract from other neuroimaging metrics. A Breath Hold (BH) hypercapnia challenge task may serve as an alternative approach. An early study in healthy young population found a close correlation between CO_2 and BH methods[3], however it remains to be seen whether the same holds in the case of an elderly population. In this study we use a data-driven approach to identify the spatial distribution of grey matter CVR networks and attempt to compare BH and CO_2 CVR maps in our cohort of adults with preexisting vascular complications.

Methods

Twelve participants were scanned using a Philips 3T MRI system. Participants had preexisting vascular complications (2-Stroke, 2-TIA, 6 Type 2 Diabetes, 6-Hypertension, 7-had moderate to severe white matter disease, and some had multiple vascular risk factors; mean age: 68±9 years). MRI protocol consisted of a single-shot, gradient echo EPI for BOLD imaging during CO_2 and BH challenges and high-resolution T1-weighted imaging for image registration. The following parameters were used for BOLD imaging: TR/TE=2000/30ms, flip angle=90°, FOV=230x187mm^2, 40 slices, acquisition matrix=64x64, in-plane resolution=3.59x2.89mm^2, slice thickness=3mm and scan durations of 8m38s and 5m18s for CO_2 and BH, respectively. T1-weighted imaging was conducted using: TR/TE=9.5/2.3ms, flip angle=8°, FOV=240x191mm^2, 140 slices, acquisition matrix=256x164, in-plane resolution=0.94x1.17mm^2, slice thickness=1.2mm and scan duration of 8m56s.

For logistical reasons participants underwent the CO_2 inhalation challenge followed by the BH challenge. Hypercapnic CO_2 levels were achieved using a feed-forward, low gas-flow system (RespirAct™, Thornhill Research Inc., Toronto, Canada) and a sequential gas delivery circuit. The gas challenge consisted of two boluses (45s and 2min) during which $PetCO_2$ was raised by ~ 10mHg from participant's baseline. BH challenge, consisted of six 15s BH at the end of expiration with 30s rest period in between. **Data analysis:** BOLD images were corrected for motion and slice time acquisition (FMRIB Software Library; FSL). One participant was excluded from subsequent analysis due to excessive motion (>3mm). Temporal-concatenated ICA (MELODIC) was performed for CO_2 and BH data separately with 20 independent components estimated in each case. To identify task-related components, the time series were regressed against the task-specific model represented by an appropriate box-car function convolved with double-gamma HRF and incorporating a response delay. We examined a range of response delays, 0s-30s and 0s-20s for CO_2 and BH respectively. Task-related components were identified as having significant correlation (R>0.5) with proposed model at any response delay. After removing established artifact/noise components, binarized maps of all task-related components were generated for two tasks and used as a means to compare. A spatial correlation coefficient (R>0.5) was used to identify closely matched CVR networks between two tasks. Subject specific Z-stats and parameter estimate maps were generated using dual regression[4]. Z-stats maps were used to compute a spatial Coefficient of Variation (COV) in the overlapping regions of correlated components and combined into a two-factor repeated measure ANOVA to examine the difference in spatial variation between two tasks. Dual regression parameter estimate images were combined across correlated components of the two tasks and permutation testing[5] was used to test for pair-wise differences between BH and CO_2 CVR network voxels. Voxels were significant if they survived correction for multiple comparisons using threshold-free cluster enhancement (TFCE). Finally, the two BOLD datasets were combined into a single temporal-concatenated ICA (note: the number of CO_2 volumes was reduced to match total BH volumes) and results of paired permutation testing were compared to the approach described above.

Results and Discussion

MELODIC revealed 16 components for CO_2 (**Fig. 1a)** and 12 components for BH that had high correlation with the task model **(Fig. 1b).** Five components for CO_2 and four for BH were identified as noise caused by head motion or contribution from ventricular CSF (Components: 9, 12, 14, 15 and 20 for CO_2 and Components: 3, 8,10 and 12 for BH). The remaining components were considered as vascular reactivity networks that were combined to produce a resultant CVR map for each of the CO_2 and BH tasks (**Fig. 1c**). CVR maps had a high degree of overlap (orange). CO_2 CVR (yellow) had a higher CVR sensitivity in the frontal pole region, while BH CVR (blue) showed an increased detection power in the inferior temporal gyrus. Spatial correlation analysis identified 6 CVR networks that were highly correlated between two tasks. The overlapping regions of these components **(Fig.2)** were used to calculate COV (std/mean) on the subject-specific Z-stats obtained from dual regression for each task. The 2x6 ANOVA produced a significant main "task" effect (F (1,10)=36.7,p<0.001), as well as significant interaction effect ("task by network", F(5,50)=8.68, p<0.001), whereby CO_2 had a higher COV than BH. The voxel-wise permutation testing identified several regions of significant task differences (corrected p< 0.05/6 networks, p=0.008) (**Fig. 3**). CO_2 CVR was increased in the fusiform, precuneus, cingulate and precentral gyrus. Combined-task ICA confirmed increased CO_2 CVR in fusiform and precuneus (p<0.05) as well as identified additional regions, i.e. thalamus and lingual gyrus (p<0.05) with higher CVR during CO_2 (results not shown). No significant increase was detected in precentral gyrus and cingulate.

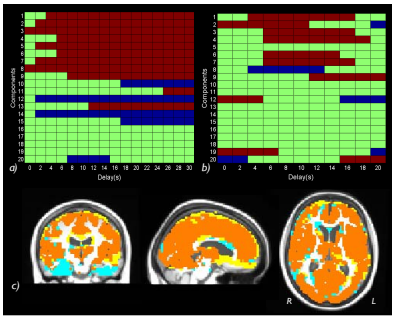

Figure 1. a) CO_2 components significantly correlated with task model for a range of delays
b) BH components significantly correlated with task model for a range of delays
c) Binarized maps of all task-related components: Yellow-CO_2, Blue – BH, Orange - both

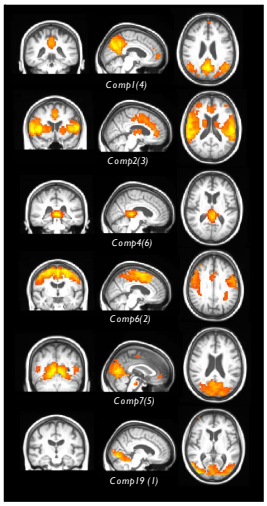

Figure 2.Overlapping regions of correlated components of two tasks, BH (CO_2)

Conclusion

The current study demonstrates that there is a high spatial correspondence in BOLD-based CVR when using CO_2 inhalation or BH approaches. Several regions, however, exhibited discrepancies between conditions, i.e. higher sensitivity to BH in inferior temporal gyrus and to CO_2 in the frontal pole region (**Fig. 1c**). Our examination of different response delays and their effect on identification of task-related ICA components highlights the importance of selecting a proper model for estimation of CVR measurements. This was particularly apparent with BH technique **(Fig. 1b).** An analysis of the COV revealed that CO_2 inhalation had higher spatial variability compared to the BH challenge. Voxel-wise differences between techniques were detected in the regions of visual object recognition, visuospatial processing and sensorimotor regions (**Fig. 3**), which may reflect hemodynamic differences between the two challenges or an effect due to underlying neuronal activation during these tasks. Future work is required to conclusively determine the nature of these differences.

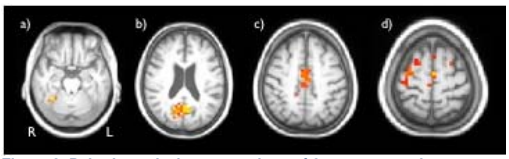

Figure 3. Paired voxel-wise comparison of 6 components between two tasks (corrected for multiple comparison, p<0.008) a) fusiform, b) precuneus, c) cingulate d) precentral gyrus

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