Substantial Flow-related Contribution in fMRI Signal Observed in Human Visual Cortex at 4T

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Introduction: Functional magnetic resonance imaging (fMRI) is widely used in both basic and clinical brain research due to its merits of real-time, noninvasiveness and high sensitivity. Gradient echo planar imaging (GE-EPI), for instance, is one of fast MRI techniques for assessing the fMRI BOLD signals. It is a common practice to use a relatively short repetition time (TR) in EPI acquisition for more signal averaging and improvement in fMRI reliability. However, we have demonstrated that the total MRI signal increase observed in the rat brain during hypercapnia challenge at 9.4T could be approximated as the superposition of 'true' BOLD (T_2/T_2*) effect and flow-related (T_1) effect, and it is likely that perfusion at micro-vascular level could significantly attribute to the observed flow-related signal change [1]. In this study, we exploited this phenomenon further to test if it still holds true in the human brain during visual stimulation at 4T.

Theory: The GE-EPI signal intensity (S_{GE}) can be described by Eq. (1): $S_{GE} = S_0 \cdot \exp(-TE \times R_2^*) \cdot \sin(\alpha) \cdot [1-\exp(-TR \times R_1)] \div [1-\cos(\alpha) \cdot \exp(-TR \times R_1)]$, where S_0 is the GE-EPI signal intensity when TE=0 and TR=∞; R_2* is the apparent transverse relaxation rate which is sensitive to susceptibility effects and BOLD [2]; R_1 is the apparent longitudinal relaxation rate which is sensitive to flow-related signal changes [3-5]; TE is the echo time; α is the flip angle of excitation pulse. Therefore, S_{GE} can be influenced by both R_2* and R_1 changes when TR is relatively short. In contrast, when TR>4-5 T_1 and TE>0, the term of $\exp(-TR \times R_1)$ approaches zero, Eq. (1) can be rewritten as Eq. (2): $S_{GE} = S_0 \cdot \exp(-TE \times R_2^*) \cdot \sin(\alpha)$. In this case, S_{GE} is independent of R_1 and its change is mainly determined by R_2* or "true" BOLD.

In this study, GE-EPIs during control (S_{ctrl}) and stimulation (S_{sti}) with variable TRs were acquired. BOLD was quantified by using Eq. (3) of BOLD = $S_{sti} \div S_{ctrl}$ (TR=9.1 s >$4T_1$). It is known that during brain activation, cerebral blood flow (CBF) will increase, resulting in an increase in R_1. The accelerated R_1 process in the tissue water during visual stimulation leads to a reduction in the saturation effect under the condition with relatively short TR and/or large flip angle, subsequently, an increase in GE-EPI signal intensity, which is added to BOLD. This flow-related signal change can be estimated by the 3rd and 4th terms in Eq. (1) as a function of TR.

Material and Method: Six healthy human subjects (three males and three females, 23-49 years old) participated in this study and one subject participated twice on different days. All of the fMRI experiments were performed on a 4T/90-cm bore human magnet (Siemens, Erlangen, Germany) system with the Varian INOVA console (Varian Inc., Palo Alto, CA, USA) using a single-loop RF surface coil (10 cm diameter). The 8-Hz, full-field reversal checkerboard was applied for visual stimulation. Scout images were acquired using a T_1-weighted TurboFLASH imaging sequence. The fMRI data were acquired with GE-EPI (TE=30ms; FOV=20cm×20cm; image matrix=64×64; 5 mm thickness) with varied TRs of 1.1, 2.1, 4.1 and 9.1 s. GE-EPI combined with the saturation-recovery preparation was used for imaging apparent T_1 (T_1^{app}) with nine varied saturation-recovery times (T_{SR}) ranged from 0.02 to 10 s. In addition, a number of GE-EPI with varied RF powers were scanned under fully relaxed condition to determine the flip angle, α, in the primary visual cortex (V1, approximately 85°). ROI data taken from the activated pixels in the visual cortex based on the fMRI maps measured with shortest TR (= 1s) were used to perform the R_1 regression and comparison of signal percent increases among the data with varied TRs.

Results: Figure 1 presents five coronal fMRI maps obtained with four TRs from a representative subject, showing a significant GE-EPI signal increase in the activated visual cortex. It also indicates that both the number of activated pixels with the same statistical threshold and the percent change of total MRI signal elevated by visual stimulation inside the ROI decline as TR increases. Figure 2 summarizes the averaged results showing the changes in total number of activated pixels and normalized (the GE-EPI signal increases at TR = 1, 2, 4 s were normalized by the 'true' BOLD, which is the percentage signal increase at TR=9 s) GE-EPI signal change with varied TRs and standard error across the seven studies. The mean of total signal increase before normalization are 3.0%, 2.7%, 2.1% and 1.8% for TR = 1, 2, 4 and 9 s.

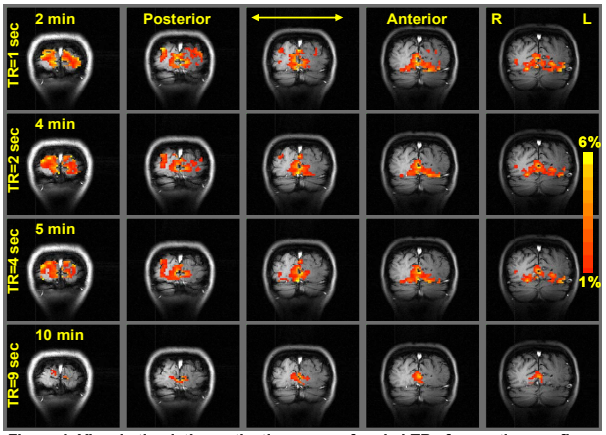

Figure 1. Visual stimulation activation maps of varied TRs for continuous five slices in a representative subject. The number of activated pixels and the magnitude of the stimulation decrease as TR increases. The total acquisition time for each TR is indicated on the top of images in the first column.

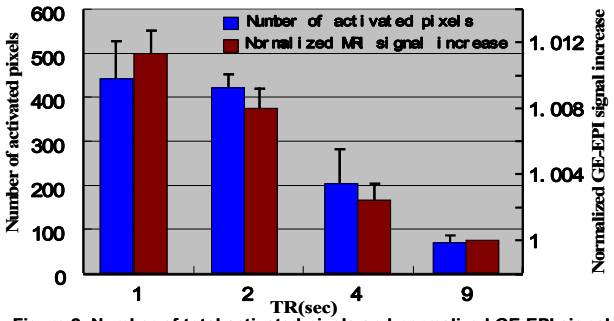

Figure 2. Number of total activated pixels and normalized GE-EPI signal increase during visual stimulation and their standard error bars as a function of varied TRs across seven experiments. The MRI signal increase of TR = 1, 2, 4 second is normalized by the signal increase when TR = 9 second to minimize the inter-subject BOLD effect variation.

Discussion: The attenuated saturation effect of magnetization with short TR is the main underlying mechanism of the observed phenomenon. Due to the longitudinal relaxation rate increases during visual stimulation, the longitudinal magnetization relaxes more (being less saturated) at shorter TRs than longer TRs, therefore, a higher total MRI signal percentage increase was observed during stimulation at shorter TRs. In addition, short TR allows more imaging average within a given total imaging acquisition time, which means an improved contrast-to-noise ratio (CNR). The higher CNR and higher percent change of total GE-EPI signal with short TR lead to more activated pixels and better fMRI quality (see Fig. 1). The measured R_1 difference ($\Delta R_1^{app} = R_{1\text{-sti}}^{app} - R_{1\text{-ctrl}}^{app}$) between control and stimulation condition in visual cortex was insignificant, and in two of seven experiments the values even appear to be negative, presumably due to a small ΔR_1 change and a large variation in R_1 measurement. However, if these two negative values were excluded and the mean of ΔR_1 for the other five experiments became 0.0036 s^{-1}, resulting in a CBF increase of ΔCBF=0.19 ml/g/min based on the relation of $\Delta CBF = \lambda \times \Delta R_1^{app}$ (λ =0.9ml/g is the blood-tissue water partition coefficient). This suggests that CBF increases approximately 40% if assuming the basal CBF=0.5 ml/g/min in the human visual cortex. This result is consistent with the majority of publications. Moreover, there is a similar trend between the predicted GE-EPI signal increase according to Eqs. (1) and (3) and the experimental results as summarized in Fig. 2. These findings suggest that the perfusion change would be the primary contribution to the observed saturation effect, although some inflow contamination could not be completely excluded.

This study indicates that the detected total fMRI signal depends not only on TE through BOLD (or R_2/R_2*) mechanism, but also on TR and flip angle through flow-related (or R_1) mechanism. The flow-related contribution becomes substantially large with a short TR (e.g., 1s in Fig. 1) and it enhances the total fMRI signal significantly. This enhancement should benefit fMRI mapping in two aspects: i) for achieving higher CNR; and ii) for improving the specificity for mapping neuronal activity since the flow-related effect is likely attributed from CBF change. The finding from the present study also suggests that caution should be exercised when quantifying the cerebral metabolic rate of oxygen ($CMRO_2$) using BOLD calibration modeling since the total fMRI signal does not reflect the "pure" BOLD if TR is not long enough (or >> T_1). Specifically, $CMRO_2$ would be overestimated if the flow-related contribution was not separated from BOLD, although this problem could be partially compensated by using the same acquisition parameters between hypercapnia calibration and fMRI measurement.

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References: 1. Wang et al, *ISMRM*, p.1561, 2009. 2. Ogawa et al, *Annu. Rev. Biophys. Biomol. Struct*. 1998. 3. Frahm et al, *NMR Biomed*, 1994. 4. Gao et al. *MRM*, 1996, 5. Kwong et al. *MRM*, 1995.