

Inverse Mapping of BOLD fMRI: 4D Magnetic Susceptibility (χ) Tomography

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ABSTRACT

Background: A brain magnetic state (in terms of magnetic susceptibility distribution χ) can be detected by T2*-weighted MRI (T2*MRI) undergoing a cascade of data transformations. The MRI transformations cause distortions (or spatial morphing), which may be undone by solving the inverse imaging or mapping problem. Upon having a dataset acquired from Blood Oxygenation Level-Dependent (**BOLD**) functional MRI, we can reconstruct the dynamic brain χ source by inverse mapping called 4D χ tomography. This chapter is to address the imaging and inverse imaging aspects of BOLD fMRI from the perspective of data mapping.

Methods: T2*MRI is described by a mathematical mapping from a real-valued continuous χ source to a complex-valued discrete T2* image, of which the T2* magnitude imaging implements a mapping from a set of real numbers ($R = (-\infty, \infty)$) to a set of nonnegative numbers ($R^+ = [0, \infty)$) that is irreversible; whereas the T2* phase imaging (with unwrapped phase) is a mapping of $R \rightarrow R$ that is reversible. A 3D χ map is reconstructed from a 3D T2* phase image by a Computed Inverse MRI (**CIMRI**) method. The dynamic 4D χ source is reconstructed by 4D χ tomography, implementing a spatiotemporal inverse mapping of BOLD fMRI.

Results: A Laplacian unwrapping algorithm can efficiently unwrap the spatially-wrapped T2* phase images, implementing spatial phase unwrapping. A complex division algorithm can extract temporal phase changes (in reference to a baseline) from a time series of T2* phase images, implementing temporal phase unwrapping. High-field (at 7T), high-resolution, finger-tapping experiments show cortical details in brain tissue magnetic images and bidirectional BOLD magnetic responses to task stimuli.

Conclusion: Brain χ tomography reproduces the brain tissue χ map by an inverse mapping of T2*MRI. In light of MRI transformation cancellation, the 4D brain χ tomography innovates brain fMRI with the accomplishment of intrinsic brain functional χ mapping.

Keywords: Blood Oxygenation Level Dependence (**BOLD**); Functional Magnetic Resonance Imaging (**fMRI**); T2*-weighted MRI (**T2*MRI**); Computed Inverse MRI (**CIMRI**); Phase unwrapping; Magnetic susceptibility (χ) tomography

INTRODUCTION

The main underlying source of brain Magnetic Resonance Imaging (**MRI**) is the brain tissue magnetic susceptibility property (denoted by χ). Through the use of Gradient-Recalled Echo (**GRE**) sequence, we can image the intracranial inhomogeneous field distribution (primarily established via brain tissue magnetization in a main field B_0). This imaging technology is described by T2*-weighted MRI (**T2*MRI**) or T2* imaging [1-3]. A neuronal activity causes a Blood Oxygenation Level-Dependent (**BOLD**) neurovascularly-coupled hemodynamic process [4-6], offering a phenotypic expression in terms of intravascular blood magnetism perturbation (denoted by $\delta\chi$). The χ -expressed dynamic brain activity can be imaged through a GRE Echo Planar Imaging (**EPI**) sequence, producing a pair of 4D T2* magnitude and phase datasets. The contrast in a T2* image is attributed to the brain tissue χ in homogeneity (including heterogeneous parenchymal tissues and dynamic BOLD $\delta\chi$ responses). Conventionally, we extract a brain functional map (fmap) from the T2* magnitude dataset (one of the BOLD fMRI outputs) and discard the T2* phase dataset. In this chapter, we will show that we can make use of the T2* phase dataset to reconstruct brain χ and $\delta\chi$ source data spaces for more direct and truthful brain functional χ mapping. The spatiotemporal magnetic susceptibility source reconstruction for intrinsic brain function and structure depiction is achieved by inverse mapping of BOLD fMRI, hence being a 4D magnetic susceptibility tomography.

MODELS AND METHODS

The models of BOLD fMRI and its inverse mapping are diagrammed in Figure 1. Specifically, Figure 1a diagrams a BOLD fMRI model for data acquisition, and Figure 1b presents two inverse mapping models: the 4D χ reconstruction model for brain χ structure imaging and the 4D $\delta\chi$ reconstruction model for brain χ functional mapping. More details about the models and methods are addressed in this section.

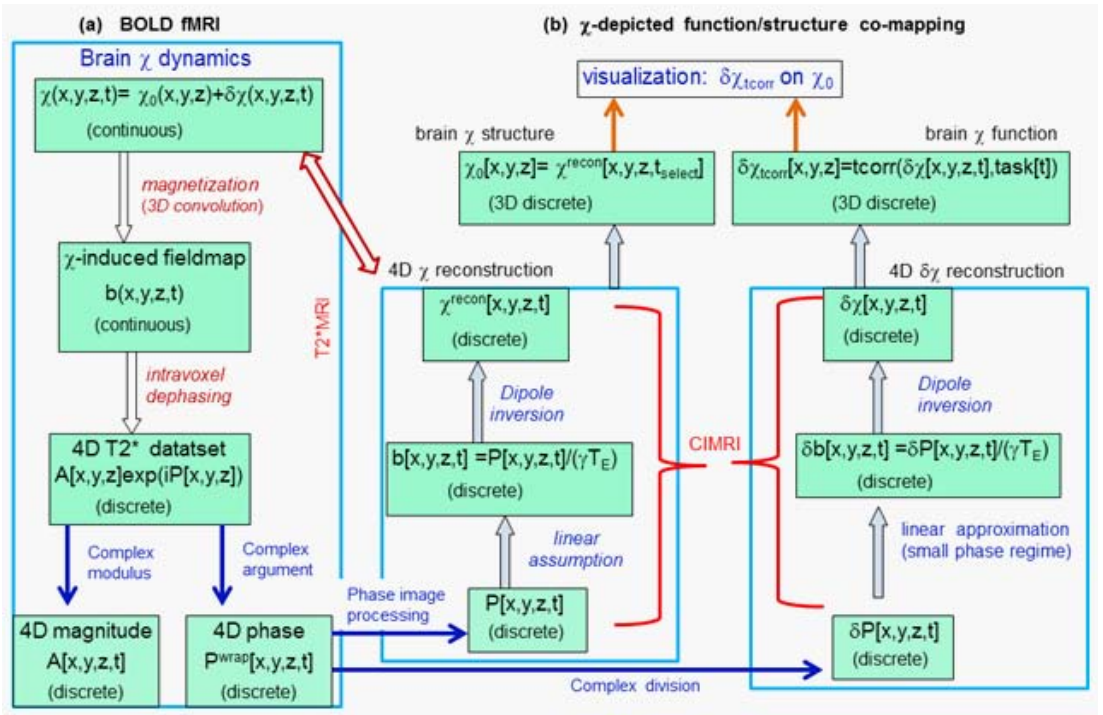


Figure 1: Diagrams of BOLD fMRI and its inverse mapping for χ -depicted functional mapping.

Source: Magnetic Susceptibility (χ) Expression of Brain Biophysiology

The underlying source of brain T2*MRI is the intracranial tissue magnetic susceptibility χ distribution, which is an intrinsic representation of a brain biophysiological state in terms of tissue magnetic property, assuming independence of MRI technology. Let $\chi_0(\mathbf{r})$ denote a static brain magnetic state, and $\delta\chi(\mathbf{r},t)$ a cerebral blood magnetism change associated with a neuroactivity (termed BOLD $\delta\chi$ response). Assuming an additive perturbation model for the brain hemodynamic process, we express a brain activity by an evolution of continuous spatiotemporal χ distributions (termed 4D χ source) [7-9] by

$$\begin{aligned}\chi(\mathbf{r},t) &= \chi_0(\mathbf{r}) + \delta\chi(\mathbf{r},t) + \text{noise} & (4D \chi \text{ source}) \\ \text{with} & \\ \delta\chi(\mathbf{r},t) &= Hct \cdot (\chi_{\text{deoxyHb}} - \chi_{\text{oxyHb}}) \cdot (1 - Y(t)) \cdot NAB(\mathbf{r}) \cdot V(\mathbf{r},t)\end{aligned}\tag{1}$$

where χ_{deoxyHb} and χ_{oxyHb} stand for the magnetic susceptibility values of deoxygenated blood (rich in paramagnetic deoxyhemoglobin) and oxygenated blood (rich in diamagnetic oxyhemoglobin), respectively, with $\chi_{\text{deoxyHb}} - \chi_{\text{oxyHb}} = 0.27 \times 4\pi \times 10^{-6}$ (dimensionless in SI metric) [10]; Hct for hemocrit (Hct=0.4 for normal blood); $Y(t)$ the blood oxygenation level ($Y \in [0,1]$); $V(\mathbf{r},t)$ the intravascular blood volume space; and $NAB(\mathbf{r})$ the local neuroactive blob distribution. The variable t indicates the time dimension of the brain activity.

Since T2*MRI is designed to sense a magnetic field map, its application to brain imaging only detects the phenotypic χ expression of a brain biophysiological state. The 4D χ expression of a brain activity in Eq. (1) serves as the underlying source of brain fMRI. In particular, the additive term $\delta\chi$ represents the χ -expressed BOLD response in a brain activity. Although the brain BOLD model [4-6] has been widely accepted from brain functional mapping and neuroimaging, a full understanding remains elusive. The simple spatial modulation model of BOLD $\delta\chi$ response in Equation (1) is useful for numerical BOLD fMRI simulations [7,9]. Notwithstanding, such a BOLD modeling is not a prerequisite for an experimental brain functional mapping study.

Imaging: Continuous $\chi(\mathbf{r},t)$ to Discrete $A^{\text{raw}}[\mathbf{r},t]$ and $P^{\text{raw}}[\mathbf{r},t]$

The imaging and inverse imaging aspects of BOLD fMRI are diagrammed in Figure 2, highlighted with data mappings with the notations: $R = (-\infty, \infty)$ (a set of all real numbers), $R^+ = [0, \infty)$ (a set of nonnegative real numbers), $R^{[-\pi, \pi]} = [-\pi, \pi]$ and $R^{[-\varepsilon, \varepsilon]} = [-\varepsilon, \varepsilon]$ (a set of real numbers in an interval).

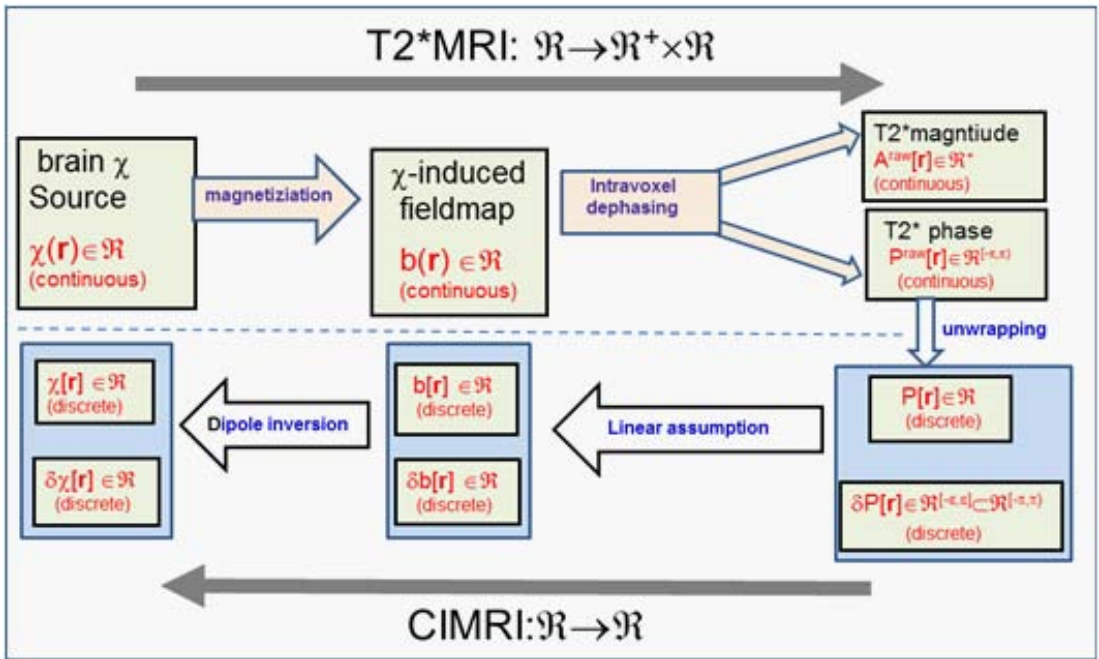


Figure 2: Data mappings of the forward T2*MRI and the inverse χ and $\delta\chi$ reconstructions.

The fact that a brain parenchyma may consist of both paramagnetic and diamagnetic constituents (e.g., $\chi_{\text{water}} < 0$, $\chi_{\text{ferritin}} > 0$, $\chi_{\text{myelin}} > 0$) gives rise to $\chi(\mathbf{r}) \in \mathcal{R}$, and that the bidirectional BOLD $\delta\chi$ response ($\chi_{\text{deoxyHb}} > 0$, $\chi_{\text{oxyHb}} < 0$) gives rise to $\delta\chi(\mathbf{r}) \in \mathcal{R}$. The dipole-convolved transformation introduces morphological change, but maintains the data range; hence, $b(\mathbf{r}) \in \mathcal{R}$.

A T2* MRI capture produces a T2* complex image in polar form (with magnitude $A^{\text{raw}}[\mathbf{r}] \in R^+$ and phase $P^{\text{raw}}[\mathbf{r}] \in R^{[-\pi, \pi]}$), implementing a multiple-valued data mapping: $R \rightarrow R^+ \times R^{[-\pi, \pi]}$. In particular, the T2* magnitude imaging implements a mapping $R \rightarrow R^+$, and the T2* phase imaging a

mapping $R \rightarrow R^{[-\pi,\pi]}$. Both are asymmetrical mappings (assuming different data ranges for source and image values), which are irreversible unless the data ranges are changed (constrained).

The T2* magnitude imaging is implemented by following data transformations:

$$\begin{aligned}
 b(\mathbf{r}, t) &= B_0 \chi(\mathbf{r}, t) * h_{\text{dipole}}(\mathbf{r}) && \text{(magnetization)} && \text{(i)} \\
 \text{with } h_{\text{dipole}}(\mathbf{r}) &= \frac{1}{4\pi} \frac{3z^2 - |\mathbf{r}|^2}{|\mathbf{r}|^5} \\
 C[\mathbf{r}, t] &= \frac{1}{|\Omega|} \sum_{\mathbf{r}' \in \Omega(\mathbf{r})} \exp(i\gamma b(\mathbf{r}', t) T_E) && \text{(intravoxel dephasing)} && \text{(ii)} \\
 A^{\text{raw}}[\mathbf{r}, t] &= |C[\mathbf{r}, t]| && \text{(complex modulus)} && \text{(iii)}
 \end{aligned} \tag{2}$$

where $*$ denotes a 3D spatial convolution, $\Omega(\mathbf{r})$ a voxel space at $\mathbf{r}$, and $|\Omega|$ the voxel size in terms of $|\Omega| = \Sigma 1$. The spatial convolution with a bipolar-valued dipole kernel imposes a dipole effect on the field map $b(\mathbf{r}, t)$ during the magnetization process, dictating a spatial morphological discrepancy between $b(\mathbf{r}, t)$ and $\chi(\mathbf{r}, t)$ [8, 11]. Technically, the dipole effect can be removed by solving an ill-posed 3D deconvolution problem [11, 12], called dipole inversion [13]. From the viewpoint of symmetrical data mapping from $\chi(\mathbf{r}, t) \in R$ to and $b(\mathbf{r}, t) \in R$, the dipole inversion is reversible. However, the complex modulus operation in Eq. (2,iii) for T2* magnitude calculation is an asymmetrical mapping, $R \rightarrow R^+$, which is irreversible (due to a nonnegative mapping like $|\pm 1| = 1$).

Simultaneously, a T2* phase is obtained from the complex T2* image by

$$P^{\text{raw}}[\mathbf{r}, t] = \text{Arg}(C[\mathbf{r}, t]) \equiv \arctan\left(\frac{\text{Im}(C[\mathbf{r}, t])}{\text{Re}(C[\mathbf{r}, t])}\right) \quad \text{(complex argument)} \tag{3}$$

where $\text{Arg}(c)$ denotes finding the principal phase angle (in a bounded range $[-\pi, \pi]$) of a complex number c . The fact that P^{raw} cannot represent the phase angle values beyond $[-\pi, \pi]$ due to $\exp(ip + in2\pi) = \exp(ip)$ (for an integer n) dooms a phase wrapping phenomenon in T2* phase imaging. Notwithstanding, a wrapped phase image can be unwrapped through the use of a phase unwrapping algorithm (see later).

It is noted that T2* phase imaging is in general a nonlinear transformation [2] due to the nonlinear complex argument operation in Eq. (3), which is originated from the trigonometric nonlinearity of spin signals irrespective of phase unwrapping [2]. In a small phase angle regime, T2* phase imaging behaves linearly [2,8,11,14] under an approximation condition: $\arctan(x) \approx x$ for $|x| < 1$.

Post Processing of T2* Magnitude and Phase Images

A T2* magnitude image is represented in a dimensionless arbitrary unit (a.u.). Usually, we scale the image values to a range in [0, 1] by

$$A[\mathbf{r}, t] = \frac{A^{raw}[\mathbf{r}, t]}{\max(A^{raw}[\mathbf{r}, t])} \quad (\text{normalization}) \quad (4).$$

In this convention, a uniform field map over a voxel space produces a lossless magnitude value (e.g., $A = 1$). Another convention is to define a T2* magnitude loss by $1-A$, which represents a uniform region with zero magnitude values.

A T2* phase image represents the voxel-averaged dephasing phase angle distribution, measured in units of radian (rad for short). Usually, a T2* phase image is severely wrapped, in an appearance of image contours. The phase unwrapping phenomenon in a 3D phase-wrapped T2* phase image may be removed by a 3D unwrapping algorithm. Perhaps the most efficient 3D unwrapping algorithm is a Laplacian algorithm [15-17], as analytically expressed by

$$P^{unwrap}[\mathbf{r}] = FT^{-1} \left\{ \frac{FT \left\{ \cos P^{raw} \cdot FT^{-1} \left(k^2 \cdot FT(\sin P^{raw}) \right) - \sin P^{raw} \cdot FT^{-1} \left(k^2 \cdot FT(\cos P^{raw}) \right) \right\}}{k^2} \right\}, \quad (5)$$

where P^{raw} denotes the raw T2* phase image, FT the Fourier transform, and FT^{-1} the inverse Fourier transform, while $k = |\mathbf{k}|$ represents the 3D discrete coordinates in the 3D Fourier domain. As a result of phase unwrapping, we can obtain an unwrapped phase image that takes on values in an unbounded range, as denoted by $P^{raw} \in [-\pi, \pi) \subset R$ and $P^{unwrap} \in (-\infty, \infty) = R$.

Meanwhile, we can calculate the temporal phase changes for a time series of T2* phase images by

$$\delta P[\mathbf{r}, t_n] = Arg \left(\frac{\exp(i P^{raw}[\mathbf{r}, t_n])}{\exp(i P^{raw}[\mathbf{r}, t_1])} \right), \quad n = [1, 2, \dots, T] \quad (6)$$

where $Arg(\cdot)$ is a complex argument as defined in Eq. (3); $P^{raw}[\mathbf{r}, t_1]$ is a selected T2* phase image (at a time point, but not necessarily the 1st time point). The selected phase image is considered as the baseline (or the reference). The complex division is essentially a phase subtraction, which extracts the phase change at a snapshot capture in reference to the baseline. More importantly, the complex division can find the relative phase change between two wrapped phases as long as the phase difference remains in a proper subset of $[-\pi, \pi)$.

The 4D $\delta P[\mathbf{r},t]$ dataset represents the pure BOLD phase changes (extracted from T2* phase images), which are always small ($|\delta P| < \pi$), assuming values in a small data range $[-\varepsilon, \varepsilon]$ with $\varepsilon < \pi$, denoted by $\delta P \in R^{[-\varepsilon, \varepsilon]} \subset R^{[-\pi, \pi]}$. Therefore, the complex division can extract the relative phase change (δP) between two wrapped phase images (P^{raw}), thus implementing phase unwrapping in time domain [3, 18].

Inverse Imaging: χ Tomography

Under linear approximations on T2* phase imaging, we can reconstruct the χ source from (unwrapped) T2* phase image by a Computed Inverse MRI (**CIMRI**) model [8,11,14], as represented by

$$\begin{aligned} b[\mathbf{r}, t] &\approx \frac{P[\mathbf{r}, t]}{\gamma T_E} \quad (\text{linear phase approximation}) \quad (i) \\ \chi^{\text{recon}}[\mathbf{r}, t] &= \frac{1}{B_0} b[\mathbf{r}, t] *^{-1} h_{\text{dipole}}[\mathbf{r}] \quad (\text{dipole inversion}) \quad (ii) \end{aligned} \quad (7)$$

where $*^{-1}$ denotes a 3D deconvolution. The CIMRI method reconstructs a discrete χ map from a discrete T2* phase image at each time point by two inverse transformations in Eq. (7). Specifically, a field map is calculated from a (unwrapped) phase image by a linear scaling transformation under a linear phase approximation in (i), and the phase-derived field map is in turn used for χ reconstruction by solving the dipole inversion problem in (ii). It is noted that the MRI parameters (e.g., B_0 and T_E) are removed (cancelled) during the inverse transformations, and that the spatial distortion (dipole effect) is corrected by solving a 3D deconvolution in (ii). In light of undoing MRI transformations and removing MRI parameter dependences, the reconstructed χ distribution provides a digital representation of the original continuous χ source and hence the χ tomography [3,11,19]. The 3D χ tomography reconstructs a 3D χ map based on the linear CIMRI model. The 4D tomography reconstructs a time series of 3D χ maps by applying 3D χ tomography to each snapshot volume.

In a similar way, we can reconstruct a 4D $\delta\chi[\mathbf{r},t]$ dataset from $\delta P[\mathbf{r},t]$ by

$$\begin{aligned} \delta b[\mathbf{r}, t] &\approx \frac{\delta P[\mathbf{r}, t]}{\gamma T_E} \quad (\text{linear phase approximation}) \quad (i) \\ \delta\chi^{\text{recon}}[\mathbf{r}, t] &= \frac{1}{B_0} \delta b[\mathbf{r}, t] *^{-1} h_{\text{dipole}}[\mathbf{r}] \quad (\text{dipole inversion}) \quad (ii) \end{aligned} \quad (8)$$

Again, the MRI parameters (B_0 and T_E) and dipole effect are removed from $\delta\chi[\mathbf{r},t]$.

The two-step inverse mappings for 3D $\chi[\mathbf{r}]$ and $\delta\chi[\mathbf{r}]$ reconstructions (from the corresponding $P[\mathbf{r}]$ and $\delta P[\mathbf{r}]$ images) are diagrammed in Figure 1b and Figure 2, which are implemented by the same procedure of CIMRI. It is diagrammed in Figure 2 that the data mapping from the spatial phase unwrapping extends the data range of wrapped phase images such that $P[\mathbf{r}] \in R$, thereby allowing

a reversible mapping onto $\mathbf{b}[\mathbf{r}] \in R$ and $\chi[\mathbf{r}] \in R$. In parallel, the temporal phase unwrapping (by complex division) shrinks the data range of phase images, thereby facilitating an inverse mapping (originated with a small data range $\delta P[\mathbf{r}] \in R^{[-\varepsilon, \varepsilon]} \subset R^{[-\pi, \pi]} \subset R$). In the result, the inverse mapping of BOLD fMRI produces two datasets, $\chi[\mathbf{r}, t]$ and $\delta\chi[\mathbf{r}, t]$, representing brain tissue χ states and pure BOLD $\delta\chi$ responses. By undoing MRI transformations and removing MRI parameter dependences, we achieve intrinsic brain functional χ mapping in the reconstructed χ source dataspace [20].

Extracting Functional Maps in 4D Dataspace

For a task-evoked brain functional mapping study, we conventionally extract an *fmap* from a 4D magnitude dataset $A[\mathbf{r}, t]$ by a task-correlation algorithm as expressed by

$$A_{\text{tcorr}}[\mathbf{r}] = \text{tcorr}(A[\mathbf{r}, t], \text{task}^*[t]) \quad (\text{magnitude fmap}) \quad (9)$$

with $\text{task}^*[t] = \text{conv}(\text{task}[t], \text{hrf}[t])$

where $\text{task}[t]$ denotes a designed task paradigm; $\text{conv}(\cdot)$ indicates a convolution operation, and $\text{hrf}[t]$ denotes a canonical hemodynamic response function. The time course $\text{task}^*[t]$ accounts for the latent and up/down shooting of hemodynamic response during an fMRI signal formation. A local brain activity appears as a blob in the 3D *fmap*, $A_{\text{tcorr}}[\mathbf{r}]$.

In a similar way, upon generating the reconstructed $\delta\chi[\mathbf{r}, t]$ dataset, we can extract the χ -depicted *fmap* by

$$\delta\chi_{\text{tcorr}}[\mathbf{r}] = \text{tcorr}(\delta\chi^{\text{recon}}[\mathbf{r}, t], \text{task}^*[t]) \quad (\chi \text{ fmap}) \quad (10)$$

with $\text{task}^*[t] = \text{conv}(\text{task}[t], \text{hrf}[t])$

In the result, we can depict a brain activity in different 3D *fmaps*: the magnitude-depicted *fmap* A_{tcorr} in the image dataspace and the χ -depicted *fmap* $\delta\chi_{\text{tcorr}}$ in the source dataspace. The *tcorr* values in a 3D *fmap* (A_{tcorr} or $\delta\chi_{\text{tcorr}}$) assume a data range of $[-1, 1]$ (dimensionless). A large positive *tcorr* value indicates a strong para-correlation response and a negative *tcorr* value for an anti-correlation response. For an easy comparison of *tcorr* maps generated from different approaches (e.g., via a transformation), we convert *tcorr* values into z-scores [21].

Considering that $\delta\chi[\mathbf{r}, t]$ is free from distortions associated with MRI transformations, we have found that $\delta\chi_{\text{tcorr}}[\mathbf{r}]$ is a more truthful depiction than the magnitude-depicted *fmap* $A_{\text{tcorr}}[\mathbf{r}]$ [20,22]. It is noted that we may extract a χ -depicted *fmap* from the reconstructed 4D $\chi[\mathbf{r}, t]$ dataspace as well. Concerning the fact the linear approximation for $\delta\chi[\mathbf{r}, t]$ reconstruction is better than for $\chi[\mathbf{r}, t]$ reconstruction, we propose to represent the χ -depicted *fmap* by $\delta\chi_{\text{tcorr}}[\mathbf{r}]$ rather than by $\chi_{\text{tcorr}}[\mathbf{r}]$. It is noted that $\delta\chi_{\text{tcorr}}[\mathbf{r}]$ corresponds to NAB($\mathbf{r}$) in the BOLD model in Eq (1).

Self-Aligned Function/Structure Association

Conventionally, we visualize the function/structure association by displaying a 3D brain *fmap* on a brain structure image (acquired by T1 imaging under a different scan or on a brain anatomical template), which requires a time-consuming and error-prone image alignment. By making use of the reconstructed $\chi[\mathbf{r},t]$ dataset for brain χ structure depiction, we can achieve self-aligned function/structure display.

We may obtain a brain χ structure image from the reconstructed $\chi[\mathbf{r},t]$ dataset by a time average. In practice, $\delta\chi$ only assumes a very small fractional portion ($< 5\%$) in a χ map; any volume in $\chi[\mathbf{r},t]$ can be selected to represent the brain structure, as denoted by $\chi_0[\mathbf{r}]$ (corresponding to $\chi_0(\mathbf{r})$ in Eq. (1)). Therefore, we obtain a discrete brain χ structure image by

$$\chi_0[\mathbf{r}] \approx \begin{cases} \chi^{recon}[\mathbf{r}, t_1] & \text{(snapshot)} \\ \frac{1}{N_t} \sum_{t=1}^{N_t} \chi^{recon}[\mathbf{r}, t] & \text{(time average)} \end{cases} \quad (11)$$

where t_1 denotes any one time point (not necessarily the 1st one) in the time series and N_t is number of snapshot volumes. In practice, $\chi_0[\mathbf{r}]$ is subject to image processing for enhancing the cortical structural details (gyri and sulci patterns). Note that a T2* magnitude image may be used to depict brain tissue structure as well. Since the brain structure image and *fmaps* are derived from the same dataset and the same source, the function/structure association is automatically self-aligned. It is mentioned that the χ -depicted brain structure assumes both positive and negative values for paramagnetic tissue ($\chi_0 > 0$) and diamagnetic tissue ($\chi_0 < 0$).

RESULTS

We have demonstrated the 4D χ tomography for reconstructing dynamic brain χ source and extracting χ -depicted brain *fmap* by a finger tapping BOLD fMRI experiment on a 7T Siemens MAGNETOM system. We used a GRE-EPI sequence to scan a healthy volunteer performing a finger tapping action with the cue of a designed task paradigm: a time course of 5 cycles of alternating ON (15s duration) and OFF (15s duration) states [3]. The other parameter settings were $T_R = 3s$, $T_E = 29ms$, $Tacq = 150s$ ($=50T_R$), voxel size = $0.45 \times 0.45 \times 1.2 \text{ mm}^3$, flip angle = 70° , matrix of $234 \times 234 \times 28$ (covering the superior brain), and 50 volumes (snapshots). The output of the finger tapping experiment was a pair of 4D T2* magnitude and phase datasets (in matrix form of $234 \times 234 \times 28 \times 50$). Figure 3a and 3b show four contiguous axial slices at $z = \{13.2, 12, 10.8, 9.6\} \text{ mm}$ (distance from brain top) in a T2* image volume. Raw T2* phase images were severely wrapped as seen in an appearance of image contours presented in Figure 3b.

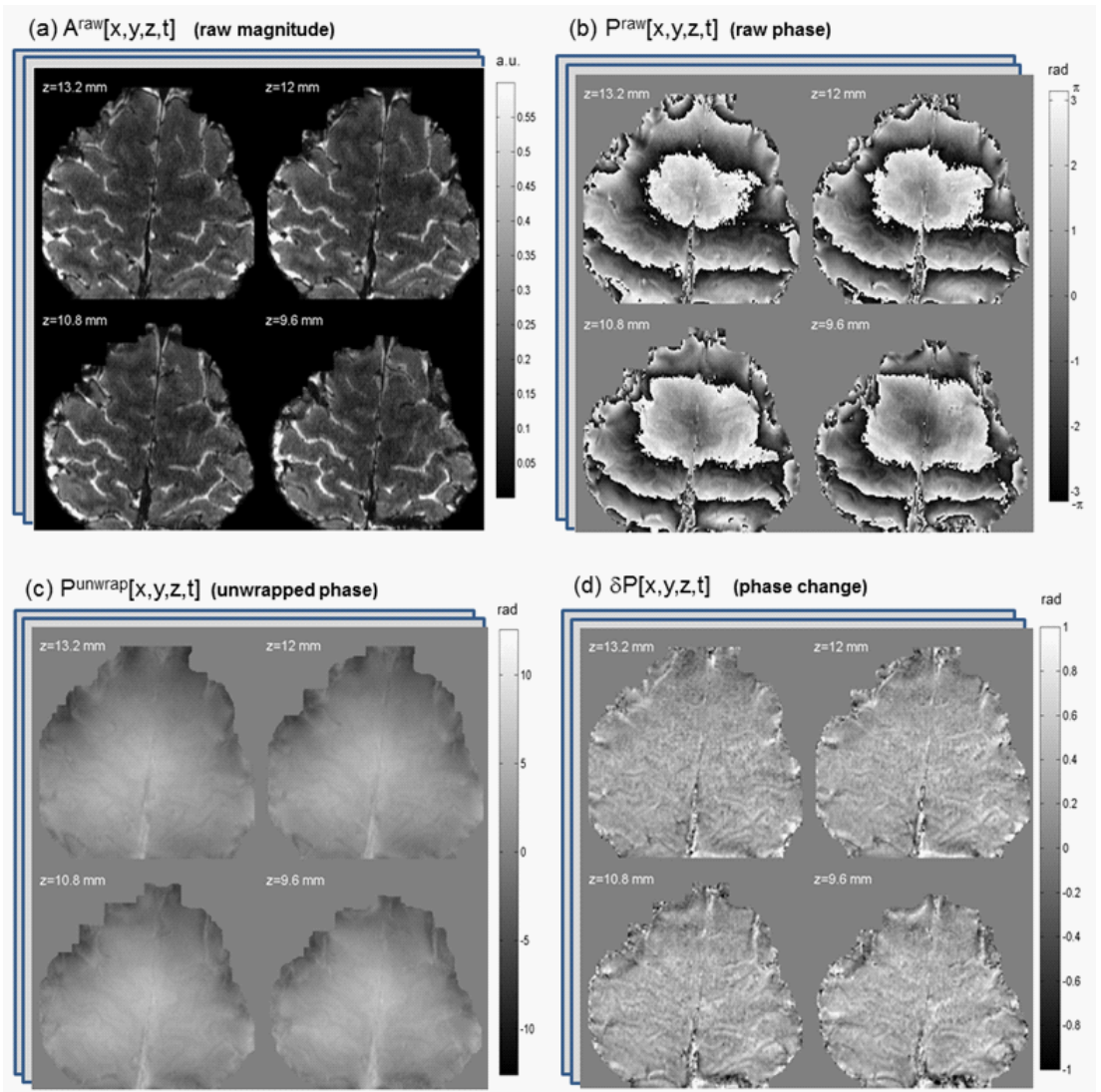


Figure 3: (a,b): Raw T2* magnitude and images acquired from a finger tapping experiment on a 7T system with a GRE-EPI sequence; (c,d) The spatially and temporally unwrapped phase images. Note the display grayscale bars for the data ranges of phase images. Units: a.u. denotes for arbitrary unit (dimensionless), and rad for radian (dimensionless).

Upon acquiring the raw 4D T2* phase dataset, we performed spatial phase unwrapping by Eq. (4) and obtained the unwrapped phase images $P[x,y,z,t]$ (Figure 3c). Meanwhile, we extracted the relative phase changes (in reference to the 1st phase volume) by Eq. (6) and obtained the pure BOLD phase change dataset $\delta P[x,y,z,t]$ (Figure 3d). Note the difference scales for the phase image displays.

After generating the unwrapped phase dataset $P[x,y,z,t]$, we performed 4D χ tomography to reconstruct a 4D $\chi[x,y,z,t]$ dataset (Figure 4a). With the same procedure, we reconstructed a 4D $\delta\chi[x,y,z,t]$ dataset (Figure 4b) from $\delta P[x,y,z,t]$. From the reconstructed $\chi[x,y,z,t]$ dataset, we selected one volume (at a timepoint) and performing high-pass filtering [3] and image enhancement to produce a 3D brain χ structure image $\chi_0[x,y,z]$ (Figure 4c). Based on the task correlation algorithm in Eq. (10), we extracted a χ -depicted 3D *fmap* $\delta\chi_{\text{tcorr}}[x,y,z]$ from the 4D $\delta\chi[x,y,z,t]$ dataspace (Figure 4d displayed with z-scores). It is seen that the brain χ image (in Figure 4c) offers more gyri and sulci details than does the brain magnitude image (in Figure 3a). Also that the χ -depicted *fmap* (in Figure 4d) reveals bidirectional task correlations at the finger motor cortex regions.

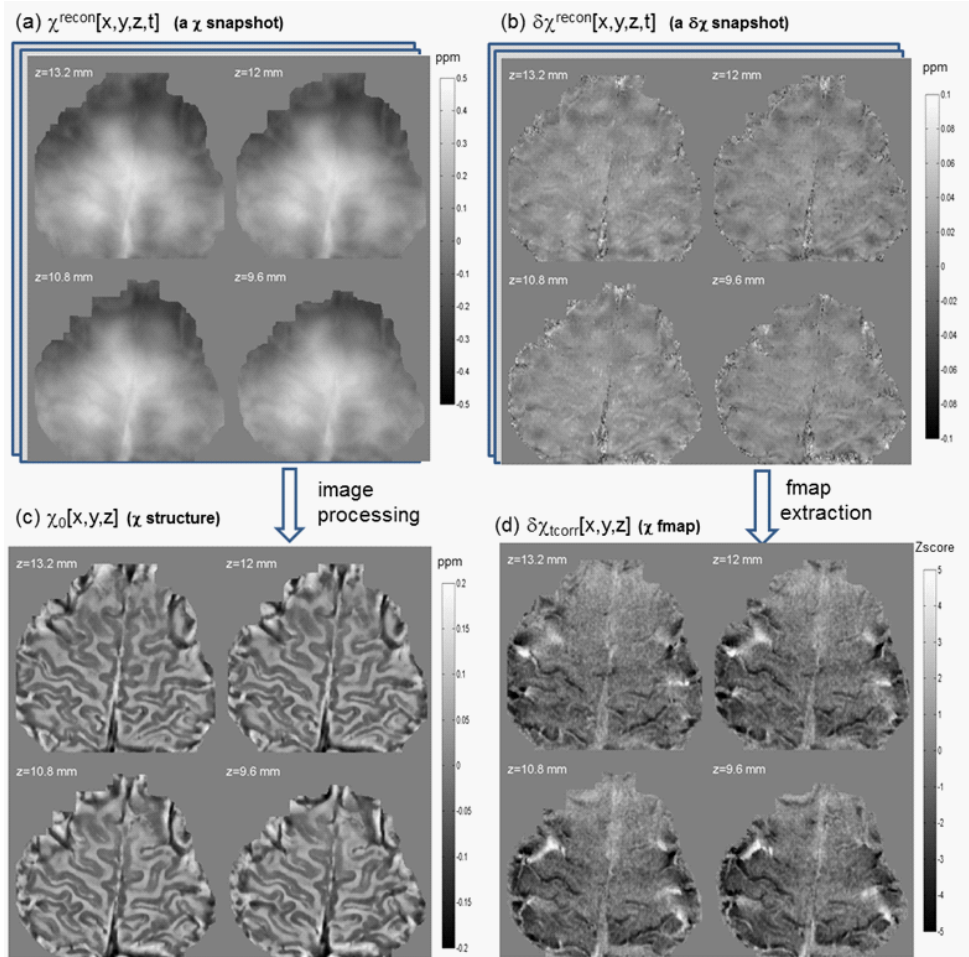


Figure 4: (a,b): The reconstructed $\delta\chi$ and χ images. (c) The brain χ structure image (a 3D χ volume in the 4D $\chi^{\text{recon}}[x,y,z,t]$ dataset); (d) The 3D χ -depicted brain *fmap* (extracted from $\delta\chi^{\text{recon}}[x,y,z,t]$ dataset). Note that the positive and negative brain chi structure depiction is reflected in the grayscale bar Units: ppm= 10^{-6} denotes part per million (dimensionless), and Zscore for z score (dimensionless).

We also extracted a magnitude-depicted map, $A_{\text{tcorr}}[\mathbf{r}]$ from $A[\mathbf{r},t]$, by the task correlation algorithm (in Eq. (9)), and displayed it in Figure 5a for visual comparison with the χ -depicted *fmap* in Figure 5b (converted into z scores). On the brain χ structure image, the 3D *fmaps* $A_{\text{tcorr}}[\mathbf{r}]$ and $\delta\chi_{\text{tcorr}}[\mathbf{r}]$ were displayed (thresholded) in Figure 5c and 5d for function/structure association visualization. High-field high-resolution BOLD fMRI offers cortical details for understanding the neurovascular coupling in a brain activity.

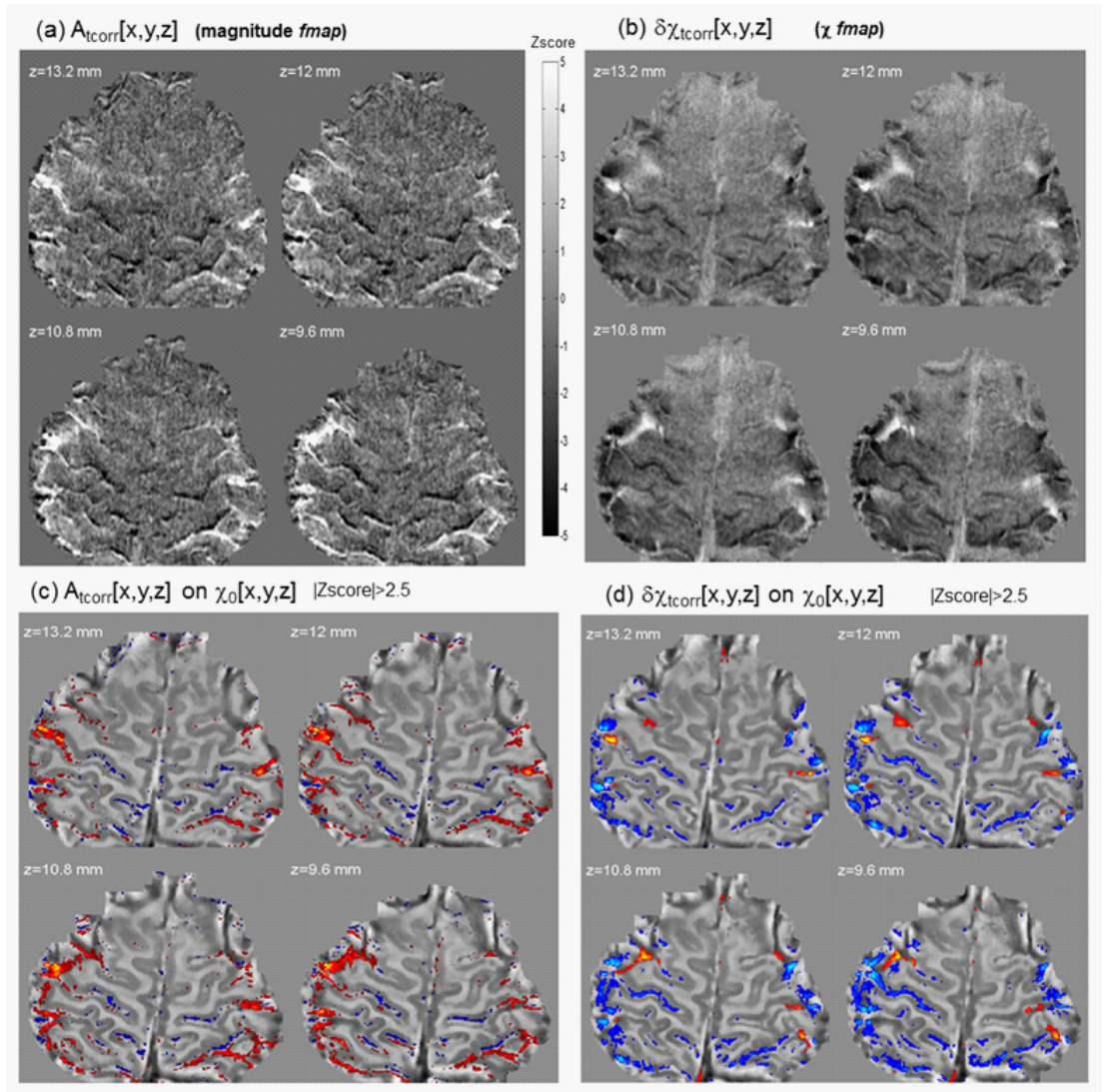


Figure 5: (a,b): The magnitude-depicted and χ -depicted *fmaps*; (c,d): self-aligned function/structure associations (thresholded *fmaps* on a brain χ structure image).

DISCUSSION AND CONCLUSION

The term “imaging” was originally used in optical imaging, referring to a spatial continuous mapping and a non-negative data mapping, from a source $\in R^+$ to an image $\in R^+$. The spatial continuous imaging has been developed into spatially discrete digital imaging by electronics and computers. Further, the computer applications in X-ray imaging brought about Computerized Tomographic Imaging (**CT**), non-invasively depicting an object interior. The data acquisition of CT implements a data mapping: $R^+ \rightarrow R^+$ (from the source of nonnegative X-ray attenuation coefficient property to the nonnegative X-ray image), which is reversible. Most excitingly, the computer applications in nuclear magnetic resonance imaging brought about MRI, which is particularly suitable for soft tissue imaging such as brain imaging. Strictly speaking, MRI is not a tomographic imaging in the sense of the morphological mismatch between image source representations [8,19]. Even for tomographic brain source reconstruction by CIMRI, the brain χ tomography reproduces negatives for diamagnetic tissue depiction (see Fig. 4c), which is a peculiar imaging modality. As diagrammed in Figure 2, the data acquisition of T2*MRI implements an asymmetric data mapping, $R \rightarrow R^+ \times R^{[-\pi, \pi]}$, which will deny an inverse mapping unless their data ranges are changed.

In the context of mathematical mapping, T2* magnitude imaging implements a mapping: $R \rightarrow R^+$, which is irreversible. Even for a nonnegative χ source ($\chi \in R^+$), T2* magnitude imaging is still confronted with another irreversibility of the nonlinear complex modulo operation [2,8,11]. Consequently, T2* magnitude imaging is irreversible for χ source reconstruction.

Meanwhile, T2* phase imaging implements a mapping $R \rightarrow R^{[-\pi, \pi]}$ that is conditionally reversible under specific conditions: 1) if the wrapped phase image is unwrapped (removing phase wrapping effect), and 2) if the phase values remain unwrapped (avoiding phase wrapping effect). The former extends the phase data range from $R^{[-\pi, \pi]}$ to R , enabling the χ reconstruction in terms of reversible mapping $R \rightarrow R$. The later confines the phase data range in a subset $R^{[-\epsilon, \epsilon]} \subset R^{[-\pi, \pi]}$ such that the T2* phase imaging in phase unwrapping condition is reversible (such as the small phase angle regime [11,14], $|P| \ll 1\text{rad}$, and small phase perturbation [3], $|\delta P| \ll 1\text{rad}$). Therefore, an irreversible mapping like $R \rightarrow R^{[-\pi, \pi]}$ may become reversible through an alteration on the data range.

T2*MRI involves two kinds of mapping: one is a spatial mapping between two spatial distributions (e.g., $\chi(\mathbf{r}, t)$ and $b(\mathbf{r}, t)$ are related by a spatial convolution), which changes the spatial morphology by a point spread function (e.g., the dipole kernel); the other is an entry-wise data mapping between two spatially-conformed distributions (e.g., $C[\mathbf{r}, t]$ and $A[\mathbf{r}, t]$ are related by a complex modulo operation), which changes the data entry values and data ranges (e.g., $|\pm 1| = 1$). In this chapter, we only addressed the data mapping aspect pertaining to the inverse mapping of T2* imaging. The inverse of the spatial mapping aspect consists in the dipole inversion in Eq (7), which is an ill-posed 3D deconvolution problem. We refer readers to different dipole inversion

solutions by truncated inverse filtering (filter truncation regularization) [23,24], iterative L1-norm or L2-norm regularizations [13, 25-28], and TV-regularized split Bregman iteration (**TVB**) [11,12,29].

In general, T2* phase imaging implements a nonlinear transformation of the χ source, reflected in the nonlinear arctan function. In small phase angle regime, $\arctan(x) \approx x$ for $|x| \ll 1$, T2* imaging exhibits a linear mapping. The complex-division-extracted phase perturbations (δP) is very small such that we can reconstruct its corresponding χ perturbation ($\delta\chi$) under the linear T2* imaging condition. In comparison, the $\chi[\mathbf{r}, t]$ reconstruction from $P[\mathbf{r}, t]$ suffers from more errors (inherent with phase nonlinearity) than the $\delta\chi[\mathbf{r}, t]$ reconstruction from $\delta P[\mathbf{r}, t]$ due to $|P| > |\delta P|$. Therefore, we propose to extract the χ -depicted *fmap* from $\delta\chi[\mathbf{r}, t]$ dataspace rather than $\chi[\mathbf{r}, t]$ dataspace.

In conclusion, the data acquisition of BOLD fMRI through the use of GRE-EPI sequence produces a 4D complex-valued T2* dataset, of which neither the T2* magnitude nor the phase is a tomographic image of a brain χ state due to the distortions introduced by MRI transformations (e.g., magnetization). This means that BOLD fMRI produces a morphed movie for a brain activity. By rendering inverse mapping, we can undo the morphing (distortion) and reproduce the original intrinsic brain states in terms of tissue χ distributions. In light of the removal of MRI transformations, the reconstructed χ source dataspace provide more truthful brain imaging and functional mapping. High-field high-resolution offers more cortical details for the self-aligned function/structure associations.

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APPENDIX: NOTATIONS AND ABBREVIATIONS

R : a set of all real numbers in a full range of $(-\infty, \infty)$; R^+ : a set of nonnegative real numbers in a range of $[0, \infty)$; $R^{[-\pi, \pi)}$: a set of real numbers in an interval of $[-\pi, \pi)$; $R^{[-\epsilon, \epsilon]}$: a set of real numbers in an interval of $[-\epsilon, \epsilon]$; $\rightarrow$: a mathematical mapping between two number sets; $(\mathbf{r}) = (x, y, z)$: continuous 3D spatial coordinate variable; $[\mathbf{r}] = [x, y, z]$: discrete 3D spatial coordinate variable; $(\mathbf{r}, t)$: continuous 4D spatiotemporal variable; $[\mathbf{r}, t] = [x, y, z, t]$: discrete 4D spatiotemporal variable.

A: magnitude (or amplitude) data (normalized in $[0, 1]$); A^{raw} : raw magnitude data; Arg: complex argument operation; C: complex-valued data; P: phase (unwrapped); P^{raw} : raw phase data (usually wrapped); $P^{\text{unwrapped}}$: unwrapped phase; δP : phase perturbation in relative to a baseline; χ : magnetic susceptibility; $\delta\chi$: temporal χ change in relative to a baseline.

BOLD- Blood Oxygenation Level Dependent; *fmap*- functional map; fMRI- functional Magnetic Resonance Imaging; T2*-MRI- T2-weighted MRI; CIMRI- Computed Inverse MRI; *tcorr*- task correlation (or temporal correlation).

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