Temporal Resolving Power of Spin Echo and Gradient Echo fMRI at 3T With Apparent Diffusion Coefficient Compartmentalization

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Abstract: The temporal resolving power of blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) at 3T was investigated in the visual and auditory cortices of the human brain. By using controlled temporal delays and selective visual hemifield stimulation, regions with similar (left vs. right occipital cortex) and different (occipital cortex vs. auditory cortex) vascular architectures were compared. Estimates of the time-to-peak (TTP) of the BOLD hemodynamic response function (hrf) were obtained using a spin echo (SE) sequence and compared to those acquired using a traditional gradient echo (GE) sequence. The hrf TTP in the visual cortex was found to be 4.73 s and 4.21 s for GE and SE, respectively. The auditory cortex response was significantly delayed, with TTPs of 4.95 s and 4.51 s for GE and SE, respectively. The GE response was able to resolve visual stimuli separated by 250 ms, whereas SE could resolve stimuli 500 ms apart. Apparent-diffusion-coefficient (ADC) compartmentalization of the BOLD signal was applied to restrict the vascular sensitivity of the SE and GE sequences. Limiting the response to voxels with ADCs $< 0.8 \times 10^{-3} \text{ mm}^2/\text{s}$ improved the temporal resolving power of GE and SE BOLD to 125 ms and 250 ms, respectively. *Hum Brain Mapp* 25:247–258, 2005. © 2005 Wiley-Liss, Inc.

Key words: mental chronometry; BOLD; magnetic resonance; vascular dynamics; brain; diffusion weighting

INTRODUCTION

Event-related functional magnetic resonance imaging (er-fMRI) has not only greatly expanded the range of cognitive activities that are assessable using fMRI [Clark et al., 1998;

Cunnington et al., 2002; Dale and Buckner, 1997; Downar et al., 2001; Rosen et al., 1998; Zhang et al., 2003] but has allowed for the temporal ordering of cognitive processes, often referred to as mental chronometry [Bellgowan et al., 2003; Calhoun et al., 2000; Formisano and Goebel, 2003; Henson et al., 2002; Liao et al., 2002; Menon et al., 1998; Miezin et al., 2000; Newman et al., 2002; Thierry et al., 1999]. The most frequently used sequence in functional studies, gradient-echo (GE) echo planar imaging (EPI), is particularly sensitive to changes in the oxygenation state of hemoglobin, commonly referred to as blood oxygenation level-dependent (BOLD) contrast [Ogawa et al., 1990, 1993]. BOLD contrast results from a complex interaction of physiologic changes, including changes in cerebral blood flow (CBF), cerebral blood volume (CBV), and the cerebral metabolic rate of oxygen consumption [van Zijl et al., 1998]. The change in

Contract grant sponsor: National Institutes of Health; Contract grant number: 5-T32-HL07614; Contract grant number: RR02305; Contract grant number: MH64045.

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Received for publication 25 June 2004; Accepted 20 September 2004

DOI: 10.1002/hbm.20094

Published online in Wiley InterScience (www.interscience.wiley.com).

BOLD contrast over time in response to a neural stimulus is referred to as the hemodynamic response function (hrf). One obstacle that limits accuracy in ordering neuronal events is that the time evolution of the hrf varies across the brain [Huettel and McCarthy, 2001; Saad et al., 2001]. A better understanding of this variation and its influence on temporal resolving power may improve modeling in *er*-fMRI, increase detection sensitivity, and enhance the utility of fMRI in ordering neuronal events.

Although recent work has shown promising results characterizing relative changes within a region of the brain [Bellgowan et al., 2003], comparing absolute timing differences between regions remains problematic [Miezin et al., 2000]. The hrf is known to vary across subjects [Aguirre et al., 1998], as well as across and within regions of the cortex within a single subject [Buckner et al., 1996; Schacter et al., 1997]. Although differences in the type and duration of neuronal activity may affect the resulting hrf [Bellgowan et al., 2003; Shmuel et al., 2002], many of these regional variations can be attributed to differences in the underlying vascular architecture [Robson et al., 1998]. For example, Lee and colleagues demonstrated the presence of significant hrf delays in large veins relative to gray matter [Lee et al., 1995]. Restricting the vascular sensitivity of BOLD contrast offers a means to reduce variability in the hrf and to potentially improve the accuracy of interregional mental chronometry.

Techniques that modify BOLD sensitivity include, for example, the use of diffusion gradients to decrease the intravascular (IV) BOLD signal contribution [Lee et al., 1999; Zhong et al., 1998] and the use of the phase angle of complex valued fMRI to remove the BOLD contribution from large, oriented veins [Menon, 2002]. The apparent diffusion coefficient (ADC) can be used to estimate the fractional contributions from blood, parenchyma, and cerebrospinal fluid (CSF) in a voxel and has been used to improve spatial localization of the BOLD signal to the site of neural activity [Song et al., 2002a,b]. Some have improved spatial sensitivity by using only the early negative BOLD response [Duong et al., 2000], although this technique remains controversial [Buxton, 2001]. One group used a combination of larger BOLD magnitude and longer hrf delay to distinguish veins from gray matter [Hall et al., 2002]. Thulborn and colleagues found that, at 3T, spin echo (SE) BOLD resolved negative and positive bands of activation in the occipital cortex in response to vertical motion, whereas traditional GE BOLD at the same resolution could not resolve these bands, suggesting an improved spatial sensitivity in SE BOLD contrast [Thulborn et al., 1997].

SE sequences are mainly sensitive to functional contrast around small vessels, whereas GE contrast also contains a significant large vessel contribution. Specifically, GE and SE sequences provide contrast to the static (T_2^*) and dynamic (T_2) transverse relaxation processes, respectively. T_2 and T_2^* effects are related such that $1/T_2^* = 1/T_2' + 1/T_2$. T_2' contributions result from static field inhomogeneities that are efficiently refocused by spin echoes. BOLD-related T_2' effects are significant around large vessels. GE BOLD con-

trast, therefore, is sensitive to changes in the fields surrounding these vessels, whereas SE contrast is relatively insensitive to these changes [Bandettini and Wong, 1995; Boxerman, 1994]. Both SE and GE are sensitive to intravascular BOLD changes and to extravascular changes around small ($\sim 20 \mu\text{M}$) vessels [Weisskoff et al., 1994]. Longer echo times have been shown to significantly reduce hrf time-to-peak (TTP) in SE at 3T but not in GE. This finding has been attributed to a reduction in venous intravascular contrast [Hulvershorn et al., 2004].

Whereas it is common to use a visuomotor stimulus to investigate temporal characteristics of the hrf [Calhoun et al., 2000; Kim et al., 1997; Menon et al., 1998; Miezin et al., 2000; Mohamed et al., 2003], studies using this paradigm have reported widely varying interregional delays. One possible confound to these results is that motor activation is an active stimulus, requiring task performance by the subject. Consequently, the reaction time and task duration can vary significantly between subjects, as well as across responses in a single trial. Restricting comparisons to passive stimuli, such as visual and auditory activation, allows the onset and length of the neural response to be more strongly associated with stimulus delivery and may reduce intrasession and intersubject variability.

In this study, the effect of vascular sensitivity on the resulting hrf and the ability to discriminate temporal delays in and across regions is examined. Estimates of the time-to-peak hemodynamic response obtained using a SE sequence are compared to those acquired using a traditional GE sequence. To make results more widely applicable, MR parameters that allow for whole brain coverage are used at the expense of temporal resolution. Activations in regions that are anticipated to have similar (left vs. right occipital cortex) and dissimilar (occipital cortex vs. auditory cortex) vascular architecture are investigated. Finally, ADC compartmentalization of the BOLD signal is investigated as a means to further improve spatial and temporal sensitivity.

MATERIALS AND METHODS

Experimental Design and Data Acquisition

The fMRI paradigm used in this study was designed to determine the minimum time between the presentation of two stimuli that could be resolved, both within (right visual cortex vs. left visual cortex) and across (right visual cortex vs. auditory cortex) brain regions. Specifically, the stimulus block consisted of 40 presentations of a single condition, namely left visual hemifield (LVH) stimulation followed, after a delay, by simultaneous right visual hemifield (RVH) and auditory stimulation. Each of the three stimuli lasted 2 s. Four delay times were used to separate LVH from the concurrent onset of RVH and auditory stimulation: 125 ms, 250 ms, 500 ms, and 1 s, with one delay used per fMRI trial. Visual stimulation consisted of a high contrast reversing black and white checkerboard wedge alternating at 8 Hz. The left wedge extended from 210 degrees to 330 degrees, while the right wedge spanned 30 degrees to 150 degrees.

The central portion of the wedge was removed to minimize fovea activation, following the example of Kastner et al. [2004]. The auditory stimulus consisted of alternating low and high complex tones, each lasting 250 ms, resulting in a 4 Hz presentation rate. The low tone was a mixture of four low frequencies at 80 Hz, 428 Hz, 1 kHz, and 1.54 kHz; the high tone contained frequencies of 890 Hz, 1.3 kHz, 2.2 kHz, and 2.7 kHz. These frequencies were chosen by analyzing the audio spectrum of the EPI scans for bands with low energy. The auditory stimulus was delivered binaurally through headphones that attenuated ambient scanner noise. A central fixation cross was presented throughout the scanning. The 6 min and 40 s stimulus block was presented pseudorandomly with timings derived using the Optseq2 software package (<http://surfer.nmr.mgh.harvard.edu/optseq/>). The timing paradigm was designed to maximize the statistical efficiency of the experiment, at the expense of the power of activation detection [Dale, 1999]. The maximum and minimum delays between successive presentations were 30 s and 0 s, respectively. The mean interval between events was 6.8 s.

Experiments were conducted in a Siemens Trio 3T whole body scanner (Siemens, Erlangen, Germany) using a bird-cage head coil for radiofrequency transmission and reception. Twelve sessions were acquired for each of the four time delays using three subjects (16 sessions per subject, 48 total sessions). Each scanning session consisted of a SE and GE trial, with the delay time randomized across both sessions and subjects. The echo times for the GE and SE trial were 30 ms and 70 ms, respectively. Both GE and SE sequences were acquired with the following parameters: repetition time (TR) = 2 s, field of view (FOV) = 240 mm, voxel size = $3.75 \times 3.75 \times 4$ mm, slices = 19, slice gap = 0, repetitions = 200, oblique slice orientation. Slice locations were manually prescribed from a coronal localizer to span both the primary visual cortex and auditory cortex. Automated motion correction incorporated into the Siemens scanner software (MOCO [Thesen et al., 2000]) was applied during data acquisition. Apparent diffusion coefficient images were acquired in each session with the same voxel size and orientation as the EPI volumes. The ADC map was constructed from images acquired using an EPI sequence (TR = 3 s, echo time [TE] = 80 ms, 3 averages), with embedded isotropic diffusion gradients of 0, 200, and 1,000 s/mm². For each subject, a single high-resolution, T1-weighted 3D-MPRAGE MRI was acquired with the following parameters: TR = 1,630 ms, TE = 4 ms, inversion time = 1,100 ms, FOV = 256 mm, voxel size = $1 \times 1 \times 1$ mm, slices = 160, oblique slice orientation.

Data Analysis

The image data from each functional trial was processed using standard techniques in SPM2 (Wellcome Department of Cognitive Neurology, London, UK) in the following order: (1) Each volume was slice time corrected to the first temporally acquired slice. Off-line motion correction was not implemented, as the Siemens image reconstruction in-

cluded automated motion correction; (2) The EPI volumes and ADC maps were coregistered with the subject's corresponding MPRAGE scan; (3) The MPRAGE was transformed into standard stereotactic space (MNI) using the automated normalization routine in SPM2. The EPI images and ADC maps were subsequently normalized using the transformation matrix from the structural normalization and resampled using a trilinear interpolation method; (4) Spatial smoothing was applied to each EPI volume using a Gaussian kernel with a full width at half maximum of 6 mm; (5) Regression of voxel time course data to the stimulus paradigm was carried out using the general linear framework for serially autocorrelated observations [Worsley and Friston, 1995; Zarahn et al., 1997]. The design matrix was constructed using a canonical hemodynamic response function plus its first derivative [Friston et al., 1998; Josephs et al., 1997]. The regressions were examined for statistical significance, and an *F*-statistic was computed for each activated voxel. Obtained *F*-values were subsequently transformed into *Z* values, and only voxels exceeding a threshold of $P < 0.001$ ($Z = 3.09$), corrected for multiple comparisons, were selected for further analysis.

Region of Interest Determination

Three regions of interest (ROIs) were defined: (1) right primary visual cortex, (2) left primary visual cortex, and (3) left and right auditory cortex. The auditory cortices were combined so that the total number of activated voxels would more closely match the number in each visual cortex (no significant differences were found in the amplitude or timing parameters between left and right auditory activation). Binary activation maps were constructed for each subject to restrict analysis to voxels activated consistently across individual sessions [Neumann et al., 2003]. These maps comprised voxels exceeding a threshold of $P < 0.01$ ($Z = 2.33$) in at least half of the scans (8 of 16 scans per subject). Activated voxels within each ROI for a given fMRI trial were those that exceeded both an individual trial threshold ($P < 0.001$) and that were within a subject's binary activation mask. For the ADC-based analysis, additional binary masks were included that contained only voxels above or below a given ADC value ($< 0.8 \times 10^{-3}$ mm²/s, $> 1.0 \times 10^{-3}$ mm²/s, or $> 1.2 \times 10^{-3}$ mm²/s). In these cases, the predefined ROI mask, the individual statistical mask, the group statistical mask, and the ADC mask were combined to define voxels of interest for each of the three regions. A single hrf response for an ROI was obtained by averaging the time courses of each voxel contained in the region.

HRF-Based Metrics

Both the individual voxel and the various ROI-based hrfs were inspected to determine the maximum signal contrast ($\Delta S/S$, in percent), and the TTP of the contrast (in seconds). To obtain the time-to-peak values, each hrf was fit to a four-parameter gamma function using the approach suggested by Neumann et al. [2003]:

Figure 1.

Single subject hemodynamic response function time-to-peak maps for each stimulus delay, with color scale in seconds. Maps include only voxels with significant ($P < 0.001$) activation. The right occipital stimulus onset was constant across delays, whereas the left occipital and auditory cortex had stimulation delays as listed. R, right; L, left.

$$f(x) = \left(\frac{x}{a}\right)^b e^{-(x-c)/d}$$

The TTP value was subsequently estimated as the product of b and d [Cohen, 1997; Glover, 1999]. For the present investigation of BOLD temporal resolving power, the TTP was used as the measure of hrf response relative to the stimulus onset. Two-tailed t -tests were performed on the derived TTP values, with variance defined as the variation across individual trials.

RESULTS

TTP Maps

Figure 1 presents gradient echo TTP maps from one subject at each time delay. The right occipital cortex (right OC) responded to the left visual hemifield activation, whereas the left occipital cortex (left OC) was activated by the right visual hemifield. For all activations, the TTP was measured relative to the onset of the block of three stimuli, such that the stimulus onset in the right OC coincided with the beginning of the measurement period, whereas the left OC and auditory cortex stimulus onsets were delayed (by 125 ms, 250 ms, 500 ms, or 1 s) with respect to the measurement onset. Faster peak times appear in warm colors (reds), with slower times in cool colors (blues). As expected the right OC (left side in images) had similar peak times for each stimulus delay (4.96 ± 0.15 s). The peak activation times in the left OC and auditory cortex moved progressively to cooler colors as the stimulus delay increased. Notably, for even the shortest delay, the time-to-peak values in the right OC were discernibly shorter than the values in either the left OC or the auditory cortex. The spatial extent of the activation was considerably more variable across runs in the auditory cortex (range, 31–182 voxels in maps presented in Fig. 1) than in the visual cortex (range, 150–206 voxels). This variability was found in both the spin echo and gradient echo trials in

all subjects. Although the cause for this variability is uncertain, all the subjects noted that the volume of the auditory stimulus and the ambient noise level was affected by the position of the head restraints.

In the ventral portion of the visual activation cluster in Figure 1, a portion of the left OC activation (identifiable by longer TTP values that vary with stimulus delay) crosses the midline into the right OC. This finding was particularly evident in the 1-s delay. The masking technique included these voxels in the right visual cortex ROI, causing hemispheric “crosstalk” in its derived time course. Close inspection of the non-normalized activation maps overlaid on their respective structural scans confirmed that this crosstalk spanned the anatomical midline, rather than being a normalization artifact. Because the central visual field was removed in both hemifield stimuli, common central fovea activation is unlikely to have caused the observed crosstalk. Furthermore, the crosstalk could not be attributed to smoothing, because an analysis using nonsmoothed data had no apparent effect on the observed crosstalk. Time-to-peak maps containing noticeable crosstalk areas were present in only a subset of the runs (~1 in 6) with no preference for left OC to right OC contamination or vice versa. The origins of this crosstalk are pursued further in the Discussion section.

Regions With Similar Vascular Architecture

The fMRI determined TTP values in left and right occipital cortex vs. the stimulus presentation delays are plotted in Figure 2. For both spin and gradient echo, the peak times in the right hemisphere were nearly constant across delays, with a slight upward trend in the derived peak time with increasing presentation delay (dashed lines in Figs. 2A and 2B). This increase was attributed to the aforementioned crosstalk. The derived TTP values in the left occipital cortex showed a strong correlation ($r^2 = 0.976$ for GE and 0.982 for SE) to the presentation delay time (solid lines in Fig. 2A,B), with a non-0 intercept that is interpreted as the inherent

Figure 2.

Group time-to-peak results in the left (solid lines) and right (dotted lines) occipital cortices (OC) plotted against stimulus delay for gradient (A) and spin (B) echo. Correlation coefficients and fitting parameters are for left OC. Time-to-peak (TTP) values obtained by subtracting the response in the right occipital cortex from the response in the left are plotted for the gradient (C) and spin (D) echo.

delay in the hemodynamic response. This delay was significantly shorter ($t(20) = 4.0$; $P < 0.001$) for the spin echo ($4.16 \text{ s} \pm 0.15 \text{ s}$) than for the gradient echo ($4.84 \pm 0.08 \text{ s}$) and reflects the different vascular sensitivities of these sequences [Bandettini and Wong, 1995; Boxerman et al., 1995]. The delay varied more across, rather than within, subjects (data not shown) and is consistent with our previous work [Hulvershorn et al., 2004].

To reduce the contribution of intersubject variation, the TTP in the left occipital cortex was measured relative to the

TTP in the right occipital cortex for each subject, with the result plotted in Figure 2C,D. This correction decreased the intercept values to $97 \text{ ms} \pm 90 \text{ ms}$ for the GE and to $5 \text{ ms} \pm 160 \text{ ms}$ for the SE. The correction improved the correlation between the left hemisphere response and the stimulus presentation delay in the gradient echo sequence ($r^2 = 0.998$), in agreement with other findings [Menon et al., 1998]. The correlation coefficient decreased slightly in the corrected spin echo data ($r^2 = 0.961$). This unexpected finding in the SE data can be explained by close inspection of Figures 2A

Figure 3.

Comparison of group time-to-peak results in the left and right occipital cortices vs. stimulus delay, for gradient (top) and spin (bottom) echo blood oxygenation level-dependent. The reference delay refers to the right OC stimulus, defined as a delay of 0 s. For all delays, the spin echo (SE) time-to-peak (TTP) values were shorter than the corresponding gradient echo (GE) values. Application of the slow apparent-diffusion-coefficient (ADC) mask ($<0.8 \times 10^{-3} \text{ mm}^2/\text{s}$) decreased TTP, whereas thresholding for

faster ADCs ($>1.0 \times 10^{-3} \text{ mm}^2/\text{s}$, or $>1.2 \times 10^{-3} \text{ mm}^2/\text{s}$) increased TTP. Differences between the left OC and right OC responses were more significant ($*P < 0.01$, $**P < 0.001$) in the GE than the SE data. Without ADC masking, the GE sequence resolved a 250-ms stimulus delay; whereas SE resolved a 500-ms stimulus delay. Application of the slow ADC mask increased the resolving power of GE and SE to 125 ms and 250 ms, respectively.

and 2B. In the gradient echo data, the difference between the predicted (linear fit) and actual TTP value for a given delay was similar in both direction and magnitude in the left and right cortex, suggesting that global TTP changes across trials were a major source of TTP variance. The TTP variance in the SE data did not show such a trend, the variance in the left and right hemispheres being uncorrelated across stimulus delays.

Figure 3 presents data assessing the temporal resolving power of spin echo and gradient echo with and without ADC masking, with error expressed as standard deviation. The derived TTP values in the left occipital cortex are compared to a “reference” TTP value, derived from the mean TTP in the right OC. Voxels with an ADC of less than $0.8 \times 10^{-3} \text{ mm}^2/\text{s}$ (slow ADC mask) contain mainly parenchymal tissue [Song et al., 2002a], whereas voxels with faster ADC values contain a significant blood vessel and/or csf fraction. Without ADC masking (Fig. 3, cross-hatched bars), the gradient echo was able to resolve a timing difference of 250 ms ($t(22) = 3.18$; $P < 0.01$), whereas the spin echo data had a temporal resolution of 500 ms ($t(22) = 3.49$; $P < 0.01$). The ROIs restricted to voxels with slow ADCs had shorter absolute time-to-peak values in both the left and right visual hemispheres at all time delays in both GE and SE, with a greater average decrease in the TTP of the gradient echo sequence (108 ms) than in the TTP of the spin echo sequence

(88 ms). The slow ADC mask increased the resolving power of both sequences to 125 ms and to 250 ms ($t(22)=3.25$ and 3.13 ; $P < 0.01$) in the gradient echo and spin echo sequences, respectively. Masks that selected for voxels with faster ADC values ($> 1.0 \times 10^{-3} \text{ mm}^2/\text{s}$ or $> 1.2 \times 10^{-3} \text{ mm}^2/\text{s}$) increased the time-to-peak for all delays and decreased the resolving power of both sequences. The spin echo sequence had too few activated voxels remaining after applying the fastest ADC mask ($> 1.2 \times 10^{-3} \text{ mm}^2/\text{s}$) to yield meaningful results.

The superior resolving power of the gradient echo vs. the spin echo sequence can be partly explained in terms of the contrast-to-noise ratio (CNR) in the voxels from where the TTP values were derived. Figure 4 presents a histogram showing the normalized voxel distribution of CNR values in the spin echo (dotted lines) and gradient echo (solid lines) data for activated voxels in all subjects and delay times. The gradient echo had a larger average CNR (1.5) than did the spin echo (0.93) and a larger CNR range.

Figure 5 illustrates a likely cause of the improved resolving power in the slow ADC-masked GE data. The histogram depicts the normalized voxel density vs. time-to-peak. The histogram contains data from all the sessions of one subject with (dotted line) and without (solid line) restriction to voxels with slow ADCs. The slow ADC mask preferentially removes voxels with longer TTP values. Fast ADC values in

Figure 4.

Histogram of the voxel distribution of contrast-to-noise ratio (CNR) in the left OC, for gradient echo (GE, solid line) and spin echo (SE, dashed line). Data are from all sessions and subjects. The mean CNR of the GE was greater than the mean SE CNR, whereas SE blood oxygenation level-dependent contrast produced a narrower distribution of CNR values.

activated voxels are associated with larger venous contributions that have been shown to have more variable hrf delays [Lee et al., 1995].

Regions with Different Vascular Architecture

Table I presents intercept values for the three ROIs (right OC, left OC, and auditory cortex), which correspond to the predicted TTP of the hrf in each region given no stimulus delay. No significant differences were found between the left and right occipital cortex. The time-to-peak in the auditory cortex, however, was significantly ($t(20) = 2.83$ and 3.09 ; $P < 0.01$) longer than the TTP in the right occipital cortex for both gradient and spin echo, respectively. Comparisons of delay-dependent timing differences between right OC and the auditory cortex, thus, are difficult to interpret, as any measured difference could be attributed to a difference in the inherent vascular response between the two regions, rather than to an actual difference in the ordering of neuronal events. As a result, delay comparisons are best made within a functionally equivalent region. Figure 6 presents the temporal resolving power of the fMRI response in the auditory cortex, using the derived intercept of the *auditory* cortex, rather than the time-to-peak response in the right OC, as the reference. As in the visual cortex, the spin echo TTP values were shorter than the corresponding GE values.

Figure 5.

Histogram depicting the normalized voxel density vs. hemodynamic response function time-to-peak. Data are from all sessions of a single subject. The results are shown with (dotted line), and without (solid line) restriction to voxels with slow apparent-diffusion-coefficients (ADC, $< 0.8 \times 10^{-3} \text{ mm}^2/\text{s}$). The effect of the ADC threshold is seen in the preferential exclusion of voxels with longer hemodynamic response times.

The slow ADC mask decreased the TTP values in both sequences, whereas the faster ADC masks increased the TTP. The temporal resolving power in the auditory cortex was less than that in the visual cortex, with both the gradient and spin echo able to resolve events spaced 500 ms apart ($t(22) = 6.6$ and 4.22 ; $P < 0.001$). Slow ADC masking increased the resolving power of the gradient echo to 250 ms ($t(22) = 3.79$; $P < 0.001$) but did not affect the spin echo result.

As mentioned earlier, previous work suggests that the TTP delay differences observed across cortical regions can

TABLE I. The hemodynamic response function time to peak, extrapolated to zero stimulus delay, by region of interest

Sequence	ROI	TTP (s)	Δ TTP (s)
Gradient echo	R occipital cortex	4.73	—
	L occipital cortex	4.84	0.11 ± 0.09
	Auditory	4.95	$0.22 \pm 0.07^*$
Spin echo	R occipital cortex	4.21	—
	L occipital cortex	4.16	-0.05 ± 0.11
	Auditory	4.51	$0.30 \pm 0.14^*$

* $P < 0.01$.

Figure 6.

Comparison of hrf time-to-peak (TTP) in the auditory cortex vs. stimulus delay, from gradient (GE, top) and spin (SE, bottom) echo blood oxygenation level-dependent contrast. The reference delay is the y-intercept (i.e., $t = 0$) extrapolated TTP, which approximates no stimulus delay. Without apparent-diffusion-coefficient

(ADC) masking, the GE and SE resolved a 500-ms delay difference (** $P < 0.001$). The slow ADC mask increased the GE resolving power to 250 ms (* $P < 0.01$) but did not improve temporal resolution in the SE data.

be partly explained in terms of the heterogeneity of the vascular architecture throughout the brain. Comparing sequences with different vascular sensitivities, such as the spin and gradient echo, can reveal if one vascular component (e.g., capillaries or draining veins) has a dominant effect on regionally specific TTP differences. Accordingly, time-to-peak delay differences between the auditory and visual cortex (audio-visual TTP delays; AVD) obtained using either the spin or gradient echo sequence were studied, as was the effect of ADC masking on these AVD differences. Table II presents TTP differences between the auditory cortex and the left occipital cortex (AVD), where the stimulus presen-

tation times were matched. AVD differences are presented for the extrapolated intercept values, as well as at each time delay. Although the inherent TTP delay in either the auditory or the visual cortex was significantly different when comparing the GE values to those obtained using the SE sequence (e.g., auditory GE TTP = 4.95 s, SE TTP = 4.51 s; see Table I), no significant difference in the AVD existed between the gradient echo (mean AVD 90 ± 139 ms) and the spin echo (239 ± 206 ms) sequences ($t(20) = 0.59$, $P = 0.55$). The ADC masking had no significant effect on the audio-visual TTP delay in either the gradient echo or the spin echo, with the largest ADC-induced change in the AVD difference

TABLE II. Difference between auditory and left visual cortex hemodynamic response function time to peak versus stimulus delay

Sequence	ADC mask (mm ² /s)	Intercept	125 ms	250 ms	500 ms	1000 ms	Mean $\pm$ SD
Gradient echo	$<0.8 \times 10^{-3}$	126	78	55	120	84	84 ± 110
	None	111	85	45	105	126	90 ± 139
	$>1.0 \times 10^{-3}$	45	65	3.8	51	59	45 ± 149
	$>1.2 \times 10^{-3}$	43	65	4.7	68	52	47 ± 157
Spin echo	$<0.8 \times 10^{-3}$	243	202	65	-19	367	153 ± 180
	None	347	219	89	219	432	239 ± 206
	$>1.0 \times 10^{-3}$	362	285	235	299	408	306 ± 214

Values are expressed in milliseconds (ms), unless otherwise indicated. ADC, apparent-diffusion coefficient.

being 43 ms in the GE and 86 ms in the SE sequence. The direction of these ADC dependent delay changes was inconsistent, with the faster ADC masking reducing the AVD difference in the GE but increasing the difference in the SE. The slower ADC mask did not change the mean AVD in the GE (from 90 to 86 ms), but decreased it in the SE (239–153 ms). The implications of the small difference in the AVD in the spin and gradient echo data, and the moderate and inconsistent effect of ADC masking on these differences will be discussed in greater length below.

DISCUSSION

In this work, the temporal resolving powers of SE and GE BOLD fMRI were compared. The GE resolved two visual stimuli 250 ms apart, whereas the SE could only resolve stimuli 500 ms apart. The poorer temporal resolving power of the spin echo sequences was attributed to lower CNR compared to the GE sequence. ADC compartmentalization of the BOLD signal was applied to restrict the vascular sensitivity of the SE and GE sequences. Limiting the analysis to voxels with ADCs less than $0.8 \times 10^{-3} \text{ mm}^2/\text{s}$ improved the temporal resolving power of GE and SE BOLD to 125 ms and 250 ms, respectively. In a related analysis, the hrf TTP in two separate regions of the brain (auditory and visual cortex) was determined for SE and GE. It was hypothesized that both the SE sequence and ADC compartmentalization would decrease the TTP variability between these two brain regions, and thereby facilitate the comparison of inter-regional hrf timing parameters. Auditory cortex hrf TTP was significantly delayed compared to the visual cortex response, but neither the SE sequence nor ADC compartmentalization significantly reduced this inter-regional delay.

A critical aspect of this work was the selection of the regions of interest in the visual and auditory cortices. In agreement with previous findings [Neumann et al., 2003], it was noted that voxels which were consistently activated across a subject's sessions tended to have a reproducible hrf. In contrast, voxels activated only occasionally were much less stable, often having widely varying shapes with multiple local minima and maxima. Moreover, previous work has shown that a significant portion of activated voxels can have a negative hrf in response to visual activation [Saad et al., 2001]. Inclusion of negative responses in the time-to-peak calculation within an ROI complicates its physical interpretation. Because the time-to-peak value as measured herein only has meaning when derived from a reproducible, positive-going hemodynamic response function, masks were created for each individual to select for frequently and positively activated voxels, realizing that, in so doing, additional functional information was being disregarded.

The range of hrf delays across voxels in an ROI was approximately 1 s, much longer than the several millisecond time delays expected for neuronal latency differences [Bullier et al., 1996; Schmolesky et al., 1998]. Instead, the variability of the timing delays suggested a vascular origin, as the transit time between the capillary bed and larger draining veins is on the order of 1 s [Bandettini, 2000].

The calculation of TTP values was complicated by crosstalk between the left and right visual cortices. Others have found that hemifield stimulation causes neuronal changes, including negative BOLD responses, in the hemisphere ipsilateral to the visual stimulation [Tootell et al., 1998]. However, because the blood supplies of the two hemispheres are quite separate, with the closest common vessels at the Circle of Willis, it seems unlikely that cross-hemispheric blood flow "stealing" would be responsible for the observed changes. Neural suppression, wherein activation in one hemifield may dampen neural activity in the contralateral hemisphere, is another possible mechanism for the cross-hemisphere effects seen, although the observation that the crosstalk appeared in the left hemisphere in some cases and the right in others, with its location varying within those hemispheres, weakens the argument for neuronal suppression being causative. Visual tracking errors and attention effects, which are more likely to vary from trial to trial, as well as in their spatial orientation, are the most likely explanation for the observed findings. Addition of a visually cued task at the central fixation point might help to reduce these errors.

The gradient echo sequence had better temporal resolving power than the spin echo sequence in the visual cortex. Previous work found that $T2^*$ (GE) BOLD contrast is approximately two times greater than is $T2$ (SE) contrast at 1.5T [Bandettini et al., 1994]. In the work, presented herein, performed at 3T, the GE contrast amplitude was on average $1.9\times$ greater than the SE BOLD contrast, with the SE having 25% higher SNR in the visual cortex. Although the SE had higher SNR, the relatively higher GE contrast resulted in an average GE:SE CNR of 1.6:1. The increased GE CNR, which translates directly into higher statistical significance, improved the accuracy in deriving the TTP parameter, as reflected in the smaller errors in the TTP values. Furthermore, as demonstrated in Table II, the TTP delay between regions was less variable in the GE than in the SE data. Efforts to elucidate a characteristic within the noise to explain this finding were unsuccessful. This could be due in part to the relatively small sample size of the current data set. An excellent in-depth analysis of the spatial and temporal characteristics of fMRI noise has been presented elsewhere [Saad et al., 2001]. Regardless of the source of the noise difference in the derived TTP between the two sequences, the CNR advantage in the GE sequence apparently outweighed the potential increase in vascular sensitivity of the spin echo sequence; thus, the gradient echo contrast was better able to distinguish small timing differences given similar vascular architecture.

In addition to comparing time-to-peak differences in spin and gradient echo sequences, the effect of ADC masking on these sequences was investigated. The slow ADC mask was expected to exclude activated voxels containing a large vascular fraction, whereas the faster ADC masks were to include voxels with large vessels almost exclusively. Large feeding arteries and arterioles could also be included in the fast ADC; however, activated voxels are more likely to in-

clude veins, which have large BOLD effects, rather than arteries, which exhibit no BOLD-dependent changes. These veins are downstream from activated regions and have delayed hemodynamic responses relative to the more proximal capillary beds. Therefore, voxels with slow ADC values are expected to have shorter TTP values than voxels with large diffusion coefficients. The slow ADC mask decreased the TTP delays in all quadrants for both the spin echo and gradient echo data, whereas the fast ADC masks increased the TTP delay as expected. Moreover, the improvement in temporal resolving power using the slow ($<0.8 \times 10^{-3} \text{ mm}^2/\text{s}$) ADC mask and its worsening when using faster ADC values agrees with earlier findings that large vessels often show unpredictable delays in their hrf [Lee et al., 1995].

The ADC masks served as a tool to modify vascular sensitivity after acquisition. Alternatively, diffusion gradients can be embedded within an EPI sequence, creating a diffusion-weighted fMRI sequence [Duong et al., 2003; Song et al., 1995, 1996]. This modification selectively dampens signal from large vessels within a voxel, rather than excluding entire voxels based on their mean ADC value. The diffusion gradients, however, decrease global SNR, which counters the effects of improved spatial sensitivity. Although it has been shown in this work that selective ADC masking can improve temporal resolving power, the ability of diffusion-weighted fMRI to likewise improve resolving power while retaining robust activation warrants further investigation.

The left and right visual hemifields had statistically indistinguishable hrf delays. This finding was expected and in agreement with other work [Menon et al., 1998], as these two brain regions have the same vascular architecture. A small but significant difference existed, however, in the inherent hrf delay between the auditory and visual cortices. It has been argued herein that this delay results from vascular architecture differences. However, the presence of underlying tonic neural activity can also contribute to the observed differences by changing, for example, the baseline activity or the neurovascular (n-v) coupling. In these experiments, the constant background scanner noise causes large tonic auditory activation, while the visual cortex should have minimal underlying activity. Similar delay differences have been found in other studies comparing hrf delays in various parts of the brain [Henson et al., 2002; Neumann et al., 2003], and these experiments were less likely to be confounded by tonic underlying neural activity. Although the mean difference in the TTP between the auditory and visual cortex ($\sim 220 \text{ ms}$ in the GE) was much smaller than the range of TTP values within either of these regions ($\sim 1 \text{ s}$), the inter-regional ROI delays are nevertheless large compared to stimulus delays commonly used in fMRI investigations of mental chronometry. Such inherent differences in hrf timings, whether due to vascular architecture differences or n-v coupling differences, severely complicate the accurate ordering of neuronal events based on hrf comparisons. As an example, one group, using a visually cued motor task, found that in some cases

the vascular response in the motor cortex preceded the response in the visual cortex [Miezin et al., 2000], in direct contradiction to the expected ordering of the neuronal events.

Because a large component of the variability in the TTP values across the brain is likely a result of the underlying differences in the vascular architecture, it was hypothesized that manipulating the spatial and vascular origins of the signal, using either a spin echo sequence or ADC masking, would modulate these delay differences. Whereas the spin echo TTP was consistently and significantly faster ($\sim 500 \text{ ms}$) than the gradient echo TTP in an ROI, the TTP differences *between* regions were smaller and failed to reach significance. For example, the TTP in the auditory cortex was 240 ms faster than the TTP in the left occipital cortex in the SE data and 90 ms faster in the GE data. Of interest, the spin echo difference was slightly *larger* than the GE difference, contrary to what was expected given the improved localization of the spin echo to the site of neuronal activation.

The slow ADC masking removes large vessel effects in both the SE and GE. However, GE BOLD contrast occurs in parenchymal tissue surrounding large vessels and this signal, which has a longer TTP, is not eliminated by the ADC masking. Therefore, the SE TTP decreases more than the GE TTP using slow ADC masking, as seen in Figure 6. ADC masking failed to significantly change the interregional TTP delay in either the gradient echo or spin echo sequence. One possible explanation for the failure of both the SE sequence and the slow ADC masks to reduce interregional differences in the TTP relative to the unmasked GE data is that the vascular response delays in the two ROIs studied are present at all levels of the vascular tree, with the delays appearing first either in the upstream arterioles or in the capillary beds perfusing the activated neurons. A similar inference was drawn by another group, who concluded that venous drainage is only partly responsible for spatial variability in response delays across the brain and that parenchyma must contribute significantly to this variance [Saad et al., 2001]. Furthermore, Moskalenko et al., using a hydrogen clearance method selective for measuring parenchymal blood flow, which is composed primarily of small vessels and associated tissue, found that response delays across voxels in the rat whisker barrel can vary by up to 6 s [Moskalenko et al., 1996a,b]. This work supports the conclusion that the inability of either the SE or the ADC masks to alter the interregional TTP delays was due to their presence at all levels of the vascular tree.

CONCLUSION

This study investigated the temporal resolving power of fMRI within and across brain regions using MR parameters compatible with whole brain imaging (i.e., long TR). Spin echo BOLD and ADC masking were compared to standard gradient echo BOLD. Spin echo sequences, because of reduced CNR, demonstrated poorer temporal resolving power than did the GE sequence. Field strengths higher than 3T are likely necessary to overcome the low CNR of SE and maxi-

mize the benefits of its improved spatial sensitivity [Duong et al., 2003; Yacoub et al., 2003]. ADC masking that restricted activation to the parenchyma increased the resolving power of both the SE and GE sequences. In the present study, the smallest stimulus timing difference, 125 ms, was resolved using the GE sequence and included only voxels with ADC values equal to or less than $0.8 \times 10^{-3} \text{ mm}^2/\text{s}$. This finding confirms that the hrf time to peak is more reproducible within regions and across sessions in parenchyma than it is in larger vessels and suggests that methods to reduce the large vessel BOLD contribution (while maintaining adequate CNR) can improve temporal resolving power.

No significant differences in the interregional hrf timing variability were found between the spin echo and gradient echo sequence, or with the application of ADC masking. This finding suggests that differences in the hemodynamic response across the brain are present in the arterioles or capillary beds, as well as in the draining veins. These differences make meaningful comparisons of absolute TTP values in the regions studied (i.e., auditory and visual cortex) problematic. It remains to be determined whether these results can be generalized to other regions.

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