

Specificity of High-Resolution BOLD and CBF fMRI at 7 T

In a recent MRM article by Duong et al. (1), the authors present fMRI results obtained at 4 T and 7 T and show some spectacular high spatial resolution activation maps of human brain. According to the authors, the methodology described enables high-resolution and high-specificity studies of functional topography of the human brain at the millimeter to submillimeter spatial scale. To arrive at this conclusion, the authors make two claims regarding the specificity of their measurements that are crucial for interpretation of the results and applicability of the methodology presented in this and previously published articles (1–3).

I believe that, despite the high quality data, the arguments to support the claims are not entirely correct. In the following I will lay out the rationale for my assertion.

The first claim the authors make rather strongly is that the presented BOLD and CBF fMRI measurements are sensitized to the brain parenchyma, with minimal contribution from intra- or extravascular signals originating from the larger veins downstream from the capillary bed (postcapillary contribution). The main arguments used to support this claim are:

- 1) The spin echo EPI acquisition that is used for the fMRI scans refocuses static intravoxel dephasing and therefore minimizes extravascular postcapillary contributions in the BOLD data.
- 2) The T_2 of venous blood at 7 T is too short to allow significant intravascular postcapillary contribution to the BOLD signal.
- 3) In the CBF measurements, signal loss due to T_1 recovery reduces venous blood labeling by the time the blood reaches the draining veins.

I have the following objections to these arguments:

- 1) Although spin echo acquisition in principle refocuses static dephasing effects (coherence loss due to the effect of, e.g., susceptibility gradients on stationary spins), this is only effective over a limited time-frame around the center of the echo. For all fMRI experiments, the authors use EPI with a very long acquisition window (between 48 and 64 ms). This leads to substantial static dephasing effects in the BOLD images, and therefore the potential for signal contributions from tissue (or CSF) surrounding veins running perpendicular to the main field. This is exacerbated by the fact that the reduced partial volume effects at high spatial resolution further enhance contributions from the macrovasculature.

- 2) At the TEs used by the authors ($TE = 40$ ms at 7 T), the argument that the signal from intravascular blood can be neglected due to short T_2 is probably correct for fully deoxygenated blood (0% oxygenation). However, blood oxygenation under normal conditions is upward from 60%, at which T_2 are substantially longer than at 0% oxygenation. Furthermore, when the oxygenation of venous blood increases, as it presumably does with activation, T_2 values of 7 T reportedly increase from around 19 ms at 60% oxygenation to as long as 50 ms in the extreme case of 100% oxygenation (4). At $TE = 40$ ms, the signal from oxygenated venous blood is therefore not negligibly small compared to signal from parenchymal tissue, and the intravascular BOLD signal cannot be excluded based on the short deoxygenated blood T_2 values alone.
- 3) The particular conditions of the CBF method used by the authors facilitate the inflow of venous label into the imaging slice (see below). This enhances the contribution of intravascular blood signal from the macrovasculature downstream from the capillary bed in the functional data.

The second claim is that BOLD and CBF are measured independently (i.e., with minimal cross-contamination). The authors specifically and repeatedly state that the CBF data does not contain substantial BOLD contrast. The main argument offered to support this claim is that in the FAIR technique (5) that is used to measure CBF, there is minimal postcapillary contribution since the nonselective inversion data shows minimal BOLD activation.

I believe there is a problem with this argument, since the nonselective inversion-recovery preparation substantially suppresses the signal from blood (and tissue), leading to a reduction in not only perfusion signal, but also BOLD signal. Therefore, based on the absence of BOLD in the nonselective inversion scan, one cannot exclude the possibility of a postcapillary macrovascular contribution to the CBF fMRI signal. On the contrary, the experimental conditions described by the authors facilitate an intravascular BOLD contribution to the CBF measurements as follows.

The FAIR technique used for CBF measurement is based on the acquisition of a perfusion-weighted scan using a slice-selective inversion prepulse and a control scan using a nonselective prepulse. The perfusion signal is obtained by subtracting the two scans. A drawback of the use of this technique for fMRI is the potential for BOLD contamination through susceptibility effects on, e.g., venous inflow. This contamination can be minimized by using a short TE, a short image acquisition window, and a reasonably (several centimeters) thick selective inversion.

In the FAIR method proposed by the authors, a long TE (40 ms), a long acquisition window (between 48 and 64 ms), and a very thin (9 or 12 mm) inversion slice for the

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flow-weighted slice-selective inversion scan are used. The long TE and acquisition window favor BOLD contrast. The thin inversion slice facilitates inflow of noninverted venous blood from areas outside the inverted slice into the imaging slice. At an inversion time (TI) of 1.2 sec, and image slice thickness of 3 or 4 mm, noninverted venous blood with flow velocities upward from 2.4–3.2 mm/sec can reach the image slice. These velocities are easily reached in the vasculature immediately downstream from the capillary bed. All these conditions, combined with the reduced partial volume effect at high spatial resolution, facilitate a macrovascular BOLD contribution to the CBF data.

In summary, I believe that, despite the high quality of the data and the great potential of high field fMRI, the claims made by the authors regarding the specificity of their methods are overreaching and not fully substantiated by the experimental evidence presented. To guarantee fMRI specificity, the contributions from the macrovasculature to the functional signals should be fully characterized and evaluated, rather than assumed to be insignificant. It is not at all evident from the data presented that the

use of spin-echo EPI at high field guarantees an elimination of macrovascular contributions to the fMRI signal.

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