Imaging oxygen extraction fraction in the visual cortex during functional activation using turbo QUIXOTIC

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Target audience: Physicists, neuroscientists, and clinicians interested in quantification of cerebral blood oxygenation

Introduction: Oxygen extraction fraction (OEF) is directly related to the cerebral metabolic rate of oxygen ($CMRO_2$), which is a neurophysiological parameter often perturbed in pathological states. As such, MR-based OEF imaging has great clinical potential for disease assessment—to evaluate stroke risk,[1] inform stroke prognosis, and evaluate tumor hypoxia.[2] PET and quantitative BOLD have been used to image OEF, but are limited by the use of radioactive tracers and challenges in modeling the BOLD signal, respectively. Recently, a MR-based approach to imaging OEF called QUIXOTIC (QUantitative Imaging of eXtraction of Oxygen and TIssue Consumption) was introduced.[3] The QUIXOTIC validation process included functional OEF imaging of the well-characterized hemodynamic response to a visual stimulus, but QUIXOTIC was limited by its long scan times required to collect the multi-echo data needed for quantification.[4] To address this issue, a turbo spin echo (TSE) variant of QUIXOTIC was introduced (tQUIXOTIC) that acquires multi-echo data in a single repetition time (TR), leading to a shorter scan time and decreased sensitivity to motion and physiological signal fluctuations over multiple TRs. In this study, tQUIXOTIC is used to measure OEF at baseline and during functional activation by a visual stimulus in order to further validate the technique, and to present a practical OEF mapping approach in clinically feasible imaging times.

Methods: OEF was measured using tQUIXOTIC, which uses velocity selective spin labeling in combination with a TSE readout to isolate T_2 decay of post-capillary venous blood.[2] The TSE module uses adiabatic 180˚ RF pulses[5] and an optimized crusher train.[3] Imaging of two healthy adult subjects (20-21 yo) was performed at 3T (Siemens Tim Trio). A block design visual stimulus (8 Hz flashing radial checkerboard with central fixation point) was used to modulate neuronal activity in the visual cortex. We used a seven slice EPI spin-echo (SE) acquisition to select the optimal slice through the visual cortex for subsequent tQUIXOTIC MRI. We fit this data using a linear signal model consisting of regressors representing the block design stimulus, a linear drift term and a constant (DC) term. Four 7 minute runs were subsequently acquired for each subject using the same stimulation paradigm. tQUIXOTIC parameters were V_{CUTOFF}=2.3cm/s, TI_{INV} = 400 ms, outflow time (TO) = 725 ms, $TE_{EFFECTIVE}$ = 12.6 and TSE readout parameters 3.9x3.9x8 mm^3, TE/TR 12.6/3000 ms, 6 echoes. Pairwise subtraction of tag and control images generated the tQUIXOTIC venous-blood weighted series.

Analysis of the tQUIXOTIC data was performed group-wise on images collected at the same echo time (TE) by fitting the linear signal model to each venous-blood-weighted time series. Maps of activation t-statistics were generated for each TE and the sixth echo t-statistic map was used to select an ROI of the ten most significantly activating voxels (exceeding $p = 0.05$ correcting for multiple comparisons) excluding the region within 10 mm of the center of the sagittal sinus (SS) to avoid contamination from SS blood. Beta-coefficients were averaged over the ROI. Exponential fits of baseline and baseline plus effect size for the even echoes determined T_2. Odd echoes were discarded due to the non-linear phase accumulation from the adiabatic inversion pulses.[5] OEF for each state was estimated using average standard values of hematocrit,[6] a T_2 to oxygen saturation calibration described by Lu, et al.,[7] and 99% arterial oxygen saturation.

Results: We observed the significant changes in T_2 and OEF reported in Table 1. Notably, relative changes in OEF are nearly identical between subjects. Figure 1 demonstrates the high quality of the exponential fits to determine T_2 at baseline and activation states. Figure 2 shows t-statistic maps and the analysis ROI overlaid on representative EPI images. The activation maps for the images at even TEs all revealed significant changes in venous-blood-weighted signal intensity during the visual stimulus, and the activation regions for each TE show strong spatial correlation.

Discussion: Average OEF at baseline is within the range of values reported in the literature, though the relative change in OEF was lower than expected.[8–10] We hypothesized that the previously described diffusion-related signal in CSF[3,11] may be contaminating the blood signal in later echoes. To test this, we fit only the first two even echoes and found **average results that more closely matched the literature: $OEF_{baseline}$ = 0.33, $OEF_{activation}$ = 0.25, %ΔOEF = -0.24**. Future development of tQUIXOTIC will address this diffusion related effect using methods described by Guo, et al.[11] Altogether, these results show that tQUIXOTIC detects and quantifies the expected change in OEF associated with visual cortex activation, further validating the technique.

Conclusion: tQUIXOTIC offers a new MR approach for clinical and functional OEF imaging and is shown to successfully detect OEF changes during functional activation. tQUIXOTIC improves upon the original method by allowing a multifold decrease in scan time, making the technique clinically feasible for OEF mapping in a single MR scan. Future experiments will use tQUIXOTIC to quantify OEF changes in different challenges—for example, gas inhalation and stimulation of cortical regions outside the visual system—and demonstrate $CMRO_2$ quantification with additional cerebral blood flow measurements. Quantitative oxygenation imaging would have major clinical implications in cases of stroke and brain tumor. The results presented here suggest that with further improvements tQUIXOTIC might be used to accurately quantify OEF in the clinic.

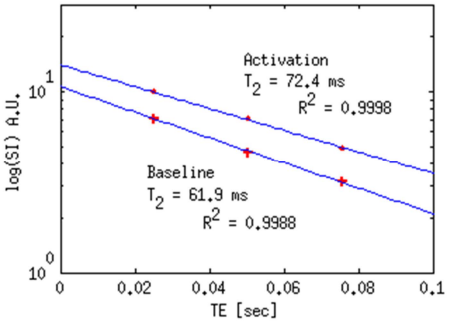

Figure 1: Example T_2 fit for subject 1, baseline and activation.

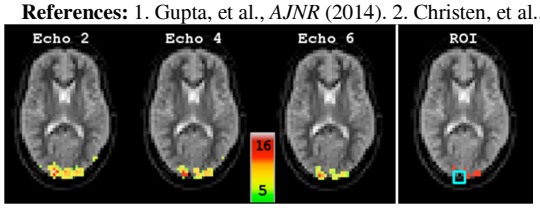

Figure 2: t-statistic activation maps and ROI (red) with SS contamination outlined blue

Subject	$T_{2,baseline}$	$T_{2,activation}$	ΔT_2	$OEF_{baseline}$	$OEF_{activation}$	%Δ OEF
1	61.9	72.4	10.5	0.34	0.29	-0.16
2	75.1	83.8	8.7	0.26	0.22	-0.15
Mean	68.5	78.1	9.6	0.30	0.25	-0.16

Table 1: Summary of results measured with tQUIXOTIC, T_2 in ms.

References: 1. Gupta, et al., *AJNR* (2014). 2. Christen, et al., *AJNR* (2012). 3. Bolar, et al., *MRM* (2011). 4. Bolar, et al., *ISMRM* (2009). 5. Conolly, et al., *MRM* (1991). 6. Wakeman, et al., *Int. Lab. Hematol.* (2007). 7. Lu, et al., *MRM* (2012). 8. Gauthier, et al., *Neuroimage* (2012). 9. Golay, et al., *MRM* (2001). 10. Oja, et al., *JCBFM* (1999). 11. Guo, et al., *ISMRM* (2011).

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