Regional Differences in the 7T BOLD-CVR Response to Ramped Hypercapnic Stimulus Suggest Pressure/Flow dependent Signal Properties

Alex Bhogal[1], Marielle Philippens[2], Jeroen C.W. Siero[1], Esben Petersen[1], Joe Fisher[3], Peter Luijten[1], and Hans Hoogduin[1]

[1]*Radiology, University Medical Center, Utrecht, Netherlands,* [2]*Radiotherapy, University Medical Center, Utrecht, Netherlands,* [3]*Anaesthesia & Physiology, University Health Network, Toronto, Ontario, Canada*

PURPOSE: To characterize differences in the cerebrovascular reactivity (CVR) response of gray (GM) and white matter (WM) to a ramped targeted hypo- to hypercapnic stimulus.

INTRODUCTION: Previously we showed a non-linear BOLD-CVR response to a hypo- hypercapnic stimulus where whole brain (WB) %ΔBOLD showed plateau behavior at high $PaCO_2$ [1]. The response behavior varied between GM and WM ROIs suggesting the existence of distinct tissue-specific CVR response. Such differences have previously been attributed to response timing delays [2][3] and/or variation in the shape of the CVR response function [4]. Nevertheless, no clear explanatory mechanisms have been purported. Here we examine these processes in detail using a slow, progressive stimulus; thus, allowing the vasculature to equilibrate to increasing $PaCO_2$.

METHODS: 8 healthy volunteers were scanned on a Philips 7T scanner using a 32 ch. receive coil. Multi-slice, single-shot GE-EPI BOLD images (α: 90°, TR/TE 3000/25ms, EPI/SENSE 47/3, voxel dim: 1.5x1.5x1.6mm, FOV: 217.6 x 68.8 x 192mm, acq matrix: 120 x 133, slices: 43, volumes: 204) were acquired throughout a 600s targeted hypo- to hypercapnic breathing challenge delivered by a RespirAct (Thornhill Research Inc, Toronto, Can) as follows: 120s baseline, 60s hypocapnia (hyperventilation), 300s hypercapnic (avg increase = 5mmHg/min) ramp, 120s baseline. BOLD timeseries data was processed in FSL: Brain extraction (BET), re-alignment (MCFLIRT), ROI segmentation of mean- image to GM-WM ROIs (FAST). BOLD data was linearly detrended using pre- and post-stimulus baseline points, then normalized to baseline ROI signal. The ramped stimulus was temporally matched to measured $PaCO_2$ values to create BOLD-CVR curves. Eroded ROIs (fig D) were used to calculate average timeseries for GM and WM. Volumes were spatially smoothed (3x3x3 Gaussian Kernel, sigma 0.65) and signal timeseries' were temporally smoothed (Loess filter, 6% regression window). Finally, sigmoidal **[y=(a+(b/(1+exp(-(x-c)/d))))]** and linear **[y=a*x+b]** models were fitted to BOLD-CVR curves. Normalized average %ΔBOLD for absolute $PaCO_2$ steps from baseline were calculated based on individual sigmoid models. CVR maps expressing changes in %BOLD per unit change $PaCO_2$ were generated based on the slope of the fitted linear model.

RESULTS: Fig A shows single subject GM/WM BOLD data. Fitted sigmoid curves highlight the different CVR response between GM and WM compartments (Fig B). At high $PaCO_2$ GM signal plateaus while WM signal shows increasing behavior followed by a plateau shifted in $PaCO_2$. Mean sigmoid model span **(b)** and midpoint **(c)** parameters were 14.7/5.2 (%ΔBOLD) and 32.8/40.5 (mmHg $PaCO_2$) for GM/WM respectively ($p<0.001$). CVR behavior and significant tissue specific differences were consistent across different subjects (Fig C). Representative single subject, voxel-wise CVR maps (Fig D) based on whole brain and eroded GM and WM ROI masks show that WM CVR is generally lower than that of GM.

DISCUSSION: Using a progressive $PaCO_2$ stimulus, we have shown clear differences in CVR behavior between GM and WM which are consistent across different subjects. Differences in relative tissue %ΔBOLD can be attributed to variations in perfusion properties or vascular density. The average midpoint shift of the GM/WM CVR curves was ±7.7 mmHg corresponding to a temporal shift of 84s. Since the relative shift in tissue response is so large we believe this difference is not solely an effect of delayed CVR response. We propose that the observed differences may be due to dynamic pressure and flow responses arising from tissue-specific structural organization of the cerebrovasculature. Assuming GM/WM vessels both exhibit CVR, a vasoactive stimulus will cause variable decreases in peripheral resistance between GM/WM compartments. The magnitude of this decrease will modulate blood flow at upstream branch points (i.e. at descending cortical, lenticulostriate arteries), affecting relative flow rates to different tissue compartments. The increasing nature of the WM BOLD signal (compared to the GM plateau) suggests that the WM CBV capacity may not be matched by CBF until high $PaCO_2$ when GM signal levels off (causing a delayed WM plateau). Alternatively, WM may react more passively. These factors may be in addition to CVR delays and structural or autoregulatory differences (smooth muscle density, astrocytes, compliance etc).

CONCLUSION: We have shown differences between GM and WM CVR response which cannot be easily explained by a delay in CVR response time. A tissue specific response function seems a more likely explanation.

REFERENCES & ACKNOWLEDGEMENTS: [1] Bhogal et al., PROC ISMRM 2013, [2] Blockley et al., MRM 2011, [3] Thomas et al., PROC ISMRM 2012, [4] Rostrup et al., Neuroimage 2005 **This study was part of the EU Artemis high profile project**

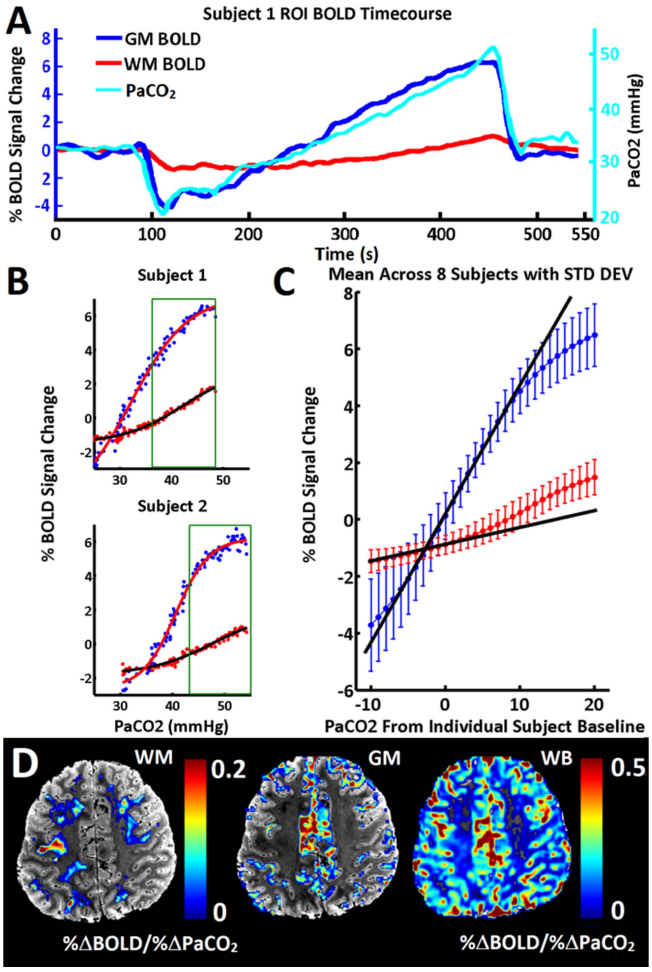

***Fig A**: GM/WM %ΔBOLD in response to hypo-hypercapnic stimulus. **Fig B**: Fitted GM (red) and WM (black) CVR response curves for 2 different subjects. Green boxes highlight non-linear response of tissues. **Fig C**: Mean normalized % signal change (with std dev) for 8 subjects. Signal change is calculated from the fitted sigmoidal model based on absolute $PaCO_2$ increases from baseline $PaCO_2$ values. The black lines highlight deviation from linearity. **Fig D**: Representative WM (left) and GM (center) ROI segmented CVR maps. Conservative GM/WM ROIs shown were also used for signal averaging to produce BOLD-CVR curves. Whole brain (WB) CVR map is shown on right. WB and GM scaling is the same.*