Task-dependent neurovascular uncoupling in Moyamoya disease

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Target audience: Researchers and clinicians interested in the impact of neurovascular coupling on BOLD fMRI.

Purpose: BOLD measurement of cerebrovascular reactivity (CVR) is emerging as a potential tool for characterizing pathology in patients with cerebrovascular disease. The presence of negative CVR, possibly indicating vascular steal, is thought to be a sensitive marker for cerebrovascular dysfunction[1]. It has been shown in brain tumor patients that regions of negative BOLD CVR exhibit neurovascular uncoupling[2]. In moyamoya disease (MMD), stenosis of the internal carotid, middle cerebral, and/or anterior cerebral arteries is associated with abnormal CVR in anterior brain regions, whereas the CVR of posterior brain regions is relatively spared. Chronic neurovascular uncoupling is suspected in affected anterior regions in MMD[1]; however, task-dependent neurovascular coupling has not been explicitly evaluated in this patient group. We sought to manipulate neurovascular coupling in MMD patients experimentally. Participants performed three fMRI tasks in which the distribution and extent of vascular demands were varied: a visual task (to target posterior, unaffected regions), a motor task (to target anterior, affected regions), and a combined visual-motor task (to elicit a more extensive vascular response including both affected and unaffected regions).

Hypothesis: When the total vascular demands of the task are more extensive, regions of abnormal BOLD CVR are particularly susceptible to neurovascular uncoupling.

Methods: Two adult MMD patients with stenosis primarily affecting the right hemisphere and four controls were studied. MRI data were acquired (3T Siemens TIM Trio, 32 channel head coil) using a dual-echo EPI pseudo-continuous ASL sequence ($TR/TE_1/TE_2$=4000/10/30ms, 3.9mm^3 voxels, 90 volumes, GRAPPA=2). Only BOLD data (2nd echo) are considered here. CVR was evaluated by using RespirAct[3] to target end-tidal CO_2 (10mmHg above baseline). The tasks consisted of viewing a reversing checkerboard (8 Hz), bilateral finger tapping, or both simultaneously (40s on/40s off x 4) and were expected to produce robust symmetric bilateral activation in healthy controls. CVR and task activation maps were generated using FSL's FEAT[4] ($z > 2.3$, $p < 0.05$, corrected). Four ROIs (left and right motor and visual regions) were defined using atlases. For each task, the laterality indices (LI) of the activation in the motor and visual ROIs were calculated based on activation extent (LI = +1: left ROI activation only; LI = 0: symmetric activation; LI = -1: right ROI activation only). Because all tasks were expected to activate an approximately symmetric bilateral network, greater laterality was interpreted as greater neurovascular uncoupling.

Results: BOLD CVR maps demonstrated that both patients had the expected pattern of pathology (i.e., abnormal CVR localized to anterior regions). In addition, more extensive regions of abnormal CVR were observed in the right hemisphere of both patients (Figure 1, left column). Bilateral activation of visual and motor regions was observed for all controls. For patient P01, activation in the right motor cortex (i.e., affected region) was greatly reduced in the visual-motor task compared to the motor task (Figure 1, Table 1). Patient P02's activation was somewhat left lateralized for the motor task, and was lateralized to an even greater extent in the visual-motor task (Table 1). In contrast, visual activation was relatively symmetric (i.e., LI $\approx$ 0) for both the visual and visual-motor tasks across patients and controls (Table 1).

Discussion and Conclusions: This work confirmed that the impact of neurovascular uncoupling must be considered in patients with cerebrovascular disease, particularly in regions of abnormal BOLD CVR. As hypothesized, the detection of neurovascular uncoupling appears to be dependent on the total extent of vascular demand. The observation of task-dependent neurovascular uncoupling has implications for interpreting CVR results. Negative BOLD CVR is generally thought to arise from vascular steal (i.e., the vessels are in a chronic state of maximal dilation and thus cannot react to a vasodilator; but see Arteaga and colleagues[5] for alternative explanations of negative BOLD CVR). In contrast, our results demonstrate that regions of negative BOLD CVR can still exhibit increased cerebral blood flow in response to task-related demands under some conditions. Our findings suggest that, in MMD-affected regions, the dynamic range of vasodilation is reduced rather than eliminated. Parametric tests of brain function may be important for understanding the full range of vascular responses in patients with chronic ischemia.

Table 1. Laterality indices (LI) in the motor and visual ROIs. An LI of 0 corresponds to bilateral activation (i.e., equal extent between the right and left ROIs). Notable left motor ROI dominance (i.e., LI ≈ 1) is observed for patients during the combined task.

	Motor ROI		Visual ROI	
	Motor task	Visual-motor task	Visual task	Visual-motor task
C01	0.051	0.065	0.009	0.007
C02	-0.255	-0.093	0.127	0.176
C03	-0.004	-0.004	0.045	0.019
C04	-0.024	-0.040	-0.169	-0.075
P01	0.046	0.885	0.160	0.050
P02	0.552	0.855	0.174	0.306

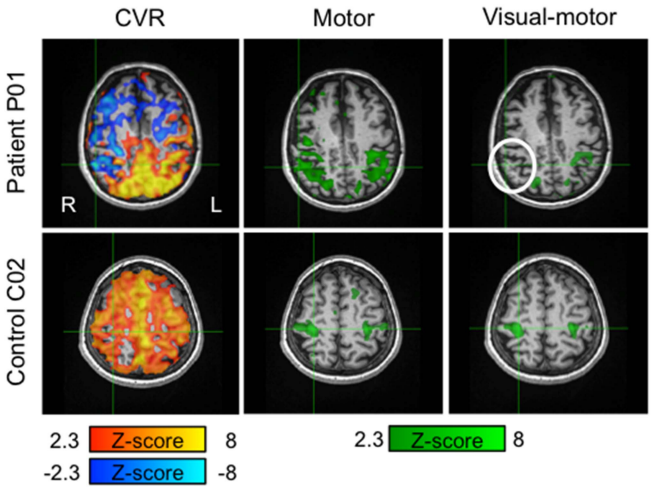

Figure 1. BOLD results for an illustrative patient and control. Left column: CVR maps. Middle column: Bilateral activation is observed in the patient and control in the motor task. Right column: In the visual-motor task, activation in the affected hemisphere is reduced in the patient (neurovascular uncoupling, white circle). The regions of neurovascular uncoupling are co-localized to regions of abnormal CVR (crosshairs).

References:
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