Inability to Directly Detect Magnetic Field Changes Associated With Neuronal Activity

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The ability to directly detect neuronal magnetic fields by MRI would help investigators achieve the “holy grail” of neuroimaging, namely both high spatial and temporal resolution. Both positive and negative findings have been reported in the literature, with no clear consensus as to the feasibility of direct detection. The aim of this study was to replicate one of the most promising published in vivo results. A second aim was to investigate the use of steady-state visual evoked potentials (ssVEPs), which give a large evoked response and offer a well-controlled approach because the frequency of the neuronal response can be dictated by the experimenter. For both studies we used a general linear model (GLM) that included regressors for both the expected blood oxygen level-dependent (BOLD) signal and the magnetic source (MS) signal. The results showed no activity that could be attributed to the neuramagnetic signals in either study, and no frequency component corresponding to the frequency of the ssVEPs. This study demonstrates that for the particular stimuli and hardware used, the sensitivity of the magnitude MRI signal to detect evoked neuronal currents is too low to be of practical use. Magn Reson Med 57:411–416, 2007. © 2007 Wiley-Liss, Inc.

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There is continuing interest in the possibility of using MRI to directly detect the magnetic fields produced by neurons (1–4). This would allow direct measurement of neuronal activity at high temporal resolution with unambiguous localization. This would be an improvement over the current leading neuroimaging techniques of functional MRI (fMRI), which has low temporal resolution, and magnetoencephalography (MEG), which offers no unique localization of activity. Earlier theoretical work showed that the magnetic fields produced by some of the brain’s strongest electrical activity, such as the alpha rhythm, should be large enough to be detected by MRI (5,6). While in vitro work has shown promise (7,8), no in vivo study has yet been reliably reproduced.

In theory, the magnetic fields generated by neurons could affect both the magnitude and phase of the MR signal. Following synaptic activity, post-synaptic ionic currents flow along the dendrites, creating the current dipoles seen with EEG and MEG. Ionic currents also flow along axons in the form of action potentials. These currents induce transient magnetic fields that can locally alter the precession rate of water molecules, and hence alter the phase and magnitude of the MR signal. Given the millions of dendrites or axons that are present in a single MR voxel, any overall phase variation at the source of activity would be expected to average out to zero, whereas loss of signal magnitude caused by intravoxel dephasing should remain due to microscopic field inhomogeneities. At a distance from the source, however, the phase variations add up to give a resultant phase change, as demonstrated in two phantom studies using an electric current dipole (5.7). Disappointingly, in vivo results obtained with phase signals are variable (1–4). The most promising in vivo studies have found changes in the signal magnitude (4,9,10), and therefore we considered only the magnitude signal in this study.

The aim of this work was twofold. The first goal was to replicate one of the most positive in vivo results from a previous study (9) that used a well-established visuomotor paradigm. That study showed clustered magnetic source (MS) activity with locations and latencies consistent with the electrophysiology and fMRI literature. In a second experiment, we investigated the use of steady-state visual evoked potentials (ssVEPs), a well-controlled approach that has also shown promise (10). ssVEPs are an attractive choice of stimulation because they give a strong electrophysiological response, and the frequency of the response can be completely controlled. If the magnetic fields from this activity can be detected, and the frequency of the measured signal follows the frequency of the driving stimulus, this would be strong evidence for the ability of MRI to directly detect neural activity.

MATERIALS AND METHODS

Experiment 1: Visuomotor Response Task

For experiment 1 we closely followed the experimental design of Ref. 9. Six subjects (three females and three males, 21–35 years old) took part.

Stimulus

The stimulus consisted of a 50-ms checker wedge presented in the lower right visual field, to which the subject had to respond as quickly as possible with a left index-finger button press. The stimulus was presented at random intervals of 0.6–1.5 s (mean interval = 1 s, step size = 0.1 s) in six blocks of 120 s interspersed with 30 s of rest, for a total time of approximately 15 min. This design differed from Xiong et al.’s (9) original study in two ways. First, Xiong et al. (9) used a longer mean interstimulus time of 2 s, and second, they achieved an effective jitter of 1.8–2.2 s (step size = 0.1 s) in the original study by changing the time of the scanning acquisition relative to the stimulus in five separate blocks, such that there was no...
The shorter mean interval between stimuli used in the present study minimizes any potential signal change due to the BOLD effect, which is a possible confound in Xiong et al.’s study, as will be discussed below. The jitter within each block prevents the subject from predicting the appearance of the checker wedge and thus helps to maintain attention.

**Scanning Parameters**

Scanning was performed on a 1.5T Siemens system using a multiecho EPI sequence with prospective motion correction (11) and three echo times (TEs) of 30, 60, and 90 ms. This allowed the optimum BOLD signal to be obtained at a TE of 60 ms (on the basis that this matches the $T_2^*$), and the MS signal to be obtained at the longer TE of 90 ms, which has been argued to be close to the optimum TE (9). A longer TE is optimum because it allows a longer period for intravoxel dephasing due to the neuronal magnetic fields (9). Five slices with an in-plane resolution of 3.5 mm were carefully positioned to cover both the primary motor and visual cortices. A repetition time (TR) of 1 s gave an interslice time of 200 ms. The stimulus presentation was synchronized with the scan timing such that the flashes occurred 50 ms or 150 ms preceding slice collection.

**Analysis**

We considered only the magnitude of the MR signal, which gave positive results in the original study (9). The data were analyzed using BrainVoyager (Brain Innovations, Maastricht, The Netherlands) on an individual basis. Preprocessing consisted of linear trend removal and a 4-mm 2D spatial filter only. A general linear model (GLM) was produced for each of the five imaging slices, which consisted of one BOLD regressor and four MS regressors. The four MS regressors comprised two motor and two visual regressors: one for the interval between 100–200 ms preceding slice collection, and one for the interval between 0–100 ms preceding slice collection, as shown in Fig. 1. For each slice from each subject, regions of “activation” (i.e., regions in which a significant amount of variance in the MR signal time course is accounted for by the regressor) associated with each regressor were carefully assessed by eye. A low statistical threshold of $P = 0.01$ uncorrected was chosen in order to fully consider any weakly activated regions. The analysis was carried out on the image sets collected at TEs of 60 ms and 90 ms.

**Experiment 2: ssVEPs**

Three subjects (two females and one male; 24, 35, and 24 years old, respectively) took part in experiment 2.

**Stimulus**

The stimulus consisted of a 6-Hz flashing checkerboard presented in 12 blocks of 120 s interspersed with 120 s of rest, for a total time of 48 min. This is similar to the method used in Ref. 10, except that in the previous study a 10-Hz flashing checkerboard was used. Throughout the experiment, a central fixation cross was displayed that randomly changed color (red, blue, and green). The subject was instructed to fixate on the cross and respond to the color changes by pressing one of two buttons.

**Scanning Parameters**

Scanning was performed on a 3T Siemens system using an EPI sequence with prospective motion correction (11), a TE of 50 ms, and a TR of 1050 ms. Six slices of 3.5-mm$^3$ resolution were positioned over the primary visual cortex. Following the design in Ref. 10, a dead time of 50 ms was introduced at the end of each TR, such that each slice was
collected at the same time with respect to the 6-Hz flash, but each volume was sampled at a different time with respect to the flashes. This produces the effect that the measurement slowly subsamples the 6-Hz signal, as shown in Fig. 2. Sampling theory states that if a periodic signal with frequency $f_1$ is subsampled at frequency $f_2$, the measured signal will have frequency components of $f_1 \pm n \times f_2$, where $n$ is an integer. In our case, $f_1 = 6 \text{ Hz}$ and $f_2 = 0.9524 \text{ Hz}$, giving an expected frequency component of 0.286 Hz within the measurable range of 0–0.5 Hz.

**Analysis**

As for experiment 1, only the magnitude of the MR signal was considered. The data were analyzed using BrainVoyager (Brain Innovations, Maastricht, The Netherlands) on an individual basis. Preprocessing consisted of linear trend removal and a 4-mm 2D spatial filter only. The elegant design of this study means that a single GLM is appropriate for all slices comprising the envelope BOLD response plus two MS regressors, since all slices have the same timing with respect to the flashes. The MS regressors were constructed using sine and cosine waves (wavelength corresponding to 6 Hz), subsampled according to the timing of the scan triggers, as shown in Fig. 2. Although the neuronal bursts in response to the light flashes are brief, the dendritic currents purported to cause the MS signal extend over several tens of milliseconds, producing the characteristic oscillatory signal seen in EEG (12). At stimulus frequencies below 10 Hz, EEG power is largely contained in the fundamental harmonic (13), which suggests that a sinusoidal model is accurate. Both sine and cosine waves were included because a linear combination of these regressors could allow for any phase in the MS signal with respect to the neural activity. Hence, detection of activation is insensitive to the exact delay time between the flash of light and the neural response. It is important to set the average magnitude of the MS regressors during the flash period equal to the resting baseline value. Otherwise, the MS regressors will simply “pick up” the signal difference between the rest and active periods that were not completely modeled by the BOLD regressor. For example, the signal at the onset and offset of activation is unlikely to be perfectly modeled by the BOLD regressor due to inaccuracies in the assumed delay and dispersion.

In each subject, we carefully assessed regions of “activation” associated with each regressor by eye. Frequency analysis was also performed on the time-course signal from regions of interest (ROIs) in the visual cortex. Two regions were chosen: one containing approximately 100 voxels where the strongest BOLD activation was seen, and one containing approximately 20 voxels in the occipital cortex where the strongest MS activation was seen. Since no significant MS activation was found, these 20 voxels were selected with the use of a nonsignificant activation threshold. The time-course data were segmented into 24 blocks of 90 s, with 12 blocks corresponding to periods when the visual stimulus was on, and 12 rest blocks. The central 90 s was chosen out of the available 120 s to avoid transition effects. A Fourier transform was performed on each block, and the resulting spectra were averaged to reveal any differences in frequency components in the respective “active” and “rest” periods. For comparison, we also performed an identical Fourier analysis on the MS regressors to identify the subsampled frequency.

**RESULTS**

**Experiment 1: Visuomotor Response Task**

All of the subjects showed BOLD activation in regions of the motor and visual cortices. In all subjects the MS regressors also accounted for some variance in the MR data ($P = 0.01$, uncorrected), but the activation was scattered evenly throughout the brain with few clusters. For each subject there were less than 100 voxels activated for each MS regressor at $P < 0.01$ uncorrected, and on average only 10 voxels at $P < 0.001$ and one voxel at $P < 0.0001$. Given that the images contained approximately 10000 voxels, it appears likely that the “activated” voxels show an effect by chance. In line with this, the data did not survive any form of correction for multiple comparisons. The number of “activated” voxels was not significantly different for the image sets collected at TEs of 60 ms and 90 ms.

Figure 3 shows the results of the subject with the best example of clustered MS activity, but, as can be seen, it
does not appear to be within the activated regions as defined by the BOLD signal. Furthermore, the activated pixels show a roughly even distribution between positive and negative correlations, whereas any MS activity should dephase the MR signal, giving only negative correlations.

Experiment 2: ssVEPs

All three subjects showed strong BOLD activity in the visual cortex. In contrast, in all three subjects the MS regressors accounted for no significant variance in the data, even at the very low statistical threshold of $P = 0.05$ uncorrected. Figure 4 shows the BOLD and MS responses from one typical subject. The MS results show only a few randomly scattered activated voxels at the $P = 0.05$ level, which cannot be considered significant given the large number of comparisons that were performed.

Figure 5 shows the results of the frequency analysis. The “BOLD region” included clustered groups of voxels from all six brain slices. The “MS region” consisted of scattered voxels within the occipital cortex on a single slice. The spectrum of the cosine MS regressor (Fig. 5g) shows a single component at 0.29 Hz, as predicted from sampling theory. None of the ROIs in any of the three subjects show a response at this frequency; however, there is a response at approximately 0.3–0.35 Hz in both the BOLD and MS ROIs. This frequency component is present in the signal regardless of whether the visual stimulation is on (red line) or off (blue line).

DISCUSSION

Even though we followed a design very similar to that used in the original study by Xiong et al. (9), we were unable to reproduce their results (Fig. 3). One explanation for this discrepancy could be the difference in timings between the two experiments. In the present study we used a mean interstimulus time of 1 s, whereas Xiong et al. used a longer time of 2 s. Two seconds could be long enough to allow small modulations in the BOLD signal to occur, and certainly long enough to see modulations in the initial dip of the BOLD signal (14). The model used by Xiong et al. did not include any possible BOLD effect, whereas we
included both MS regressors and BOLD regressors in our GLM. Our use of a 1-s interval, however, effectively removes the possibility of detecting BOLD modulations, and could therefore explain the apparent contradiction between the two studies. Other minor differences between the two studies, such as field strength (present study: 1.5T; original study: 1.9T) and voxel size (present study: 3.5 mm isotropic; original study: 3 × 3 × 6 mm), are unlikely to have a major effect on the results. Chu et al. (3) offered a further explanation for the discrepancies, i.e., that the design of the Xiong et al. (9) study, which involved multiple time-staggered runs, is prone to artifacts related to variations across the runs, such as fatigue and attention. We reduced this potential confound by instead jittering the stimulus presentation within a single run.

The results of experiment 2 also fail to show clustered activity corresponding to the MS regressors (Fig. 4b), despite a very strong BOLD response (Fig. 4a). The frequency analysis identified a frequency component in the MR signal time course of 0.3–0.35 Hz (Fig. 5), which is close to the predicted MS frequency of 0.29 Hz. However, the component has equal amplitude during both visual stimulation and rest, and therefore cannot be due to neuronal magnetic fields. The component is most likely due to ongoing, spontaneous physiological fluctuations, such as movement due to respiration, as was observed in a previous work (15).

An alternative to our strategy of subsampling the 6-Hz neural signal would be to directly sample the activity using a single-slice acquisition with a TR of ≤80 ms. This would have the added benefit of directly sampling the physiologic noise, which would allow these components to be easily identified. One drawback of a low TR is that the high degree of partial saturation makes the signal sensitive to spin history effects, and hence more sensitive to movement.

Recent in vivo studies have shown some success in directly detecting neuronal fields with MRI (1,2,4). One study found increased power in the alpha frequency range (8–12 Hz) of the MR phase signal when the subjects closed their eyes (1), which suggests that alpha waves may be directly detectable. However, the magnetic field variations produced by alpha waves are an order of magnitude larger than evoked fields, and indeed in the same study the signal from evoked fields could not be detected. Interesting work by Chow et al. (4) shows the possibility of detecting magnetic field changes produced by action potentials along the optic nerve. This is a new approach compared to previous work, which focused on the direct detection of dendritic fields in the cortex. Given the lack of a sound consensus in this emerging field of research, we believe it is important for all positive results to be replicated and all negative results to be reported.

CONCLUSIONS
We were unable to replicate the positive findings of Xiong et al. (9) or to detect a MS signal from ssVEPs. Thus, this study adds support to previous work (1,3) and demonstrates that the sensitivity of the magnitude MRI signal for detecting evoked neuronal currents is too low to be of practical use for the particular stimuli and hardware used in this work.

REFERENCES


