Task-correlated physiology reveals vascular-neural networks

Molly Gallogly Bright[1], Joseph Whittaker[1], Ian Driver[1], and Kevin Murphy[1]
[1]*CUBRIC, School of Psychology, Cardiff University, Cardiff, Wales, United Kingdom*

Target Audience: Those interested in neurovascular interactions or mapping and understanding functional brain networks.

Purpose: Neurons and cerebral blood vessels are tightly coupled in both structure and function to protect brain metabolism. Using simultaneous neural and vascular stimuli, we have identified coupling of neural and vascular processes at the network level, providing the first visualization of co-localized networks of neural and vascular origin[1]. Here we repeat the experiment in the same subjects, but without a hypercapnic vasodilatory stimulus, to better understand when vascular-neural network pairs can be observed and how this impacts our interpretation of BOLD fMRI.

Methods: A 3-back working memory task and a visual stimulus (radial 8 Hz flashing checkerboard) were presented in an orthogonal block design. In the original experiment (Exp1), simultaneous global vasodilation was induced via blocks of CO_2 inhalation. Ten healthy subjects were scanned using this paradigm, 3 times each, using a 3 Tesla GE HDx scanner and BOLD-weighted GE-EPI sequence. The 30 datasets were averaged together to reduce the confound of intrinsic signal fluctuations and to isolate signals time-locked to the neuro-vascular stimulus. Independent Component Analysis (ICA)[2] was used to identify pairs of spatially similar networks, one correlated with the neural stimulus and the other with the hypercapnia paradigm[1]. In the new experiment (Exp2) reported here, no hypercapnia stimulus was given and end-tidal (ET)CO_2 levels were passively monitored via a nasal cannula. Eight of the original subjects were scanned. The Exp2 time-series associated with the vascular-neural network pairs identified in Exp1 were extracted, and temporal correlations with the neural stimuli and $ETCO_2$ fluctuations were calculated to determine the network's origin.

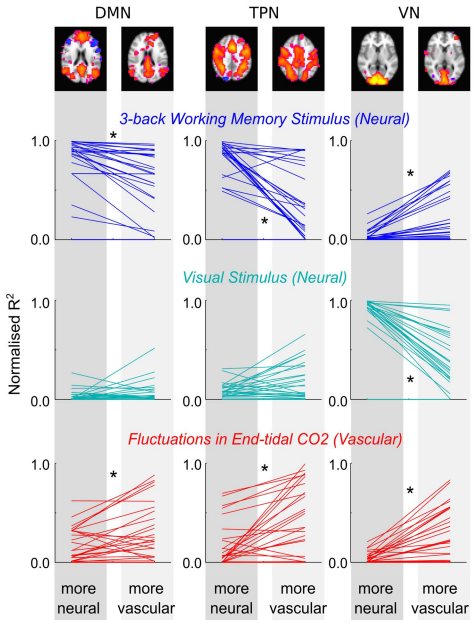

Fig 1. Pairs of spatially similar networks were identified in Exp1. The associated time-series were extracted for each of the datasets in Exp2, and the relative variance explained by the neural stimuli or vascular fluctuations was calculated (normalised R^2). Significant differences are indicated (paired t-tests, *p(corrected)<0.05).

Results: In Exp2, we observe that the network pairs first identified in Exp1 (Default Mode Network (DMN), Task Positive Network (TPN), and Visual Network (VN)) divide the data into two time-series; one significantly more correlated with the neural task and one significantly more correlated with (now un-controlled) vascular fluctuations (Fig 1). This provides supporting evidence that functional brain networks are comprised of coupled vascular-neural networks, even in the absence of an external vasodilatory stimulus. We also observed significant anti-correlation between group mean $ETCO_2$ levels and the 3-back stimulus ($r = -0.24$, $p=1x10^{-5}$), demonstrating consistent task-correlated changes in physiology. This structure is most apparent when $ETCO_2$ is averaged across the 3-back stimulus blocks (Fig 2; $r = -0.48$, $p=0.01$), and it drives the significant relationship between the vascular Visual Network time-series and the 3-back stimulus. Finally, ICA of the group average data in Exp2 did not isolate the vascular-neural network pairs as cleanly as in the Exp1 data, indicating that the hypercapnia stimulus of Exp1 assisted in extracting these components. However, ICA did identify a new network (Fig 3) with high spatial similarity to the known motor network[3] and temporally anti-correlated with the 3-back task. Bilateral deactivation is unlikely during a stimulus involving a button press; instead, this network is likely another *vascular* network that was identified via positive correlation with task-correlated $ETCO_2$ (block-averaged data, mean $r = 0.37$).

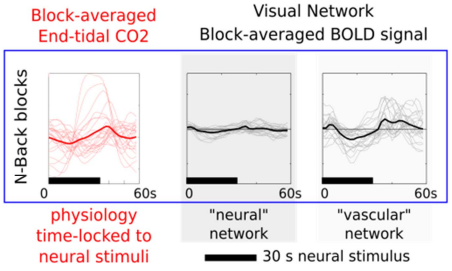

Fig 2. Block-averaged end-tidal CO_2 levels demonstrate physiologic changes correlated to the 3-back stimulus, causing a significant relationship between the "vascular" Visual Network time-series and 3-back task.

Discussion: Unlike neural stimuli, there is no vascular stimulus that targets a functional network. However, the data collected in Exp2 replicates the findings in Exp1, and identifies an additional network derived from task-correlated physiologic changes. There are few reported instances in the literature of task-related physiology[4], and this confound may have critical effects in standard BOLD experiments, causing "activation" in multiple vascular networks that may be difficult to differentiate from neural network responses.

Conclusion: Using results from two studies, with and without an external vascular stimulus, we demonstrate that functional brain networks are comprised of close coupling between networks of vascular and neural origins. Task-correlated changes in subject physiology significantly affect multiple vascular networks and may mimic, spatially and temporally, neural network activations.

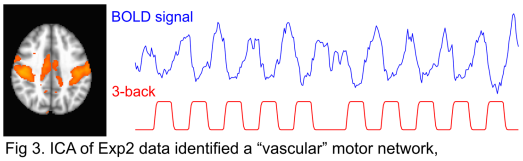

Fig 3. ICA of Exp2 data identified a "vascular" motor network, anti-correlated to the 3-back task ($r = -0.43$) but positively correlated with the block average ETCO2 fluctuations ($r=0.37$).

References: [1]Bright et al (2014) Proc. ISMRM #441; [2]Smith et al (2014) Neuroimage 23:S208-19; [3]Smith et al (2009) PNAS 106:13040-45; [4]Birn et al (2009) Neuroimage 47:1092-1104.
Acknowledgements: Funded by the Wellcome Trust [WT090199].