MAPPING HYPERCAPNIC CEREBRAL VASOREACTIVITY USING BOLD fMRI: REGIONAL VARIATION AND CORRELATIONS

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INTRODUCTION: Functional MRI has been used to map regional cerebrovascular reserve capacity (CVR) [1-3]. Hypercapnia induced by CO2-breathing is the most commonly used approach to challenge the vascular system with minimal, if any, neuronal or metabolic effects. Previous studies have primarily focused on CVR measurements for a few manually selected regions of interest (ROI) [3] or performed whole brain gray matter/white matter comparisons [1]. Regional differences in the BOLD signal to hypercapnia have also been reported but BOLD signal change has not been normalized to changes in end-tidal CO2 (EtCO2) [4,5]. We note that this normalization is crucial for correct quantification of CVR as EtCO2 (and thus PaCO2) is the 'input function" to the cerebral vasculature and it may be different in different individuals due to variations in breathing rate, breathing depth, lung function etc (e.g. Fig. 1). It should also be noted that none of the previous studies have reported any correlation among regional CVRs or between CVR and physiologic parameters. The purpose of this study was thus to fill in the lacuna in currently existing BOLD hypercapnia literature. This study used hypercapnic (5% CO2 breathing) BOLD fMRI to explore the whole brain distribution of CVR in healthy individuals using both voxel based and region of interest (ROI) analysis. Physiologic parameters were simultaneously recorded during scan. Measured EtCO2 was used as regressor for later analysis of functional data. CVR characteristics across brain regions and subjects were investigated.

METHODS: Whole brain imaging was performed using single shot gradient echo EPI, on a 3T Philips MR imaging system. Eight healthy subjects (mean age: 26.33±3.77) were recruited with informed consent. Subjects were positioned on patient table with physiologic monitoring probes attached. Nose was closed by a nose clip and the subject breathed room air or 5% CO2/air mixture through a mouthpiece. A researcher was positioned inside the magnet room for duration of scan. The operator instructed this researcher to switch between room air and gas mixture through special headsets (so, subject was not aware of the switch). The MR session started with a localizer and was followed by CO2 BOLD scan. Scan parameters were: TR/TE=3000/30ms, # slices 25, thickness 6mm, FOV 220mm, matrix 128x128, # dynamics 141. During first minute of scan, the subject breathed room-air followed by 4 minutes of 5% CO2 breathing and final 2 minutes of air breathing. Physiologic parameters including heart rate (HR), arterial oxygenation (sO2), breathing rate (BR) and EtCO2 were simultaneously measured (Novametrix Medical Systems, CT; MEDRAD, Pittsburgh, PA).

Functional imaging time series was processed using SPM2. Pre-processing included motion correction, normalization to MNI template space and smoothing with 6mm (FWHM) kernel. Voxel-by-voxel GLM was carried out using simultaneously-measured end-tidal CO2 waveform as a regressor for functional time series. Resultant parameter estimate images were used for generating CVR maps. ROI analysis on functional data and physiologic data processing were done using in-house MATLAB scripts. The MNI template has been parcellated into 116 regions of interest [6]. These ROIs were applied to pre-processed functional time series. BOLD signals within each ROI were spatially averaged to obtain an averaged time series. This time series was linearly regressed against the EtCO2 to obtain the CVR value for each ROI (in units of % BOLD signal change/mm Hg EtCO2). CVR values within multiple ROIs belonging to the same anatomic region were averaged to yield results for 9 regions on which further statistical analysis were performed (all tests thresholded at 2 tailed uncorrected $p<0.05$).

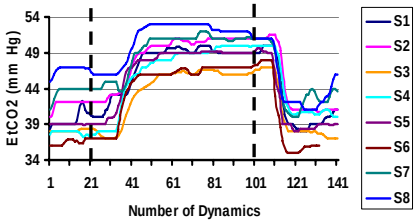

Fig. 1. EtCO2 waveforms for individual subjects. The vertical dashed lines indicate start and stop of 4 minutes of CO2 breathing.

RESULTS AND DISCUSSION: Measured EtCO2 waveforms for each subject are shown in Fig. 1, showing similar general patterns but also manifesting significant variations across individuals. The corresponding averaged CVR map for the group is displayed in Fig 2. As can be seen gray matter revealed higher CVR as compared to other regions.

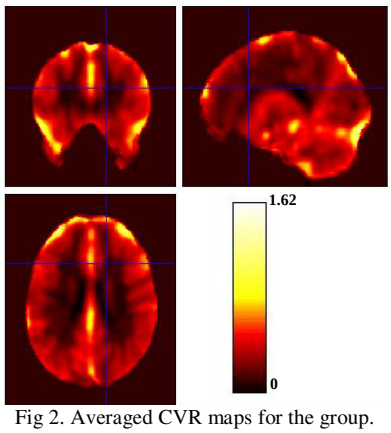

Fig 2. Averaged CVR maps for the group.

Hypercapnia-induced BOLD signal, without normalizing against EtCO2 (therefore, is not called CVR), was 3.49±0.49%. After normalization, CVR averaged over the whole brain was 0.34±0.07, in units of % BOLD signal/mm Hg of EtCO2 change. This agrees with values reported in literature [1]. All subjects showed an overall positive CVR. An ANOVA performed on regional CVR, revealed highly significant differences across the 9 regions ($p<3.26\times10^{-6}$) (Fig.3). Amongst these regions, cerebellum had highest vascular responsiveness and insula revealed minimal capacity for vasodilatation. This may be due to different vascular density or cerebral blood volume (CBV) across regions [5]. Interestingly, correlation analysis performed across subjects revealed significant correlations in many regions. (Table 1). The remaining regions also showed positive correlations, and they are likely to become significant when more subjects are studied. Hence, our data suggest that the CVR appears to be a global parameter for an individual. For example, a person with higher (compared to group average) vascular reactivity in frontal region tends to have higher CVR in all other brain regions, even though within the subject there are heterogeneities across regions. This finding is relevant when one aims to compare CVR between a control group and a patient group. According to our data, it seems that a relative CVR measure (e.g. using cerebellum CVR) would be more sensitive in detecting group differences as it removes the effects of global CVR variations across subjects. There was no correlation between observed regional CVR and age of subject, heart rate or breathing rate at the selected significance threshold. There was no significant lateralization in global CVR for a paired t test comparing the left vs. right hemispheres.

In summary, this work provides a reference value for CVR in different brain regions in young, healthy controls. In addition, we found that regional CVRs are correlated and there appears to be a global factor specific to each person. Based on this, we recommend the use of relative CVR instead of absolute CVR in group comparisons.

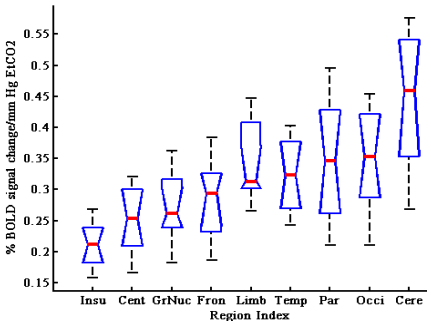

Fig.3: Boxplot of CVR across 9 anatomical regions arranged in ascending order. Insu: Insula, Cent: Central region, GrNuc: Sub cortical gray nuclei, Fron: Frontal, Limb: Limbic, Temp: Temporal, Par: Parietal, Occi: Occipital, Cere: Cerebellum

REFERENCES: 1) van der Zande *et al.* Neuroradiology 47:114 (2005); 2) Kastrup *et al.* MRI 19:13 (2001); 3) Lythgoe *et al.* MRI 17:495 (1999); 4) Rostrup *et al.* NeuroImage 11:87 (2000); 5) Kastrup *et al.* NeuroImage 10:675 (1999); 6) Tzourio-Mazoyer *et al.* NeuroImage 15:273 (2002)

	Insu	Cent	GrNuc	Fron	Limb	Temp	Par	Occi	Cere
Insu	1	0.769(0.025)	0.818(0.013)	0.641(0.087)	0.705(0.051)	0.699(0.053)	0.583(0.129)	0.377(0.358)	0.594(0.121)
Cent		1	0.931(0.001)	0.782(0.022)	0.694(0.056)	0.915(0.001)	0.916(0.001)	0.808(0.015)	0.716(0.046)
GrNuc			1	0.711(0.048)	0.869(0.005)	0.894(0.003)	0.828(0.011)	0.812(0.014)	0.824(0.012)
Fron				1	0.526(0.181)	0.592(0.123)	0.740(0.036)	0.545(0.162)	0.296(0.477)
Limb					1	0.716(0.046)	0.727(0.041)	0.741(0.035)	0.832(0.011)
Temp						1	0.846(0.008)	0.775(0.024)	0.689(0.058)
Par							1	0.886(0.003)	0.694(0.056)
Occi								1	0.818(0.013)
Cere									1

Table 1: Correlation across regional CVR [Notation: Correlation coefficient r (significance level p)]. Colored boxes show positively correlated significant pairs (uncorrected 2 tailed $p<0.05$)