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Short communication

Two pitfalls of BOLD fMRI magnitude-based neuroimage analysis: Non-negativity and edge effect

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ABSTRACT

BOLD fMRI is accepted as a noninvasive imaging modality for neuroimaging and brain mapping. A BOLD fMRI dataset consists of magnitude and phase components. Currently, only the magnitude is used for neuroimage analysis. In this paper, we show that the fMRI-magnitude-based neuroimage analysis may suffer two pitfalls: one is that the magnitude is non-negative and cannot differentiate positive from negative BOLD activity; the other is an edge effect that may manifest as an edge enhancement or a spatial interior dip artifact at a local uniform BOLD region. We demonstrate these pitfalls via numeric simulations using a BOLD fMRI model and also via a phantom experiment. We also propose a solution by making use of the fMRI phase image, the counterpart of the fMRI magnitude.

1. Introduction

Neuronal activity results in blood oxygenation and blood flow changes in cerebral cortex, which is described as a BOLD (blood oxygenation level dependent) process. Under linear neurovascular coupling assumption and toward MRI measurement, the BOLD process can be represented by the blood magnetism property perturbation in terms of susceptibility map, which can be measured by functional magnetic resonance imaging (fMRI) technology (Ogawa et al., 1992, 1993; Boxerman et al., 1995a,b; Howseman and Bowtell, 1999; Uludag et al., 2009). The physical principle of fMRI is based on the transverse relaxation of nuclear spins in a BOLD-induced inhomogeneous field resulting from the blood magnetization in a main magnetic field. In practice, a BOLD fMRI procedure produces a 4D dataset, which consists of a 3D volume of the field of view (FOV) and 1D event time. (Note that the echo time T_E for MRI scanning is typically fixed as a protocol parameter.) At an event time, a 3D volume is acquired as a snapshot of the dynamic BOLD process in the FOV. By equipping a standard fMRI pulse sequence (typically an EPI) with the complex output, we obtain a complex-valued dataset consisting of both magnitude and phase; where the magnitude is used for neuroimage analysis based on a fundamental assumption: the magnitude image may represent (or correlate with) the intracortical neuroactivity (albeit qualitatively and empirically). Meanwhile, the phase image is not widely accepted for neuroimaging yet, perhaps, due to the following reasons: (1) some MRI scanners may not be equipped with complex output, (2) the fMRI phase mechanism remains unclear, and (3) the phase image looks noisy and textural, hence not providing for straightforward interpretation (in contrast, the magnitude image contains smooth and compact blobs that are more intuitive for depicting local activations by default). In this report, we will clarify that the underlying source of fMRI modality is the magnetic susceptibility perturbation induced by a biophysiological BOLD process (including blood oxygenation, CBF, CBV, etc.) and show that there are two pitfalls inherent to the fMRI magnitude: one is the magnitude's non-negativity that prevents differentiating a positive susceptibility perturbation from a negative one, the other is an edge effect inherent to the intravoxel dephasing mechanism of BOLD signal formation, which has been observed as an edge enhancement effect (Cho et al., 1996).

A standard BOLD fMRI study is concerned with relatively long signal increases. The long time average (T_E ~30 ms) and the prevailing response peaks at a voxel or a local region may suppress a transient "initial dip" and a shallow "post-stimulus undershoot" phenomena (Arthurs and Boniface, 2002; Logothetis, 2002; Buxton, 2010), which are observable by high spatiotemporal resolution experiments with a technique such as optical imaging. Limited by penetration (~mm depth) and 2D projection, the optical imaging modality can only capture the oxygen-related events at the epidermis and dermis layers of barrel cortex, but fails to observe activity inside cortex or interior brain regions. This problem can be well solved by fMRI. As aforementioned, fMRI is confronted with a low temporal resolution that may not resolve a small transient negative

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BOLD state in a region; however, its high spatial resolution feature may reveal the co-occurrence of deactivation and activation in a 3D snapshot. In the magnitude image of fMRI, the negative signal is represented by its magnitude, thus confounding with the positive signals. The non-negativity of the magnitude is an inevitable issue. In this paper, we suggest a way to recover the bipolar-valued (positive/negative) susceptibility source by making use of the fMRI phase image.

2. Theory and methods

We diagram a BOLD fMRI model in Fig. 1 which includes two modules: neurophysiology and fMRI technology. In the neurophysiological module, we describe a local neuronal activity in a cortical FOV by a neuroactive blob, denoted by NAB(x,y,z), which represents a low-pass-filtered spatial distribution of intracortical local field potentials and random spikes (Arthurs and Boniface, 2002; Logothetis, 2002). Under a linear neurovascular coupling assumption (Hoge et al., 1999; Arthurs et al., 2000), we describe the BOLD response to NAB(x,y,z) in terms of magnetic susceptibility property perturbation (at an event time), as expressed by

$$\Delta\chi(x,y,z) = \mathrm{NAB}(x,y,z)\cdot(\chi_{\mathrm{BOLD}} - \chi_{\mathrm{baseline}})\cdot \mathrm{FOV}(x,y,z) \tag{1}$$

where FOV(x,y,z) denotes a vasculature-filled cortex FOV that encloses the NAB, $\chi_{\mathrm{BOLD}} - \chi_{\mathrm{baseline}}$ denotes the magnetic susceptibility perturbation induced by a BOLD process (in reference to baseline). It is noted that $\Delta\chi$ may take on negative values unless the baseline is properly selected as the global minimum (or even smaller) of the magnetic susceptibility distribution of a BOLD state, i.e., $\chi_{\mathrm{baseline}} = \min\{\chi_{\mathrm{BOLD}}(x,y,z)\}$. Due to the fact that deoxyhemoglobin is paramagnetic (with positive susceptibility) and oxyhemoglobin is diamagnetic (with negative susceptibility), a susceptibility map (χ_{BOLD}) of a BOLD state without baseline reference ($\chi_{\mathrm{baseline}} = 0$) may be positive in some regions and negative in others; that is, $\chi_{\mathrm{BOLD}}(x,y,z)$ usually assumes a bipolar-valued distribution over a FOV. Observing at a voxel or region in FOV, we acquire a BOLD signal course whose phase part may consist of peaks and valleys, corresponding to positive and negative magnetic susceptibility values.

The BOLD fMRI model assumes that the neuroactivity in a cortical FOV can be represented by the neuron-induced BOLD susceptibility perturbation, which serves as the underlying source for fMRI detection. The fMRI technology module in Fig. 1 is to tomographically reproduce the spatial distribution of $\Delta\chi(x,y,z)$ (a 3D snapshot of a dynamic BOLD process at an event time). However, the output of fMRI is not identical to its target source as addressed below.

During an fMRI procedure, the susceptibility map is spatially transformed into a fieldmap through blood magnetization in a main field B_0, which is a 3D convolution as expressed by (Chen et al., 2011b; Haacke et al., 1999).

$$\begin{aligned}
&\Delta B(x,y,z) = B_0\cdot\Delta\chi(x,y,z) * h(x,y,z) + \varepsilon(x,y,z)\\
&\text{with } h(x,y,z) = \frac{3z^2-(x^2+y^2+z^2)}{3(x^2+y^2+z^2)^{5/2}}\\
&\text{and } \iiint h(x,y,z)dxdydz = 0,\\
&\quad \iiint h(x,y,z)|dxdydz > 0 \quad \text{for } h(0,0,0)\equiv 0
\end{aligned} \tag{2}$$

where * denotes convolution, and $\varepsilon(x,y,z)$ the noise. It is noted that the 3D kernel $h(x,y,z)$ takes on positive, negative, or zero values; that is, it bears a zero surface at $h(x,y,z) = 0$, in the appearance of an hour glass (Chen et al., 2011b). The kernel's spatial integration produces a zero, but its absolute integration is nonzero; such a property indicates that the kernel acts as a 3D texture extractor during fieldmap establishment from the viewpoint of image processing. It is noted the zero integration at the bottom of Eq. (2) holds for the setting of $h(0,0,0) = 0$. In this case, the 3D convolution transforms a plateau of susceptibility map to a centrally dipped patch (a large plateau may result in zeros at the central region of the patch) while only extracting the vessel boundaries (an edge is a sort of texture).

After the fieldmap establishment via Eq. (2), the MRI technology produces a complex dataset that may spatially correlate with fieldmap (but not identically reproduced). During fMRI signal detection or image acquisition, the FOV is spatially partitioned into a multivoxel image (an array of voxels). For a dynamic BOLD process at a specific time, the BOLD voxel signal is formed by an intravoxel dephasing mechanism, which is expressed (for the static regime that ignores the diffusion) by

$$\begin{aligned}
&C(x,y,z,\mathrm{T_E}) = \frac{1}{|V|}\sum_{(x',y'z')\in V(x,y,z)} \exp[-i\gamma\cdot\mathrm{T_E}\cdot\Delta B(x',y',z')]\\
&\text{with } \bigcup_{(x,y,z)} V(x,y,z) = \mathrm{FOV}
\end{aligned} \tag{3}$$

where $V(x,y,z)$ represents a voxel, and $|V|$ the voxel volume, $\mathrm{T_E}$ denotes the echo time for gradient echo signal, and $C(x,y,z,\mathrm{T_E})$ the complex-valued fMRI dataset for the FOV. It is noted that the output of the tomographic fMRI detection on a BOLD state is not an identical reproduction of the target source, that is, $C(x,y,z)$ appears dissimilar to $\Delta\chi(x,y,z)$ due to the transformations in Eqs. (2) and (3).

Due to the factor $1/|V|$ in Eq. (3), the magnitude is bounded by [0,1]. Given a complex number, we can always find its phase angle in one trigonometric period $[-\pi,\pi)$. Therefore, from the complex output $C(x,y,z,\mathrm{T_E})$, we can extract its magnitude $\mathrm{A}(x,y,z,\mathrm{T_E})$ and phase $\Phi(x,y,z,\mathrm{T_E})$, which satisfy the following relations

$$\begin{cases} 0 \le A(x,y,z,\mathrm{T_E}) \equiv |C(x,y,z,\mathrm{T_E})| \le 1\\ -\pi \le \Phi(x,y,z,\mathrm{T_E}) \equiv \angle C(x,y,z,\mathrm{T_E}) < \pi \end{cases} \tag{4}$$

where the magnitude is normalized to 1 by $\max(\mathrm{A}) = \mathrm{A}(\mathrm{T_E} = 0) = 1$, and the phase angle is bounded by $[-\pi,\pi)$ which accommodates possible phase wrapping cases (phase angles beyond the trigonometric period are folded back into the period). We should mention that large phase angles among voxel signals from a spatial context may cause a phase wrapping problem, which can be recovered by phase unwrapping methods; we do not cover the large angle regime in this paper.

It is seen in Eq. (4) that the magnitude is limited by non-negativity while the phase angle is not. In this paper, we address the signal magnitude non-negativity which produces a signal ambiguity: a positive susceptibility perturbation ($\Delta\chi > 0$) and a negative one ($\Delta\chi < 0$) may produce the same magnitude. In order to reveal the relationships among the magnitude $\mathrm{A}(x,y,z)$, the phase $\Phi(x,y,z)$, and their common susceptibility source $\Delta\chi(x,y,z)$, in what follows we develop an approximate theory.

Due to nonlinear trigonometry associated with proton spin processions in Eq. (3), large precession angles may incur instable chaotic signal behaviors (Chen and Calhoun, 2010), thus hindering an analytic formulation. The small angle condition $(\exp(-i\phi)\approx 1 - i\phi)$ (Chen et al., 2011c), termed small angle regime henceforth, allows us to analytically describe the BOLD contrast mechanism. As such, the BOLD signal in Eq. (3) can be approximated by

$$\begin{aligned}
&C(x,y,z,\mathrm{T_E}) \approx \frac{1}{|V|}\sum_{(x',y'z')\in V(x,y,z)} [1 - i\gamma\cdot\mathrm{T_E}\cdot\Delta B(x',y',z')]\\
&\quad \text{for} |\gamma\cdot T_E\cdot\Delta B| \ll 1
\end{aligned} \tag{5}$$

We are concerned with the complex signal change, denoted by δC, with respect to $\mathrm{T_E}$ and in reference to its initial value (at $\mathrm{T_E} = 0$), as