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Transients may occur in functional magnetic resonance imaging without physiological basis

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Functional magnetic resonance imaging (fMRI) has revolutionized the study of human brain activity, in both basic and clinical research. The commonly used blood oxygen level dependent (BOLD) signal in fMRI derives from changes in oxygen saturation of cerebral blood flow as a result of brain activity. Beyond the traditional spatial mapping of stimulus–activation correspondences, the detailed waveforms of BOLD responses are of high interest. Especially intriguing are the transient overshoots and undershoots, often, although inconclusively, attributed to the interplay between changes in cerebral blood flow and volume after neuronal activation. While physically simulating the BOLD response in fMRI phantoms, we encountered prominent transient deflections, although the magnetic field inside the phantom varied in a square-wave manner. Detailed analysis and modeling indicated that the transients arise from activation-related partial misalignment of the imaging slices and depend heavily on measurement parameters, such as the time between successive excitations. The results suggest that some transients encountered in normal fMRI recordings may be spurious, potentially compromising the physiological interpretation of BOLD signal overshoots and undershoots.

fMRI phantom | overshoot | undershoot | BOLD | fMRI

Since the advent of the blood oxygen level dependent (BOLD) imaging method (1–4), functional magnetic resonance imaging (fMRI) of human brain function has spread so rapidly that currently as many as eight new fMRI papers appear each day. The proper analysis of fMRI data (5) and the relationship between the fMRI signal and the underlying brain activity (6) continues to receive much attention, whereas the basic physics of the signal acquisition is considered to be sufficiently understood. Accordingly, computer simulations are used to successfully model the effects of different imaging parameters on the measured signals (7–9).

Such computational methods can, however, oversimplify factors affecting the signal acquisition and the MR signal. To scrutinize the behavior of the BOLD response in more detail, we recently introduced physical “fMRI phantoms” (10, 11) in which the BOLD signals can be physically simulated by accurately controlling current flow within a conducting medium.

The MRI signals of the brain arise from protons that are excited with radio frequency pulses applied at the protons’ Larmor frequency in a static magnetic field (B_0). With brief gradient fields, a slice of protons (e.g., perpendicular to the magnet’s main axis z) can be selected. In a typical fMRI experiment, several (up to 50) slices are repeatedly excited while a subject performs a task or perceives stimuli. Soon after an excitation, the protons start to precess at slightly different frequencies because of local magnetic field inhomogeneities that arise from tissue properties, especially from a blood oxygenation level that varies according to neuronal activity. The field inhomogeneities result in dephasing, or transverse relaxation, of the originally synchronously precessing protons and thereby in a decay of the magnetic resonance signal (T_2^* effect); this effect eventually gives rise to the BOLD contrast. Another simulta-

neous phenomenon is the longitudinal relaxation. After each excitation, the protons start to return toward thermal equilibrium through energy exchange with the surroundings, and the characteristic time of return (T_1) depends on the sample (for a review of fMRI methods, see e.g., ref. 12). During an fMRI experiment, the excitations are repeated so fast (e.g., once every 0.5–5 s) that the spin population reaches a pseudo steady state (different from the thermal equilibrium), such that the remaining nuclear magnetization is the same before each excitation. It is assumed that this pseudo steady state is not disrupted by small changes in the magnetic field caused by neuronal activity. Models connecting the fMRI signal, hemodynamics, and neural signaling have been developed to better understand the underlying brain function (13). However, a universally applicable model for short-lived transient deflections, most prominently the overshoot after stimulus onset and the poststimulus undershoot, remains to be found (14). Here, we demonstrate that some BOLD signal transients can be spurious, emerging by a non-physiological mechanism that has not been previously proposed to our knowledge.

Results

We studied fMRI signals in a well-controlled setting, devoid of confounding factors such as movement, using two fMRI phantoms modified from our previous design (10). The experimental setup is explained in *Methods* and illustrated in Fig. 1A.

Fig. 1B shows the mean signal intensity from a 12-voxel region of interest (ROI) in the middle of the gradient phantom. The plot shows clearly that changing ΔB_z between the “activation” and “rest” levels introduced, in addition to the sustained responses, overshoots and undershoots closely resembling similar phenomena in real fMRI recordings, although the current driving the phantom and thereby producing the ΔB_z was devoid of any transient overshoots or undershoots (settling time 0.1 ms; see *SI Text*). The plots in Fig. 1C show that the shape of the response depended on the echo time (TE), so that increasing TE from 25 to 70 ms increased the sustained contrast and decreased the relative contributions of the onset transients.

To scrutinize the possibility that prominent fMRI transients could arise from the field changes *per se*, we imaged the uniform phantom that generated a locally constant field change. Fig. 2 illustrates that biphasic transient signals occurred both after ΔB_z changed from the rest period to active, and vice versa. The initial positive transients were stronger and shorter than the following undershoot deflections of opposite polarity. The sustained signal component was slightly higher at activation than in rest, which can be attributed to a minor field inhomogeneity produced even in this Maxwell coil configuration. The amplitudes of the tran-

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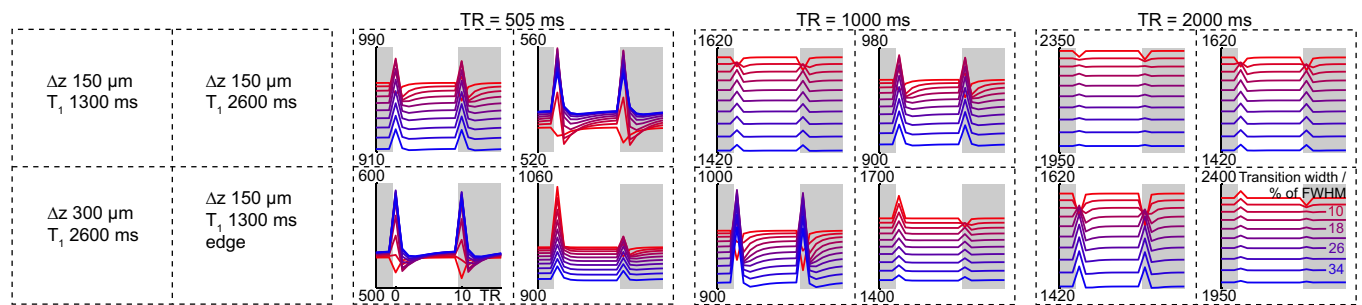


Fig. 3. Simulations. The fMRI signal was simulated for the TRs applied in Fig. 2C. The subplots demonstrate the simulation results for parameters indicated in the leftmost box. The apparent displacement of the whole volume was Δz , except for the subplots marked edge, where B_z remained constant at slices below the one observed. T_1 values of the simulations are shown. Transition width as a percentage of full-width at half-maximum (key: bottom right) indicates the steepness of the slice profile. Both measurements and simulations show that the signal, after step changes of B_z , is modulated to a new level through periods of similar transient deflections.

excitation pulse. If any additional field with a z -component is superimposed on the gradient, the site of the excited protons is determined by the resultant field, instead of just the gradient.

In vivo, the difference in magnetic susceptibility between oxygenated and completely oxygen-depleted red blood cells is $4\pi \times 0.264 \times 10^{-6}$ (15), which modulates B_z by $10\text{-}\mu\text{T}$ in a 3-T external field. Because the slice selection gradient applied during the excitation of our 3-mm thick slice was $5\text{ mT}\cdot\text{m}^{-1}$ ($15\text{ }\mu\text{T}$ across the slice), the field related to the susceptibility change would represent, at the exact location of the red cell, a $\approx 70\%$ shift in the position of the slice, whereas for whole blood, with activation-induced oxygenation change, the shift would be 5% (see *SI Text*). As a result, without actual movement, protons in a given slice could be excited along with those of a spatially neighboring slice, a different slice than before the BOLD response; or they could receive excitations belonging to both slices, if they reside near the slice border. As is schematically illustrated in Fig. 4 (for phantom), essentially, the temporal consistency of the excitations would break down, hence transient overshoots or undershoots could occur before a new pseudo steady state, even after completely flat on-off-type changes in the underlying physiology. As shown in Fig. 4, the transients can be quite different for different slices and slice acquisition orders. Although the signal in Fig. 4 stabilizes immediately after an excitation, in reality, because of finitely steep and overlapping excitation profiles, the undershoots last longer, as can be seen in Figs. 1–3.

The shapes of the transients depend on several imaging parameters, dynamics of the field change, and physical factors, all of which will be briefly discussed next. Additional discussion on the bipolar nature of the transient is provided in *SI Text*.

The clear effects of the imaging parameters on the size of the transients are informative in designing methodologically clean measurements. For example, one can radically decrease the transients by increasing the strength of the slice selection gradient and adjusting the excitation pulse so that the slice thickness remains stable; this suppression of transients occurs because the susceptibility-related field change decreases in relation to the thickness of the slice. Technically, the scanner software in use modulated slice thickness by scaling the slice select gradient while keeping the bandwidth of the excitation pulse unchanged. Therefore, a thicker slice was selected just by using lower gradient amplitude, whereby the ΔB_z caused by the phantom misplaced the slices further than with stronger gradient. In control experiments an approximately linear relationship between transient amplitude and slice thickness was observed.

In principle, more pronounced transients will occur at higher fields because susceptibility-related field augmentation increases linearly with the main field, and T_1 is longer in higher magnetic

fields. In practice, high-field scanners usually have stronger gradients, and thus the effect on transients depends on the details of how slice selection is implemented.

Further, reducing the flip angle decreased the transient amplitude (see Fig. S3).

The transients are also sensitive to the details of the excitation profile: abrupt slice profiles maximize independence of signals from the neighboring slices, but, as shown by the simulations, they amplify the transient amplitudes in case of step responses. However, the optimal slice profile depended on the transition time between rest and active conditions, which might be unknown beforehand in human BOLD signal recordings.

Long TE reduced the proportional amplitude of the transients with respect to the sustained amplitudes.

Increasing TR reduced transients unequivocally in the phantoms. However, in vivo this effect depends on the slew rate of the BOLD response and the rate of longitudinal relaxation. For example, if the BOLD signal changes slowly, the apparent slice position would not be too different at a short TR (e.g., 500 ms). At a longer TR, however, the difference would increase, but the longitudinal magnetization would have more time to relax and thereby reduce the transients. If, however, the BOLD signal change would mostly occur within one TR, the discrepancy between the apparent and actual slice positions would produce distinct transients, even though longitudinal relaxation would damp the amplitudes of the transients especially at long TRs. Further, in the brain, BOLD transients last longer than in our measurements (where the B_z changes were instantaneous). Because the hemodynamic response, during which magnetic susceptibility changes, builds up gradually, changes of B_z are similar during several successive TRs. Thus, individual transients line up and produce the long-lasting resultant transient. These observations were supported by simulation. Additionally, because with short TR the amplitude and width of the overshoot transient correlate with the abruptness of the hemodynamic change, it is possible that the amplitudes of the transients would carry useful information on the rate of the hemodynamic response. Because of the impact of T_1 on the transient amplitudes, we predict particularly strong transients in brain regions neighboring compartments of cerebrospinal fluid.

Transient BOLD responses occurring, e.g., after the onset of a stimulus block or a task, are quite common in human brain imaging. Some of them have been considered as artifacts arising from subject movement (16, 17), but for transients that cannot be attributed to motion, the generation mechanisms have remained elusive. For example, the spatial distribution of the transients is unexpected: after sustained visual stimulation, the transients can be bilateral while the conventional sustained BOLD response is contralateral (18), or the transients at block

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Supporting Information

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SI Text

Details on Experiments. All experiments were performed on two phantoms (uniform and gradient phantom) with a standard gradient recalled (GRE) echo planar imaging (EPI) pulse sequence on a 3-T whole body MRI scanner (Signa Excite 3.0T; GE Healthcare; software rev. E2.0_M4_0502.b), equipped with an eight-channel phased array head coil (Signa Excite). The field of view was 20 cm for the uniform and 19 cm for the gradient phantom. In all experiments, the image matrix was 64×64 voxels, slice thickness/gap between slices 3.0 mm/0.0 mm, flip angle 90° . Frequency was encoded from left to right. Other parameters, TR, TE, and number of time points were adjusted between measurements. The data from the first block of data (10 or 30 TRs) was discarded in each experiment to allow the longitudinal magnetization to reach pseudo steady state and to start from the beginning of a block.

The fMRI phantoms were made of 18.6-cm (uniform phantom) and 18.8-cm (gradient phantom) hollow acrylic cylinders of 16/20-mm inner/outer diameters. The cylinders were filled with ion-exchanged water and plugged with finger tips of a vinyl disposable glove. The coils, wound of 0.15-mm copper thread to the approximate center of the tube, were separated by 1.73 cm; this Maxwell's coil configuration aimed to produce a considerably homogeneous field or linear gradient field for the uniform phantom and the gradient phantom, respectively. In the uniform phantom, the pair of coils was wound in the same direction so that both coils induced positive B_z ; in the gradient phantom the directions of the coils were opposite, so that one of the coils induced positive B_z and the other negative.

As the coils were wound of a single contiguous thread in each phantom, the wire went twice between the coils for length of the 1.73-cm separating distance (Fig. 1A); those parts were aligned parallel to the tube's central axis. From the tubes, the wires were twisted and led to the receiver device approximately perpendicularly to the direction of the main field of the magnet (z direction). The current in the coils surrounding the phantoms was controlled with Presentation software (version 12.0 Build 01.23.08; Neurobehavioral Systems) via a fiber-optic signal pathway. A receiver device, powered by a battery, controlled the electrical switching of the "stimulus periods" by opening and closing a logic gate between the lead ends of the coils; the duration of the stimulus periods was varied between 7.5 and 30 s (5 or 15 TRs). Only step-transition stimuli were applied.

The phantoms were positioned in the central region of the head coil, with the axes of the cylinders along the z direction. Coarse alignment was guided by the alignment lights of the scanner, and the alignments were improved by measuring the tubes' distances from the rails of the head coil to within 1 mm between two measurement locations ≈ 10 cm apart in each of the cases, thus the axes of the head coil and the phantoms were within 0.6° from each other. The two phantoms were scanned in successive sessions.

After each setup process, a localizer scan was acquired to verify the good alignment and serve as the base to place the slices for the rest of the measurements. During the localizer scans, the phantoms were in the activation condition, meaning that no current was applied to the coils.

Stacks of nine (five) transverse slices, perpendicular to the z direction, were assigned for the uniform (gradient) phantom. With the uniform phantom, the landmark set in the middle of the coils was used as the location of the middlemost slice. With the gradient phantom, the signal slightly decreased in the area

between the coils and was used as the positioning reference. The region of interest was chosen from slice 5 for the uniform phantom (slice 2 for the gradient phantom), being thus the third (fourth) slice in the interleaved acquisition order and the scanning of the slice began after $2/9$ ($3/5$) TRs, e.g., at 444 ms (1,200 ms) for TR = 2,000 ms. The step adjustment of the field was triggered by the excitation pulse of the first slice of the volume, and the delays of the system from triggers to stimuli were on the order of 10 ms. Settling times (time to reach step-transition amplitude) of the current in the Maxwell coils, measured outside the magnet environment, were <0.1 ms.

Details on Simulations. The simulations were carried out on a column of 22,001 discrete elements of length $1 \mu\text{m}$ and indefinite width, spanning 2.2 cm in the direction of the signal displacement (i.e., z -direction); the middlemost 3,000 elements thus depicted an ideal 3-mm-thick slice. The simulation included exciting the middlemost slice and the slices next to it at correct times.

Two apparent slice displacements, 150 and 300 μm , were applied. The choices were based on assuming that the blood volume occupied by red cells (hematocrit) is $\approx 45\%$ and the modulation of the venous oxygenation 0.16 or, as percentage, 26% (1). Multiplying the displacement caused by the $10\text{-}\mu\text{T}$ modulation between completely oxygenated and oxygen-depleted erythrocytes by 7.2% ($45\% \times 0.16$) yields a displacement of 144 μm , which would relate to the changes of whole blood in veins, if only as an average.

Before excitations, the longitudinal magnetization available in each element $M_z(z, t)$ was evaluated on the basis of time elapsed after the previous simulated excitation ($t - t_-$) and the T_1 assigned for the sample:

$$M_z(z, t) = M_z(z, t_-) + (M_0 - M_z(z, t_-))(1 - \exp(-(t - t_-)/T_1)), \quad [1]$$

where z , t , M_0 , and t_- are the z -coordinate of the element, time, magnetization in thermal equilibrium, and time of the previous evaluation of magnetization, respectively.

The power deposited in the proton population is a function of z and the slice profile. The effects of the excitation pulses were approximated by different slice profiles [$P(z)$, normalized between 0 and 1], with maximum intensity corresponding to a 90° flip angle, which determined how much longitudinal magnetization was transferred to the excited pool. The transverse magnetization was then calculated as

$$M_{xy} = \sum_k M_z(k, t) \sin(\pi/2 \cdot P(k)). \quad [2]$$

Sigmoid curves were used to link zero-level power to a constant power in $P(z)$. The widths of the sigmoid curves were varied to simulate different excitation pulse profiles, and the nominal slice thickness (3 mm) in the simulations was defined as the full width at half maximum of the profile. The new longitudinal magnetization value was recorded so that it could be used in the following simulation step. The signal was stored in the case of the middlemost slice.

Perfect spoiling of transverse magnetization between excitations was assumed, i.e., the signal was supposed to emerge only from the newly excited magnetization. Transverse relaxation was omitted as it plays no fundamental role in the proposed mechanism of transient generation. A flowchart of the simulation is shown in Fig. S1.

Fig. S2 illustrates the signal acquired in the simulations. Here, the longitudinal magnetization immediately before an excitation was used as the pool of excitable spins. The excitation of the indicated slice profiles and locations yielded the postexcitation longitudinal magnetization; the signal was calculated from the

difference of the preexcitation and postexcitation longitudinal magnetizations according to Eq. 2.

In Fig. S3, the flip angle was varied between acquisitions. Reducing the flip angle made the transients weaker.

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