Feasibility of QUantitative Imaging of eXtraction of Oxygen and TIssue Consumption (QUIXOTIC) to assess functional changes in venous oxygen saturation during visual stimulus

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Introduction: Functional MRI has been extensively used to indirectly measure changes in neuronal activation via the BOLD (blood oxygenation level dependent) effect. While BOLD fMRI provides a relative signal that fluctuates based on changes in venous oxygenation, the absolute value of venous oxygen saturation at baseline and during activation is unknown. Additionally, the BOLD response is highly variable, resulting in large intersubject differences in response size, leading to decreased statistical power in group comparisons [1]. Recently, Lu and colleagues [2] have shown that baseline venous blood oxygen saturation modulates the BOLD response amplitude in a predictable way, thus providing a physiologic explanation for the variability. These observations suggest that an fMRI technique able to directly evaluate functional changes in absolute venous oxygen saturation may be a more repeatable and physiologically relevant way to assess neuronal activation. A newly developed fMRI technique called QUantitative Imaging of eXtraction of Oxygen and TIssue Consumption (QUIXOTIC) MRI allows direct measurement of venous oxygen saturation (Yv) [3]. QUIXOTIC MRI involves exclusively imaging blood spins flowing above a cutoff velocity (V_C) on the venous side of circulation. In this study, we assess the feasibility of using QUIXOTIC to quantitatively measure functional changes in local venous oxygen saturation, in response to a visual stimulus.

Methods: Three healthy human volunteers were scanned (2 male, 1 female, ages 25 to 27) at 3T (Siemens Tim Trio, 32-channel head coil). A block design visual stimulus was used to modulate neuronal activity in the visual cortex. The stimulus consisted of two minute presentations of an 8 Hz flashing radial checkerboard (with central fixation point), interleaved with two minutes of the fixation point alone, for a total of 10 minutes (i.e. 3 OFF epochs and 2 ON epochs). Subjects were instructed to gaze at the fixation point for the duration of the scan. During this time, a QUIXOTIC pulse sequence [3] equipped with a GRE-EPI readout was used to acquire a time series data set. The functional experiment was performed twice, once with $TE_{EFFECTIVE}$ = 20 ms and once with $TE_{EFFECTIVE}$= 60 ms. A dual-echo approach is required for T_2 measurement of the venous-targeted blood pool and subsequent Yv estimation. QUIXOTIC scan parameters were V_C = 2.1 cm/s, TI_{INV} = 400 ms, TI = 722 ms, $TE_{EFFECTIVE}$ = 20/60 ms and GRE-EPI parameters were TE/TR = 12/3000 ms, 4 slices, 3.9x3.9x10 mm^3. Raw time series data were smoothed and motion corrected. A sequence of venous-blood-weighted images was generated by pairwise subtraction of tag and control images. Functional analysis was performed by fitting a linear signal model to the venous-blood-weighted series. The model consisted of regressors representing the block design stimulus, a linear drift term, and a constant (DC) term. Maps of t-statistic were subsequently generated for each $TE_{EFFECTIVE}$ acquisition; a voxel was considered activated if its t-statistic value was above a threshold corresponding to p = 0.005. Activated voxels common to both experiments were used to create a common region of interest (ROI). Averaging the time course of all voxels within this ROI generates a mean activation time course, one for each $T_{EEFFECTIVE}$ acquisition. β coefficient values from the linear model fit to these mean time courses were used for T_2 measurement. β_{DC}, representing the baseline signal, and (β_{DC} + β_{EFFECT}), representing the signal during activation, were plotted against $TE_{EFFECTIVE}$ and fit with a single exponential to estimate $T_{2,BASELINE}$ and $T_{2,ACTIVATION}$, respectively. These T_2 values were then converted to Yv using a calibration curve [4,5].

RESULTS and DISCUSSION: The activation maps revealed significant changes in venous-blood-weighted signal during the checkerboard presentation. Figure 1 shows representative EPI images overlaid with the QUIXOTIC activation ROI containing voxels activated in both functional runs. Figure 2 shows the corresponding functional time course for the activated region (linear drift term removed) for the $TE_{EFFECTIVE}$ = 20 ms run; β_{DC} and β_{EFFECT} are labeled. Figure 3 plots β_{DC} and (β_{DC} + β_{EFFECT}) versus $TE_{EFFECTIVE}$ and the corresponding $T_{2,BASELINE}$ and $T_{2,ACTIVATION}$ fit curves. Table 1 summarizes T_2 and Yv results from all three volunteers. Significant changes in absolute Yv during visual stimulus are observed.

The reported values for ΔYv are comparable to those found in [6] and [7] (accuracy of baseline Yv is discussed in reference [3]), but are slightly lower that those reported by others in [8] and [9]. This may be due to inclusion of blood from veins draining from unactivated regions, which will dilute the overall oxygen concentration in the activated blood pool, biasing $T_{2,ACTIVATION}$ (and subsequently $Yv_{ACTIVATION}$) towards the baseline level. To avoid this problem, venous oxygen saturation should be measured only in post-capillary venules immediately distal to sites of neuronal activation. To exclusively target blood in these small vessels, future studies will employ so-called "velocity bracketed" QUIXOTIC [3]. This modification to the standard QUIXOTIC approach introduces an upper velocity limit, and will thereby target blood in a velocity range, as opposed to only above V_C. This approach will eliminate signal from larger veins, yet still preserve signal in smaller venules, and is especially necessary for regions containing a high density of draining veins (like the visual cortex). In this way, it will be possible to measure oxygen saturation changes in only post-capillary venular (PCV) blood, regardless of vessel-type within a voxel. Such an approach should also improve spatial accuracy of the QUIXOTIC fMRI technique, as changes in PCV oxygen saturation should be tightly localized to regions immediately distal to neuronal activation.

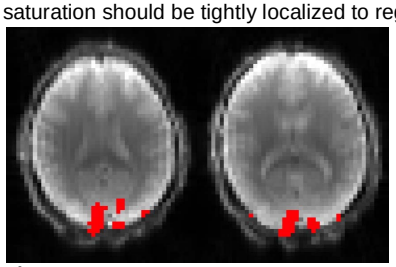

Figure 1. Activation ROI in mid slices from Subj 1

Subject	$T_{2,baseline}$ (ms)	$T_{2,activation}$ (ms)	$\Delta T_{2,activation-baseline}$	$Yv_{baseline}$ (%)	$Yv_{activation}$ (%)	$\Delta Yv_{activation-baseline}$ (%)
1	49.4	73.6	24.2	57.2	70.7	13.5
2	53.3	73.2	20.1	59.8	70.5	10.7
3	49.0	73.9	24.9	57.0	70.8	13.8
Mean/SD	**50.6 ± 2.4**	**73.6 ± 0.4**	**23.1 ± 2.6**	**58.0 ± 1.6**	**70.7 ± 0.2**	**12.7 ± 1.7**

Table 1. Summary of results from VT-VSSL functional visual cortex activation

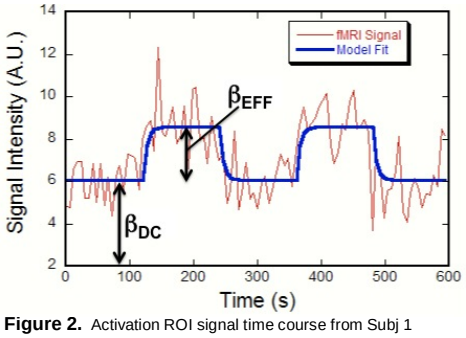

Figure 2. Activation ROI signal time course from Subj 1

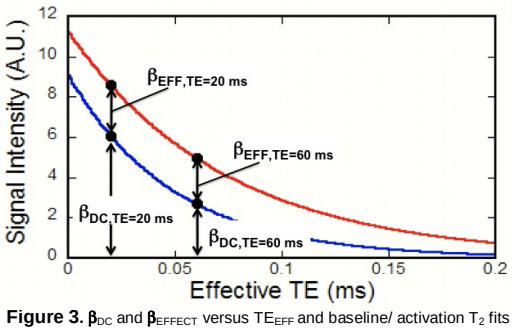

Figure 3. β_{DC} and β_{EFFECT} versus TE_{EFF} and baseline/ activation T_2 fits

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