Large Influence of Flow-related Contribution on fMRI Signal: A 9.4T Study using Hypercapnia

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Introduction: The functional MRI (fMRI) method is based on the blood oxygenation level dependence (BOLD) contrast, which is the result of interplay among the CBF, CBV and $CMRO_2$ changes in response to brain stimulation[1]. From the standpoint of NMR physics, BOLD associated with the susceptibility change will affect T_2/T_2*, in contrast, the perfusion change quantified by CBF and/or inflow effect will change the apparent T_1 processing in both blood and tissue water, in particular, when the blood water exchanges rapidly with the brain tissue through capillaries. Therefore, the measured percent change of fMRI signal elevated by brain activation could be determined by both T_2/T_2*-sensitive BOLD and T_1-sensitive flow-related signal; and the relative contributions between them depend on many factors, such as field strength, imaging pulse sequence and acquisition parameters, and imaging contrast[1-4]. However, it is still elusive whether the flow-related component could significantly attribute to the fMRI signal, and if yes, how much macro-vascular contribution to this component. The primary goals of this study are: i) to quantitatively investigate the contributions of BOLD and flow-related signal to the total percent signal change detected by gradient-echo EPI (GE-EPI) in the rat brain cortex at 9.4T when CBF is elevated by hypercapnia (6% CO_2); and ii) to identify the major source of the flow-related signal contribution to the total signals change detected by fMRI.

Theory: The magnitude of GE-EPI signal intensity (S_{GE}) can be described by Eq. (1): $S_{GE} = S_0 \cdot \exp(-TE \times R_2^*) \cdot \sin(\alpha) \cdot [1-\exp(-TR \times R_1)] + [1-\cos(\alpha) \cdot \exp(-TR \times R_1)]$, 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; R_1 is the apparent longitudinal relaxation rate which is sensitive to flow-related signal changes; TR and TE are the repetition time and echo time respectively; α is the flip angle of excitation pulse. When $TR > 4T_1$ and $TE > 0$, the term of $\exp(-TR \times R_1)$ tends to be zero, Eq. (1) can be rewritten as Eq. (2): $S_{GE} = S_0 \cdot \exp(-TE \times R_2^*) \cdot \sin(\alpha)$. Under this condition, S_{GE} is independent upon R_1 and mainly determined by R_2* and BOLD. The GE-EPIs during normocapnia control (S_{ctrl}) and hypercapnia (S_{hyper}) with variable TRs were acquired. BOLD was quantified by using Eq. (3) of $BOLD = S_{hyper} \div S_{ctrl}$ ($TR = 12.1 \text{ s} > 4T_1$). It is known that during stimulation or hypercapnia, CBF will increases, resulting in an increase in R_1. The accelerated R_1 process in the tissue water during hypercapnia leads to a reduction in the saturation effect under the condition with relatively short TR and/or large α, subsequently, an increase in GE-EPI signal intensity. This flow-related signal change can be determined by the 3rd and 4th terms in Eq. (1) as a function of TR using the values of α, normocapnia R_1 and hypercapnia R_1', that can be experimentally measured as in the present study.

Material and Method: A total of 9 rats (2% isoflurane anesthesia) showing a positive BOLD change during hypercapnia were included for the summarized results. R_1 measurement and functional MRI with and without bipolar diffusion gradient were acquired before (i.e., normocapnia for control) and during stable hypercapnia condition, which was induced by switching to an inhalation bag with mixed gases (6% CO_2, 34%O_2, 58% N_2O and 2% isoflurane) for 20-30 minutes. All MRI experiments were conducted on a 9.4T horizontal animal magnet (Magnex Scientific, Abingdon, UK) interfaced to a Varian INOVA console (Palo Alto, CA, USA). A butterfly-shape surface coil (long axis of 2.8 cm; a short axis of 2.0 cm along the animal spine) was applied. Two GE- EPI sequences were applied to image R_1 based on the saturation-recovery-T_1 image method with nine recovery times ranging from 0.008 to 10 s; and to acquire functional MRI signals using conventional GE-EPI with six TRs (1.1, 2.1, 3.1, 5.1, 8.1 and 12.1 s) and a fixed total sampling duration of 1 min for each TR. Bipolar diffusion gradients in three dimensions were inserted between the excitation pulse and GE-EPI acquisition for both the pulse sequences (FOV=3.2cm×3.2cm; matrix size = 64×64; three continuous slices with 1mm thickness; TE: 22-24 ms). Three b factors (0, 518, 1019 $s \cdot mm^{-2}$) were achieved by adjusting the diffusion gradient strength up to 45 gauss/cm. In addition, a number of GE-EPI with varied RF powers were scanned to optimize α for achieving high SNR in the region of interest and to quantify the profile of α used by Eq. (1). The MRI data analysis was performed using the STIMULATE software package (CMRR, University of Minnesota) and the Matlab software package (The Mathworks inc.). A Matlab least-square nonlinear curve fitting program was used to perform the R_1 regression. The inflow-related signal change and BOLD elevated by hypercapnia were simulated as functions of TR (0 to 13 s), flip angle (40-160°) and R_1' increasing from 0.485 to 0.52 s^{-1} according Eqs. (1) and (3). The fMRI data taken from a region of interest (ROI) located in the rat sensory cortical region without large vessels and sinus vein were used to perform the R_1 regression analysis and BOLD quantification. The experimental results were compared to the simulation results.

Results and discussion: Figure 1a shows the simulation results of flow-related signal change and its dependence on TR, flip angle and R_1' increase caused by hypercapnia. In general, shortening TR or increasing α and R_1' will result in a large increase of percent signal change detected by fMRI owing to the flow change during hypercapnia. Figure 1b displays the comparison results of total fMRI signals (i.e., attributing to BOLD and flow-related components) as a functional of TR. These results were obtained by two approaches: i) direct measurements using GE-EPI with varied TRs; and ii) prediction using the experimentally measured values of α, R_1 and R_1' under each condition and TR according to Eqs. (1) and (3). In this figure, the total fMRI signal can be approximated by the superimposition of the true BOLD measured at TR=12.1 s and the extra signal increase caused by the elevated flow and reduction of saturation effect during hypercapnia. There are excellent agreements between the direct measurement results (full cycles in Fig. 1b) and predicted results (lines in Fig. 1b) under three conditions with varied b factor. The relative signal contribution from the flow-related component increases rapidly when shortening TR, and approaches the similar value of BOLD at TR≈1 s.

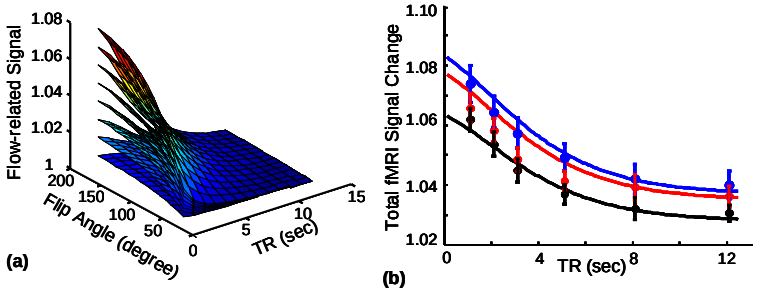

Fig. 1 (a) Simulation results of flow-related signal increase as functions of TR and flip angle. GE signal ratio without R_2* component. Each layer represents the result corresponding to the R_1' value increasing from 0.485 to 0.52 s^{-1} with an increment of 0.005 s^{-1} (bottom up; R_1=0.48 s^{-1}). (b) Comparison of total fMRI signal changes elevated by hypercapnia as a function of TR between direct GE-EPI measurement results (full cycles and SEM bars) and predicted results (color lines) using the experimentally measured R_1, R_1' and α values according to Eqs. (1) and (3) with three diffusion b factors (blue color: b=0; red color: 518; black color: 1019 $s \cdot mm^{-2}$; n: 5-16).

The application of bipolar diffusion gradients resulted in a slight BOLD reduction without statistical significance among three b factors ($0.06 < p < 0.41$). Moreover, the R_1 values obtained from both control and hypercapnia conditions were found to be independent on the b factor ($0.32 < p < 0.92$). The large b factor (1019 $s \cdot mm^{-1}$) should suppress the blood water signals in large vessels on both arterial and venous sides. This could explain the small BOLD reduction owing to the suppression of intravascular BOLD signal from large venues at high field when strong diffusion gradients are applied. Nevertheless, the application of strong diffusion gradients could not significantly change the behaviors of flow-related signal change during hypercapnia. This is evident in Fig. 1b; showing the similar dependence of flow-related signal change upon TR with three b factors and suggesting a negligible inflow effect from large vessels. Overall results indicate that the flow-related signal change measured during hypercapnia is likely originated from the perfusion change, possibly plus the inflow effect from small arterioles near capillaries.

Conclusion: The findings from this study have several important impacts. The majority of fMRI applications are conducted with short TR (e.g., 1-2s) for gaining SNR through signal averaging. Under this circumstance, the flow-related contribution to the total fMRI signal can increase substantially, and even become similar or larger than the BOLD signal; thus, it has to be taken into account for quantifying the true BOLD, especially for $CMRO_2$ quantification based on BOLD calibration. On the other hand, because the flow-related signal is originated from perfusion and/or arteriole inflow effect (at least at high field) reflecting micro-vascular flow processing, its contribution to fMRI signal should significantly enhance the contrast-to-noise ratio and improve specificity for mapping functional neuronal activity.

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