Atypical BOLD fMRI response is co-localized with abnormal resting perfusion in patients with arteriovenous malformations

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Target audience: Researchers developing methods for pre-treatment BOLD fMRI mapping; clinicians evaluating brain function in patients with abnormal perfusion.

Purpose: Pre-treatment mapping of eloquent cortex neighbouring a surgical target has become an established clinical application of blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI). However, in patients with abnormal perfusion such as arteriovenous malformations (AVMs), it can be difficult or impossible to interpret BOLD fMRI results due to the hemodynamic nature of the BOLD signals and the indirect coupling between BOLD signals and neural activity. For example, previous research has demonstrated inconsistent functional mapping results between BOLD and MEG in a patient with AVM, which was hypothesized to result from BOLD mislocalization due to abnormal brain perfusion[1]. We sought to measure brain perfusion and BOLD activation in AVM patients in order to evaluate whether perfusion information can clarify the interpretation of BOLD fMRI mapping.

Method: Seven patients with AVMs were evaluated using 3T MRI (Siemens). Resting state (i.e., task-free) BOLD fMRI data were acquired with the following parameters: TR 2.21s, TE 30ms, flip angle 90°, bandwidth 2442Hz/pixel, 42 3.5mm interleaved slices, 64×64 matrix, 224×224mm^2 FOV, 136 volumes, GRAPPA factor 2. To evaluate perfusion, pseudo-continuous ASL data were acquired with the following parameters: TR 4s, TE 9.9ms, flip angle 90°, 25 6mm ascending slices, 64×64 matrix, 224×224 mm^2 FOV, bandwidth 2442Hz/pixel, label duration 1.48s, post label delay 1.2s, GRAPPA factor 2, 30 control-tag pairs. A T1-weighted 3D MPRAGE structural image was also acquired with the following parameters: TR 2.3s, TE 2.98ms, TI 900ms, flip angle 9°, 256×256 matrix, 1mm isotropic voxel size, GRAPPA factor 2. For comparison, resting state BOLD fMRI data were also acquired from 12 healthy controls.

Perfusion values were calculated using ASLtbx[2]. Regions with abnormally high perfusion were identified using an existing approach in which the perfusion maps are thresholded based on the values in the putamen contralateral to the AVM[3]. Functional connectivity analysis of the motor network was performed using FSL[4]. A 6mm radius spherical seed in the left motor cortex was defined based on previous literature[5]. This seed did not overlap with the abnormally perfused region for any patient. Voxels demonstrating significant connectivity with the seed region were identified using a corrected cluster threshold ($z > 2.3$, $p < 0.05$).

AVMs were manually identified by an expert on the basis of gadolinium-enhanced imaging, performed on a 1.5T GE Signa Excite HD using a 3D fast spoiled gradient acquisition (1mm isotropic voxel size). Gadovist (1cc/10kg) was manually injected immediately before the scan. For one patient, the gadolinium-enhanced image was not available; the T1-weighted image was used instead.

Regions of interests (ROIs) were defined for each patient. The ROIs were: 1a) the region with abnormally high perfusion, excluding the AVM; 1b) the region contralateral to 1a; 2a) the remainder of the affected hemisphere; and 2b) the region contralateral to 2a (Fig. 1). The interhemispheric functional connectivity between these two pairs of ROIs was tabulated for each patient. These ROIs varied across patients; thus, the functional connectivity in the controls was evaluated for each patient's set of ROIs. The primary metric of functional connectivity was extent (i.e., the number of voxels significantly correlated with the seed).

Results: The functional network identified in the control group was bilaterally distributed as expected (Fig. 2A). In patients, atypical functional connectivity was observed, although the pattern depended on the particular AVM location and morphology in each patient. Atypical connectivity tended to be co-localized to the region of abnormally high perfusion (Fig. 2B). The ROI analysis revealed that interhemispheric connectivity within the patients' motor networks was greatly reduced between the abnormally perfused ROI and the contralateral region; compared to controls, patients demonstrated only 50% of the interhemispheric connectivity between these regions. The interhemispheric connectivity between the remainder of the affected hemisphere and the corresponding contralateral region was less attenuated (patient connectivity values were 84% of that of controls). In some patients, we also observed a similar phenomenon when using a task-based fMRI approach, such that a region of atypically absent activation was co-localized to a region of abnormally high perfusion (Fig. 3)

Discussion and Conclusions: We demonstrated that atypical BOLD functional connectivity and activation is preferentially localized to regions of abnormally high perfusion in AVM patients. This work confirms that perfusion abnormalities may partially explain atypical BOLD activation. Thus, atypical activation must be very carefully interpreted in AVM patients, even in regions several centimetres away from the AVM. More work is needed to explore the impact of the particular network or task under investigation. The development of disease-specific pre-treatment mapping protocols is currently underway, with the goal of providing more interpretable functional brain maps for planning interventions in patients with abnormal perfusion.
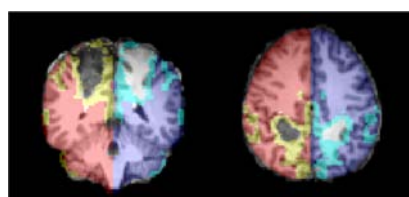

☐ 1a. Abnormally perfused ROI
☐ 1b. Contralateral to 1a
☐ 2a. Remainder of lesioned hemisphere
☐ 2b. Contralateral to 2a

Fig 1. Regions of interest identified in each patient. Interhemispheric functional connectivity was evaluated between the yellow and cyan regions versus the red and blue regions to determine the relationship between abnormal perfusion and atypical connectivity.
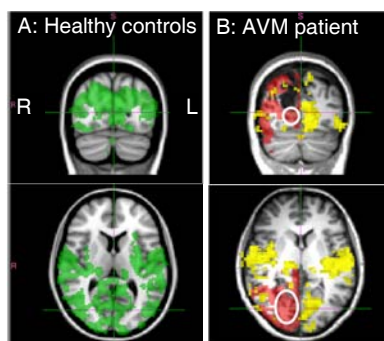

Fig 2. A: Group map of the functional network under investigation (green). **B:** An illustrative patient is shown. Functional connectivity (yellow) was particularly reduced in regions with abnormally high perfusion (red). White ovals highlight examples.
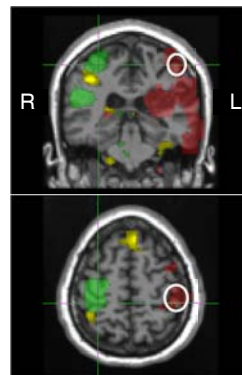

Fig 3. Task-based fMRI results in an AVM patient. The hand-sensory activation in the unaffected hemisphere is typical (green), but activation for the other hand (yellow) is absent in the contralateral hemisphere (white ovals); this area is co-localized to the region of abnormally high perfusion (red).

☐ Left hand sensory task
☐ Right hand sensory task
☐ Abnormally high perfusion

References: [1]Juenger H et al (2009) *J Neurosurg Pediatrics* 4: 333-338; Wang Z et al (2008) *Magn Reson Imaging* 26: 261-9; [3]Wolf et al (2008) *AJNR* 29:681-7; [4]Smith et al (2004) *NeuroImage* 23: S208-19; [5]Zhang et al (2009) *Neurosurgery* 65: 226-36.