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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.

Keywords

Computational Neuroimaging; BOLD fMRI; BOLD susceptibility; edge enhancement; small angle regime

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, Tank et al. 1992; Ogawa, Menon et al. 1993; Boxerman, Bandettini et al. 1995; Boxerman, Hamberg et al. 1995; Howseman and Bowtell 1999; Uludag, Muller-Bierl 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

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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, and 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, Hong et al. 1996).

A standard BOLD fMRI study is concerned with relatively long signal increases. The long time average ($T_E \sim 30\text{ms}$) 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 ($\sim\text{mm}$ 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 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, Atkinson et al. 1999; Arthurs, Williams 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

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

where $FOV(x,y,z)$ denotes a vasculature-filled cortex FOV that encloses the NAB, $\chi_{BOLD} - \chi_{baseline}$ denotes the magnetic susceptibility perturbation induced by a BOLD process (in reference to baseline). It is noted that χ 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., $\chi_{baseline} = \min\{\chi_{BOLD}(x,y,z)\}$. 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 ($\chi_{baseline} = 0$) may be positive in some regions and negative in others; that is, $\chi_{BOLD}(x,y,z)$ 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 $\chi(x,y,z)$ (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, Chen et al. 2011; Haacke, E. M., 1999)

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

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, Chen et al. 2011). 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

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

where $V(x, y, z)$ represents a voxel, and $|V|$ the voxel volume, T_E denotes the echo time for gradient echo signal, and $C(x, y, z, T_E)$ 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 $\chi(x, y, z)$ 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 $C(x, y, z, T_E)$, we can extract its magnitude $A(x, y, z, T_E)$ and phase $\Phi(x, y, z, T_E)$, which satisfy the following relations

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

where the magnitude is normalized to 1 by $\max(A) = A(T_E=0) = 1$, 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 ($\chi > 0$) and a negative one ($\chi < 0$) may produce the same magnitude. In order to reveal the relationships among the magnitude $A(x, y, z)$, the phase $\Phi(x, y, z)$, and their common susceptibility source $\chi(x, y, z)$, in what follows we develop an approximate theory.

Due to nonlinear trigonometry associated with proton spin precessions 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, Chen et al. 2011), 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

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

We are concerned with the complex signal change, denoted by δC , with respect to T_E and in reference to its initial value (at $T_E=0$), as calculated by $\delta C(T_E)=C(T_E)-C(T_E=0)$.

Accordingly, the magnitude and phase of $\delta C(T_E)$ connote the signal intensity loss (i.e. signal magnitude decay) and signal phase angle accumulation, respectively. In the small angle regime, we have

$$\begin{cases} \delta A(x, y, z, T_E) \equiv |\delta C(T_E)| \approx \gamma \cdot T_E \cdot |\bar{b}(x, y, z)| \\ \delta \Phi(x, y, z, T_E) \equiv \angle \delta C(T_E) \approx \gamma \cdot T_E \cdot \bar{b}(x, y, z), \end{cases} \text{ for } |\gamma \cdot T_E \cdot \bar{b}| \ll 1 \quad (6)$$

$$\text{with } \bar{b}(x, y, z) \equiv \frac{\sum_{(x', y', z') \in V(x, y, z)} \Delta B(x', y', z')}{|V|}$$

where the small angle condition $|\gamma \cdot T_E \cdot \bar{b}| \ll 1$ is a corollary of $|\gamma \cdot T_E \cdot B| \ll 1$ for $\bar{b} = \max(B)$ (the average is always less than the individual maximum). The intravoxel-averaged coarse fieldmap $\bar{b}$ is a low-resolution version of the fine fieldmap B in Eq. (2). According to Eq. (6), the nondecay magnitude case ($A=1$) gives rise to $\delta A=0$ (interpreted as no signal or no contrast), and the stationary phase angle ($\Phi=0$) to $\delta \Phi=0$ (interpreted as no field perturbation). Henceforth, we refer the magnitude to δA and the phase to $\delta \Phi$, in place of A and Φ hereafter. It is noted that the small angle regime (for both individual spin precession angle $|\gamma \cdot T_E \cdot B| \ll 1$ and the collective voxel signal angle $|\gamma \cdot T_E \cdot \bar{b}| \ll 1$) is determined by $T_E \cdot B$ (with $B \propto B_0$); therefore the small angle condition for high field fMRI can always be reached by presetting a small T_E .

It is seen in Eq. (6) that the magnitude decay is attributed to the absolute value of the intravoxel field average; where the average statistics suppresses the intravoxel spatial population information and the magnitude operation prevents the discrimination of positive and negative values. In comparison, the phase is linearly proportional to both T_E and $\bar{b}$ without involving the nonlinear absolute value operation; therefore, the phase image can represent the fieldmap (different by a constant factor) by retaining the signs for positive or negative field values.

When addressing Eq. (2), we mentioned that the fieldmap is a texture-enhanced version of the susceptibility source due to the textural enhancement by a 3D convolution with a bipolar-valued kernel. From the viewpoint of image processing, a textural extractor can serve as edge detector as well: which enhances a boundary and suppresses a uniform region. In particular, the 3D convolution converts a uniform region to a smaller uniform region (not necessarily to zero if the kernel integration, or its DC term, is nonzero) due to the kernel spread. The 3D convolution thus provides an edge enhancement and a plateau dipping during the fieldmap establishment.

Upon observation of the intravoxel dephasing formula in Eq. (3), we notice that the voxel signal is determined by the intravoxel field inhomogeneity, irrespective of the spatial

distribution within the voxel. Since large inhomogeneous fields mainly occur at vascular boundaries due to the texture-enhanced convolution in Eq. (2), it is expected that conspicuous signals will be observed at the vascular boundaries as connoted in Eq. (3). In what follows we will show that the “edge effect” associated with the intravoxel dephasing model is a pitfall of magnitude-based neuroimage analysis.

For a local uniform region on a fieldmap, the edge effect will manifest as a spatial interior dipping phenomenon in the magnitude pattern as explained by

$$C(x, y, z, T_E) = \exp(-i\gamma \cdot T_E \cdot c) \quad (7)$$

with $c = \bar{b}(x, y, z) = \text{const}$

which gives rise to

$$\begin{cases} A(x, y, z, T_E) = |C(x, y, z, T_E)| = 1 \\ \Phi(x, y, z, T_E) = \angle C(x, y, z, T_E) = \gamma \cdot T_E \cdot c \end{cases} \quad (8a)$$

and

$$\begin{cases} \delta A(x, y, z, T_E) = 0 \\ \delta \Phi(x, y, z, T_E) = \gamma \cdot T_E \cdot c \end{cases} \quad (8b)$$

Therefore a voxel having homogeneous interior will produce a nondecay signal magnitude ($\delta A = 0$). Hence a region (embedded in a cortical FOV) that contains a patch of uniform voxels will produce a spatial dip in the magnitude image. It is noted that the fMRI magnitude formation is due to the spin precession dispersion (statistical average) within a voxel, irrespective of the intravoxel spatial population or configuration. That means, an increasing edge and a decreasing edge will produce the same magnitude, and a plateau (assuming a local uniformity with any constant value) at a fieldmap will produce a dip in the magnitude image. In comparison, the phase pattern can represent the fieldmap not only in spatial conformance (different by a constant factor) but also in preserving the negative and positive signs, as given in Eq.(8).

In Fig. 2, we illustrate a spatial dipping phenomenon with a Gaussian susceptibility blob (with 1D scenario). The depth of the dip is dependent upon T_E and B_0 , and the dip shape is dependent upon the plateau on the fieldmap. Note that the theoretical explanation on the “edge effect” in Eqs. (7) and (8) and its illustration with a central dipping example are not subject to the small angle regime.

For a large blood vessel, we can calculate its fieldmap by a cylinder model (Haacke, Brown et al. 1999). The uniform interior will produce a small plateau ($b \approx 0$) at the vessel center and a conspicuous edge at vessel boundary on the fieldmap. A plateau will produce a dip in the magnitude image. Accordingly, it is understandable that the dark spots in a magnitude image of high-resolution fMRI are due to the dips at vessel centers. In practice, the cortex contains many small vessels (3~15 microns in diameter); therefore it is unlikely to observe

conspicuous dips inside the small vessels, especially in a typical millimeter-resolution fMRI experiment. Nevertheless, it is possible in principle that the intravoxel average may produce a plateau on a susceptibility map and on a fieldmap due to randomness of intracortical vasculature, thus causing a dip at the activation center. It is expected the dipping phenomenon would be observed in ultra high spatial-resolution fMRI.

In summary, the magnitude image of fMRI is related to the fieldmap by nonlinearly mapping a bipolar-valued distribution to a non-negative distribution. The magnitude cannot reflect the negativity of a field value or a subsequent negative action, thus causing an ambiguity between a positive activation and a negative deactivation. The edge effect causes dips at local uniform BOLD activation regions. In comparison, the phase image is linearly dependent upon the fieldmap and the susceptibility source can be reconstructed as long as the 3D deconvolution is well solved.

3. Simulation and phantom experimental results

In this section, we demonstrate, with numerical simulation and phantom experiment, the spatial interior dipping phenomenon inherent to the fMRI magnitude mechanism.

Numerical simulation

Given a blob-shaped fieldmap (in form of a Gaussian distribution) in the FOV in Fig. 3(a) (2D slice display), we calculate the fMRI dataset using Eq.(3), and present the magnitude image in Fig. 3(b), which shows that there is a dip in the image due to a relative plateau at the top of the Gaussian-shaped fieldmap. The numeric profile along a scanline across the center of the 3D Gaussian sphere in Fig. 3(b) is presented in Fig. 3(c). The spatial dipping phenomenon is understandable from the illustration in Fig. 2. This numerical simulation is not limited to small angle regime.

Phantom experiment

We used a tube filled with diluted Gadolinium (Gd) (dilution=0.4mL/30mL) and conducted a MRI experiment on a Siemens Trio 3T scanner. The complex MRI dataset was acquired by a modified standard Siemens pulse sequence (with $T_E=3\text{ms}$). The Fig. 4 shows the geometry of the phantom experiment, which consists of a water tank and a Gd-filled tube; the tube axis was posed perpendicular to the main field during MRI scan. Three orthogonal slices (at $x=0, y=0, z=0$ of the FOV) of the fMRI magnitude image are shown at the top row in Fig. 5, where we can clearly see a dark line at the tube axis. Correspondingly, the slices of the phase image are shown at the middle row, which are considered as the fieldmap (different by a constant factor). It is noted that the phase image inside the FOV (the water tank) remains phase unwrapped. From the fieldmap, we calculated the susceptibility map by a 3D deconvolution process (an abstract was presented in (Chen, Caprihan et al. 2011), details will be reported separately). The reconstructed susceptibility map is shown at the bottom row in Fig. 5, which reveals the uniform Gd susceptibility distribution inside the tube. Fig. 6 provides a numerical comparison with a scanline profile along a diameter of the tube. Upon observation of the images in Fig. 5 and the plots in Fig. 6, it is seen that the reconstructed susceptibility is close to the ground truth (uniform tube interior), the

magnitude suffers a central dip artifact, and the phase image is different from the susceptibility map due to a spatial convolution blurring.

4. Discussion and conclusion

Based on MRI T2* contrast mechanism, which is the underlying principle for BOLD fMRI signal and image formation, we show that the magnitude-based neuroimage analysis may suffer two inevitable pitfalls: non-negativity and edge effect. These pitfalls are universally present with all the settings of fMRI modality, not limited to the condition of small angle regime. The non-negativity is due to a nonlinear mapping from a bipolar-valued distribution to a positive distribution, and the edge effect is due to the intravoxel dephasing model (the 3D convolution of the blood magnetization contributes an edge enhancement as well). We can overcome the magnitude pitfall by making use of its phase counterpart in order to more accurately compute the susceptibility source.

The non-negativity issue means that a negative fieldmap may produce the same magnitude image as a positive fieldmap (the fieldmap plays an intermediate role in BOLD fMRI, see Fig. 1). Since the fieldmap is related to the BOLD susceptibility map by a 3D convolution, which is a linear spatial transformation, the non-negativity issue also translates to the susceptibility source. Another pitfall is the central dip effect that occurs at a fieldmap plateau during MRI detection, which has been observed as an edge enhancement phenomenon (Cho, Hong et al. 1996). Based on the intravoxel dephasing mechanism, we show that the presence of a dip in a multivoxel magnitude image is due to the lack of precession dispersion inside a voxel. In other words, the BOLD signal intensity (magnitude) is attributed to the intravoxel inhomogeneous fieldmap which is in turn due to the susceptibility perturbation associated with a BOLD process. Since the 3D convolution kernel is characteristic of positive and negative lobes and bears a 3D zero surface (Chen, Z., Z. Chen, et al. (2011b), the 3D convolution plays a role of textural enhancement during fieldmap establishment from a susceptibility source. As a result of intravoxel dephasing on a fieldmap, the BOLD signal reveals large intensity decays at vascular boundaries where the susceptibility has a discontinuous jump from intravascular blood space to extravascular tissue bed.

Both the non-negativity and the edge effect are undesirable for neuroimage analysis. Specifically, the nonlinear relationship between the magnitude and fieldmap prevents the differentiation from a susceptibility increase to a susceptibility decrease, or from an activated blob to a deactivated blob. A local uniform activation region produces a plateau in the fieldmap which in turn produces no signal decay or no image contrast due to nondecay magnitude ($\delta A=0$). Furthermore, a plateau in the fieldmap with a positive value is in differentiable from its negative counterpart. Obviously, the dips on the resultant magnitude image will jeopardize the neuronal or vascular origin depiction. Fortunately, these problems inherent in the fMRI magnitude are not present in the phase counterpart. Given an fMRI phase image, we can reconstruct the susceptibility source by solving a 3D inverse problem by two steps: from phase image to fieldmap and from fieldmap to susceptibility source (which is a 3D ill-posed deconvolution problem (Chen, Caprihan et al. 2011)).

One may consider a solution to overcome the magnitude's non-negativity pitfall by adding a positive offset to a susceptibility perturbation to ensure a non-negative susceptibility distribution. However, such a practice requires adjusting the on-resonance frequency (corresponding to a rotated coordinate system) of the coil detectors. Another shortage associated with the offset strategy is that: it may violate the small angle regime, cause phase wrapping problems and instable signals, and prevent the analytical treatment of the magnitude and phase behaviors (as presented herein).

For analytic presentation of the magnitude's nonlinear mapping and non-negativity attributes, we report a special case of the small angle regime, which allows us to formulate the relationships among the phase, fieldmap, and susceptibility, and to avoid the phase unwrapping problem. As mentioned previously, the magnitude pitfall is universally present for all phase angle values. In practice, a large phase angle regime (typically resulted from a long T_E) may be used for improving fMRI with a high signal-to-noise ratio. The upper bound for an fMRI experiment can be estimated by $Hct \cdot (1-Y) \cdot \chi_{do} \cdot \gamma \cdot T_E \cdot B_0$. For example, in a typical 3T fMRI study, the phase angle is bounded by 13 rad (calculated for the following settings $Hct=0.4$, $Y=0.6$, $\chi_{do}=0.27 \times 4\pi \times 10^{-6}$, $\gamma=267.5$ rad/ms/mT, $B_0=3000$ mT, $T_E=30$ ms). Obviously, this phase angle limit (13 rad) falls within a large angle regime. However, when the texture extraction effect by the 3D convolution in Eq. (2) is accounted for, the fieldmap values are greatly reduced such that the phase angle values may fall into a small angle regime if the spatial kernel integration acts a factor of, for instance, 1/15. These issues will be investigated in future work.

For an fMRI dataset acquired in large angle regime, we may be confronted with phase-wrapped signals, and we cannot describe the signal behavior by analytical approximations as presented herein. However, we may perform numerical simulations in a manner as reported in (Chen, Z. and V. D. Calhoun (2010)). The small phase angle is always desirable for functional neuroimaging by fMRI modality, as evidenced from the fact: a small or ultra-short T_E is always used for high-field and high-resolution fMRI.

Currently, BOLD fMRI is typically carried out on a 3T scanner with $T_E \sim 30$ ms and at millimeter voxel resolution. In cerebral vascular cortex (gray matter), it will be unlikely to observe a significant spatial interior dipping artifact due to the following aspects: 1) it is unlikely for cortical vasculature to form (by spatial random superimposition) a local uniform field patch that is larger than a voxel size, due to the vascular sparseness (2% spatial occupancy); 2) the voxel size (1~3mm) is far larger than cortical vessel sizes (3~15 microns in diameter), therefore, the intravascular dips are not resolvable within a voxel signal; 3) a slight dip on a magnitude image may be obscured by noise; and 4) a spatial smoothing operation is usually applied to a raw fMRI dataset, which may also suppress slight dips. Nevertheless, it is expected the spatial dip artifact will emerge in ultra-high spatial resolution fMRI.

In conclusion, we attribute the fMRI signals to the source of susceptibility perturbation. When the neuroactivity-induced susceptibility perturbation assumes a negative distribution (due to a relative expression in reference to a non-global minimal baseline or due to the negative diamagnetic susceptibility property of deoxyhemoglobins), the magnitude image of

the fMRI data fails to discriminate a negative deactivation from a positive activation. The intravoxel dephasing mechanism imposes an edge effect on the fMRI magnitude image, which manifests as a spatial dipping phenomenon at a local uniform activation. As a solution to avoid the pitfalls inherent with the fMRI magnitude-based neuroimage analysis, we suggest exploiting the fMRI phase (which comes with the magnitude of the fMRI output as a counterpart without extra effort) and rendering an inverse procedure to reconstruct the susceptibility source for underpinning the neuronal origin.

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Fig. 1.

A BOLD fMRI model for neuroimaging. In the neurophysiology module: a local neuroactivity is represented by a 3D blob, which induces a BOLD process that can be characterized in terms of blood's magnetic susceptibility perturbation. In the MRI technology module: The BOLD susceptibility source is magnetized in a main field to establish a 3D fieldmap, which is tomographically imaged by MRI with an output of complex-valued dataset. The task of neuroimage analysis is to underpin a neuroactivity based on a BOLD fMRI dataset.

Fig. 2. Illustration of the edge effect associated with BOLD signal magnitude (1D scenario). Its T_E -dependence and non-negativity can be described by a central dipping phenomenon. The illustration is not subject to small angle regime.

Fig. 3. Numerical simulation of the edge effect associated with BOLD image magnitude (2D scenario). The central region of a blob bears a dip at its magnitude image of fMRI data.

Fig. 4. Configuration of MRI experiment with a Gd-tube phantom. A tube filled with diluted gadolinium was inserted in a large water tank and placed in a 3T scanner for MRI scanning (with the tube axis being perpendicular to the main field).

Fig. 5. Gd-tube phantom experiment results. Three orthogonal slices of the 3D images are shown. The magnitude image (the signal intensity loss map) of the Gd-tube contains a central dip artifact. The phase image of the Gd-tube represents its fieldmap. The susceptibility image was reconstructed from the fieldmap by a 3D deconvolution. (Ground truth: the Gd-tube has a uniform interior). It is noted that the water tank region meets the phase-unwrapped condition (the outside is a don't-care region) and that the phase image appears morphometrically dissimilar with the susceptibility source.

Fig. 6. Numerical profiles of the scanline along a diameter of the Gd tube in a water container (see Fig. 5). The ground truth is that: along a Gd-tube diameter is of flat distribution. The magnitude image bears a central dip artifact and the phase-based susceptibility reconstruction is close to the truth.