Magnetic Resonance Imaging 46 (2018) 121–129

Contents lists available at ScienceDirect

Magnetic Resonance Imaging

journal homepage: www.elsevier.com/locate/mri

Original contribution

Estimation of physiological sources of nonlinearity in blood oxygenation level-dependent contrast signals

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ARTICLE INFO

Keywords:
BOLD signal
Multi-echo
Gradient-echo
Nonlinearity
TE-dependence
Chemical exchange

ABSTRACT

Blood oxygenation level-dependent (BOLD) contrast appears through a variation in the transverse relaxation rate of magnetic resonance signals induced by neurovascular coupling and is known to have nonlinear characteristics along echo time (TE) due to the intra-vasculature. However, the physiological causes of this nonlinearity are unclear. We attempted to estimate the physiological information related to the nonlinearity of BOLD signals by using a two-compartment model. For this purpose, we used a multi-echo gradient-echo echo-planar imaging sequence and developed a computational method to estimate the physiological information from the TE-dependent BOLD signals. The results showed that the average chemical exchange time in the intra-vasculature varied during stimulation, which might be the essential source of the nonlinearity.

1. Introduction

Functional magnetic resonance imaging (fMRI) with blood oxygenation level-dependent (BOLD) contrast has been widely used for noninvasive measurement of brain activation [1–4]. Brain activation is measured as a fractional change in image intensity caused by a variation in the transverse relaxation rate of MRI signals. The transverse relaxation rate is affected by the concentration of deoxygenated hemoglobin (deoxy-Hb) in blood that is modulated by physiological factors, such as the cerebral blood volume (CBV), cerebral metabolic rate of oxygen, and cerebral blood flow. The fractional change shown by BOLD signal tends to increase in proportion to echo time (TE). The actual BOLD signals related to brain activation have often shown some nonlinear aspects with change in TE [5–7]. Additionally, it has been reported that the amount of the nonlinearity varies during brain activation [8] or with different types of visual stimuli [9].

The relationship between TE-dependent BOLD signals and a change in the transverse relaxation rate has been investigated by using a model that assumes a single compartment. To estimate the first-order approximation of the change in the transverse relaxation rate, a single-compartment model has been used previously; in this model, the relationship with BOLD signals is determined by the equation, $\Delta S/S \cong -\Delta R_2 \cdot \mathrm{TE}$ for spin-echo (SE) sequences or $\Delta S/S \cong -\Delta R_2^* \cdot \mathrm{TE}$ for gradient-echo (GE) sequences, where $\Delta S/S$ is the fractional change in image intensity, TE is the echo time, and $\Delta R_2^{(*)}$ is the change in the transverse relaxation rate [10,11]. If the changes in T_1 (longitudinal relaxation rate), inflow, and motion are considered, the relationship is expanded to $\Delta S/S \cong \Delta S_0/S_0 - \Delta R_2^* \cdot \mathrm{TE}$ where $\Delta S_0/S_0$ is the fractional change in initial signal intensity when TE = 0 [11]. However, a simple linear approximation based on the single-compartment model with only one transverse relaxation rate cannot accommodate the nonlinearity in TE-dependent BOLD signals.

In a two-compartment model, the BOLD signal literally consists of two distinct types of transverse relaxation rates originated from intravascular (IV) and extravascular (EV) spaces [12]. The two-compartment model previously has been applied to quantitatively predict the contributions of IV and/or EV to the BOLD signal [7,13]. In the previous experimental studies on the TE-dependence of ΔS/S, a linear dependence on TE was found in brain parenchyma [5,7,14–18]. It has been demonstrated that BOLD signals from the EV space are almost linearly dependent on TE within the commonly used TE ranges [19]. In contrast to the EV space, some studies have shown that the nonlinearity was attributable to an effect of deoxy-Hb in the IV space, where a fast chemical exchange between plasma and deoxy-Hb induced accelerated dephasing of nearby water protons and hence, shortened T_2 and T_2^* [5,20,21]. Thus, the nonlinearity of BOLD signals could possibly be used to separate IV and EV components by estimating values of parameters based on the model.

A phenomenon of chemical exchange is often pH-dependent. Thus, the pH dependence of exchangeable protons at the protein surface has been demonstrated [22], and chemical exchange saturation transfer MRI has been used for pH imaging [23,24]. In recent fMRI studies,

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https://doi.org/10.1016/j.mri.2017.10.017
Received 9 December 2016; Received in revised form 13 October 2017; Accepted 31 October 2017

Table 1
Parameters used in two-compartment model.

Components	Parameters	Constant-valued	Location-dependent	Stimulus-dependent
Intra-vascular	Intrinsic transverse relaxation rate in blood	$R_{2,IV,0}{}^{*}$	–	–
	Additional transverse relaxation rate by deoxy-Hb	$R_{2,IV,Hb}{}^{*}$	–	–
	Blood oxygenation level	Y	–	ΔY
	Water exchange time	τ_{ex}	–	$\Delta\tau_{ex}$
Extra-vascular	Transverse relaxation rate	$R_{2,EV}{}^{*}$	–	$\Delta R_{2,EV}{}^{*}$
–	Blood volume fraction of venous blood	–	V	ΔV

Table 2
Preparation of variable parameters for simulation.

Parameters	Unit	Min. value	Increment	Max. value
τ_{ex}	[ms]	1	1	10
V	[%]	1	1	15
$\Delta R_{2,EV}{}^{*}$	[s^{-1}]	− 2.0	0.02	0.5
ΔY	[%]	− 5.0	0.2	20.0
ΔV	[%]	− 0.2	0.01	1.0
$\Delta\tau_{ex}$[a]	[ms]	-τ_{ex}	0.2	10-τ_{ex}

[a] The range of this parameter was used in the two compartment model with time-varying $\Delta\tau_{ex}$.

activity-evoked change in pH on a visual-related cortex of a human brain has been demonstrated [25–27]. However, the fast chemical exchange in the two-compartment model has been assumed to be determined by a fixed time constant; i.e., an average chemical exchange time in the chemical exchange model. Across the previous studies, the chemical exchange time has been chosen in a range from 0.6 to 10.0 ms depending on experimental conditions [28–32]. Additionally, it has been shown through computer simulation that the chemical exchange time had a significant effect on the nonlinearity of IV BOLD signals as a function of TE [5]. Therefore, the chemical exchange time may not be a constant value and may vary under brain activation. Thus, a model that incorporates the change would be more accurate for estimation of parameters, such as CBV, than a model that assumes fixed exchange time.

For assessing the nonlinearity of BOLD signals, the multiple-TE measurement was required. In most of the previous studies [28–32], in-vitro and/or in-vivo blood samples were prepared for estimating the chemical exchange time by using the Carr–Purcell–Meiboom–Gill sequence. However, it is too time-consuming to acquire multiple-TE data in a typical fMRI experiment for in-vivo examination of perception/cognition. It is practically difficult for a human brain to reproduce cognitive and perceptual activations over long time scales. Therefore, multi-echo GE echo-planar imaging (EPI) was used to obtain TE-dependent BOLD signals because it needs only the time to obtain additional echo signals without additional repetition of measurements. Additionally, GE-EPI may provide the benefit of showing the nonlinearity because it produces a higher contrast-to-noise ratio in BOLD signals than does SE EPI.

In this study, we attempted to estimate the physiological information related to the nonlinearity of BOLD signals by using the proposed two-compartment model that includes a variable in the chemical exchange time. For this purpose, we used a multi-echo GE-EPI sequence to measure one modality and developed a computational method to estimate the physiological information from the TE-dependent BOLD signals. The goodness of fit for a model was verified by considering the complexity of the model. The parameters estimated from the models were compared with those in the literature.

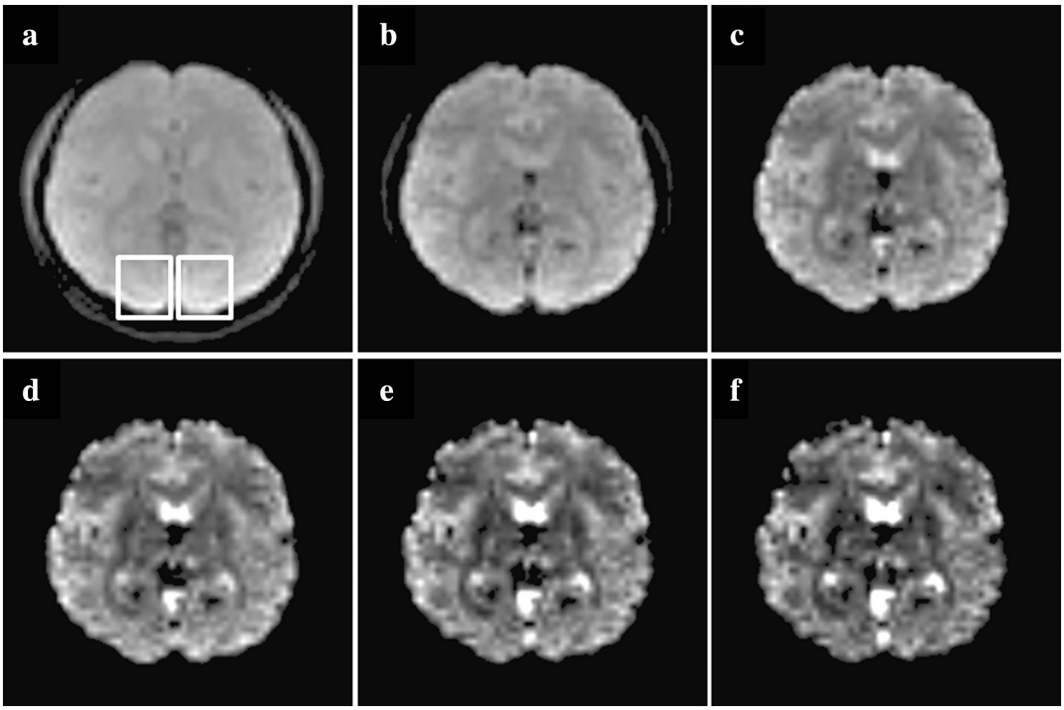

Fig. 1. Images obtained from multiple echo times. (a–f) Images obtained at TEs of 11, 26, 41, 56, 71, and 86 ms, respectively. The region of interest was defined at the posterior region of each hemisphere of the brain (white boxes at (a)), where a voxel cluster was chosen to be activated with the given visual stimulus ($p < 0.001$) for all TEs. A cluster around the occipital sinus was excluded.