

Spatial Specificity of High-Resolution, Spin-Echo BOLD, and CBF fMRI at 7 T

In his letter, Dr. Duyn expresses concerns regarding the spatial specificity of our spin-echo (SE) BOLD and CBF-based functional mapping signals (1) because of inherent T_2^* weighting in EPI images, blood contributions to SE BOLD, and BOLD effects in CBF-based fMRI. Detailed verification or discussion of these points was beyond the scope of our article (1), since it was submitted as a *Note* (although published as a *Communication*) addressing technical issues of high-resolution SE BOLD and CBF fMRI in humans at 4 and 7 T where EPI confronts major difficulties. Consequently, our remarks on the spatial specificity of fMRI were based on animal studies at high fields (2,3). However, the issues voiced by Dr. Duyn were indeed mentioned in the original article (1), and were fully dealt with in two articles published shortly afterwards (4,5). Our responses to Dr. Duyn's three points are summarized below.

Point #1. T_2^* contribution to SE BOLD during readout time: The description of this well-known problem in Dr. Duyn's letter is essentially identical to our own discussion of it in the Discussion section (1), where we further stated that "these effects are currently under investigation." The sum of all non- T_2 contributions to SE BOLD fMRI were determined as the intercept of activation-induced signal change vs. TE data, and were reported in our follow-up articles (4,5). The non- T_2 effects in our 4 and 7 T human fMRI data were found to be quite small (10–15% of the total stimulus-evoked percent signal change at TE approximating gray matter T_2). Furthermore, based on two different experimental approaches, most of these non- T_2 effects were ascribed to "inflow" rather than to T_2^* effect associated with EPI readout (4). Although differences in EPI readout time exists between experiments described in Refs. 1 and 4, the T_2^* effect is still expected to be small in Ref. 1. The most likely explanation for the absence of significant T_2^* contribution in our studies is that most of the "power" in the image (especially for a large activated area relative to the field of view) comes from the central k -space lines where the T_2^* contribution is small.

Point #2. Blood contribution to SE BOLD at 7 T: First, a correction, the TE in the SE BOLD studies at 7 T was 50 ms

(1), not 40 ms as claimed in Dr. Duyn's letter. The BOLD contribution from blood to SE fMRI was extensively addressed in one of our follow-up articles (5). Calculations performed to estimate this blood BOLD effect, as presented in Dr. Duyn's letter or in our article (5), suffer from uncertainties in assumptions regarding the T_2 of blood (derived from ex vivo measurements which strongly depend on hematocrit, temperature, oxygenation, average life time of water in the erythrocyte, and interpulse delay between RF pulses) and conditions in vivo (volume fraction of venous blood and venous oxygenation at rest and during activation) (5). However, we also experimentally examined the total blood contribution to SE BOLD fMRI, arising from both inflow and BOLD mechanisms, by utilizing flow-sensitive gradients for suppression of blood signals (i.e., IVIM). These experiments confirmed that at TE values approximating the gray matter T_2 , the total blood contribution in the human brain was small at 7 T (5), which agrees with our modeling (5) but not with the calculation presented by Dr. Duyn in his letter.

Point #3. Contribution of venous inflow/BOLD effects to the CBF signal: Dr. Duyn claims that we "specifically and repeatedly state that the CBF data does not contain substantial BOLD contrast." On the contrary, we call attention to our sentence "the functional maps ... largely reflect CBF changes, although there could be some BOLD contamination" (p. 591 of Ref. 1). Another clarification concerns Dr. Duyn's criticism that we use the statement "in the CBF measurements, signal loss due to T_1 recovery reduces venous blood labeling by the time the blood reaches the draining veins" to support the absence of venous BOLD effect in CBF fMRI. This is a misinterpretation. This particular point has nothing to do with the BOLD contribution: it deals with tagged spins appearing in the venous side after they go through capillaries, thus giving rise to CBF-based signal change in venous vessels.

Leaving these confusions aside, Dr. Duyn's concern, a subtle point, is the presence of different intravascular BOLD contributions to slice-selective and nonselective inversion recovery (ssIR vs. nsIR, respectively) images in the FAIR technique. In the nsIR image, blood magnetization within and outside the imaging slice will be small after a TI of 1.2 sec following the inversion pulse. Whereas in the ssIR, depending on direction and length of venous vessels, and the velocity of venous blood, relatively fast-flowing blood in large veins may move from uninverted regions into the imaging slice. Thus, after a TI of 1.2 sec, there will be essentially fully relaxed venous blood signal in the imaging slice which will be a source of intravascular BOLD effect. To minimize this potential problem, Dr. Duyn suggests using a short EPI readout time, a thick inversion slab, and a short TE. A short EPI readout is always desirable, as is well known, and as emphasized in

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our original (1) and subsequent (4,5) articles. The other two suggestions, however, are problematic. In our study, an inversion slab thickness of 9–12 mm was used to maximize the CBF contrast. A thicker slab would decrease potential venous inflow effects, but it will also increase arterial spin transit time to the imaging slice, leading to a reduction of perfusion contrast (a problem addressed by Dr. Duyn (6) and others). A short TE is appropriate to minimize BOLD contribution to the CBF signal at low fields where apparent venous-blood T_2 is relatively long (3). However, the apparent T_2 of venous blood is markedly shorter at high fields; therefore, the short TE approach will *not* minimize, but rather maximize, the BOLD contribution which peaks at TE $\sim T_2$ of blood (see fig. 1 in Ref. 5). In contrast, the use of a long TE at 7 T or higher fields suppresses blood signals (see Point #2) and, consequently, all blood-related effects. Of course, the *extravascular* SE BOLD contribution increases at long TE, but this is *identical* for nsIR and ssIR, and is thus eliminated in the CBF calculation. The lack of a draining-vein contribution to the CBF fMRI signal is further supported by an animal study using a much thinner inversion slab (5 mm), a longer inversion delay (1.5 sec), and gradient-echo TE of 31 ms at 4.7 T (7). Essentially no “activation” was observed in the large draining veins. Blood-related effects in the CBF signal will be even less at 7 T and a spin-echo time of 40 ms.

In summary, the issues raised by Dr. Duyn were not ignored in our original Note (1) and they were amply addressed experimentally in our immediate follow-up studies (4,5), both of which further demonstrated the improved specificity provided by SE-based BOLD and CBF fMRI at 7 T.

REFERENCES

1. Duong TQ, Yacoub E, Adriany G, Hu X, Ugurbil K, Vaughan JT, Merkle H, Kim SG. High-resolution, spin-echo BOLD, and CBF fMRI at 4 and 7 T. *Magn Reson Med* 2002;48:589–593.
2. Lee S-P, Silva AC, Ugurbil K, Kim S-G. Diffusion weighted spin echo fMRI at 9.4 T: microvascular/tissue contribution to BOLD signal changes. *Magn Reson Med* 1999;42:919–928.
3. Duong TQ, Silva AC, Lee S-P, Kim S-G. Functional MRI of calcium-dependent synaptic activity: cross correlation with CBF and BOLD measurements. *Magn Reson Med* 2000;43:383–392.
4. Yacoub E, Duong TQ, Van De Moortele PF, Lindquist M, Adriany G, Kim SG, Ugurbil K, Hu X. Spin-echo fMRI in humans using high spatial resolutions and high magnetic fields. *Magn Reson Med* 2003;49:655–664.
5. Duong TQ, Yacoub E, Adriany G, Hu X, Ugurbil K, Kim SG. Microvascular BOLD contribution at 4 and 7 T in the human brain: gradient-echo and spin-echo fMRI with suppression of blood effects. *Magn Reson Med* 2003;49:1019–1027.
6. Yongbi MN, Yang Y, Frank JA, Duyn JH. Multislice perfusion imaging in human brain using the C-FOCI inversion pulse: comparison with hyperbolic secant. *Magn Reson Med* 1999;42:1098–1105.
7. Duong TQ, Kim DS, Ugurbil K, Kim SG. Localized cerebral blood flow response at submillimeter columnar resolution. *Proc Natl Acad Sci USA* 2001;98:10904–10909.

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