Estimation of FMRI response delays

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Abstract

We present an efficient algorithm using the Hilbert Transform for estimating the delay of the BOLD response to neuronal stimulation. With minimal additional computations, the algorithm estimates parameters generated in the widely used cross-correlation method and simplifies the interpolation required to estimate the response delay from the cross-correlation function. We examined errors in the Hilbert-based delay estimate associated with the use of DFT on short-duration discrete signals and proposed a method for minimizing these errors. Furthermore, we compared the delay estimates obtained with the Hilbert method to those obtained using the onset of the BOLD response. The Hilbert method resulted in less variance in the delay estimate despite the potential for higher variability in the latter part of the BOLD response. This improved delay estimate was attributed to the reduced sensitivity of the Hilbert method to noise contamination compared to the onset method.

Keywords: Functional magnetic resonance imaging; Activation latency; Hilbert transform; Spectral leakage; Phase estimation

Introduction

Functional magnetic resonance imaging (FMRI) is a noninvasive imaging technique that produces a series of brain images reflecting the time course of neuronal activity associated with some stimulus. Blood oxygenation level-dependent (BOLD) FMRI provides an indirect measure of neuronal activation by quantifying concomitant localized changes in blood oxygenation levels.

The vast amount of data generated during an FMRI scan requires automated techniques for detecting and characterizing activated voxels throughout the brain. In addition to simply detecting cortical areas involved in processing a given stimulus, there is a growing interest in exploiting differences in FMRI response delays between neighboring brain areas. Such differences can be used to efficiently map multiple brain areas during single scans (DeYoe et al., 1996; Engel et al., 1997; Sereno et al., 1995). In addition, there are data to suggest that distributions in response delays can be used to study mental chronometry (Menon et al., 1998).

An established method for automatically detecting activated voxels and estimating their response delays searches for those voxels with an FMRI response that correlates significantly with a reference time series (Bandettini et al., 1993). This pattern-matching algorithm assumes that the FMRI response signal is a scaled, time-shifted, noisy version of the reference time series. We present a variation on that method that is computationally efficient and offers high-resolution estimates of the time delay between the FMRI response and the reference time series. This method uses the Hilbert transform (\(H[\cdot]\)) and discrete Fourier transforms and has been briefly introduced by Saad et al. (2001), where FMRI response delays and their significance were examined. In this article we detail the theoretical derivation and practical application of the Hilbert-based response delay estimator. Special attention is given to the computa-
tional advantages and challenges for this estimator when applied to digital time series.

Finally, we compare the Hilbert-based response delay estimator to an estimator introduced by Menon et al. (1998). This estimate uses the onset time of the rising phase of the FMRI response to estimate the response delay with respect to some reference time series. This use of the rising phase to estimate delay contrasts with the Hilbert estimate that uses the entire FMRI response (rise, plateau, and descent). Menon et al. (1998) suggest that the variability in delay estimate using only the rising phase of the FMRI response is less than that obtained using the entire FMRI response. Compared with the rising phase of the FMRI response, the plateau and descent portions of the response may be more variable. Consequently, when using the entire FMRI response to estimate delay, the variance of the estimated delay should increase. In this study, we used empirical FMRI data and simulated signals to investigate the variability of the FMRI response delay for two different estimators, a Phase estimator, based on the Hilbert transform, and an Onset estimator, based on the onset of the rising portion of the FMRI response. We sought to determine whether the Onset estimate does indeed yield less variance in estimated response delay than the Phase estimate. We also compared the sensitivity of each of the two estimators to noise.

Methods

Phase estimator using Hilbert Transform

The time delay between two time series may be estimated with high temporal resolution using a computationally efficient Hilbert Transform algorithm. As outlined below, this algorithm takes advantage of Fast Fourier transforms and analytic signals to compute the cross-correlation function between two time series and its Hilbert Transform. The response delay is then estimated by interpolation around the zero crossing of the Hilbert Transform of the cross-correlation function.

Model for reference and FMRI response signals

Ultimately, our goal is to determine the time delay (Δt) between an ideal signal x(t) and its time shifted version x(t - Δt). In practice, however, x(t) and x(t - Δt) cannot be measured without additive noise. Rather, we measure signals, r(t) and s(t), that may be modeled using Eq. (1) (Bendat and Piersol, 1986).

\[ r(t) = x(t) + m(t) \]
\[ s(t) = \alpha x(t - \Delta t) + n(t), \]

where m(t) and n(t) are additive noise components. For FMRI, x(t) represents the time course of neuronal stimulation filtered by the hemodynamic response with zero time delay. The measured FMRI response, s(t), is a scaled and time-shifted version of the ideal response, x(t), plus additive noise, n(t). For purposes of studying brain function, it is the delay, Δt, between s(t) and r(t) that we seek to estimate. Note that in this study, m(t) is null because the reference signal was modeled without additive noise. However in the general, m(t) need not be null as in the case where r(t) is obtained from empirical measurements.

Estimation of delay

For two measured signals, r(t) and s(t), the time delay, Δt, may be estimated using the cross-correlation function, R_{rs}(τ), defined as:

\[ R_{rs}(\tau) = E[r(t)s(t + \tau)] = E[x(t)\alpha x(t + \tau - \Delta t)] \]
\[ + E[m(t)\alpha x(t + \tau - \Delta t)] + E[n(t)x(t)] \]
\[ + E[m(t)n(t)] = \alpha R_{xx}(\tau - \Delta t) + \alpha R_{mx}(\tau - \Delta t) + R_{ns}(0) + R_{mn}(0). \]

Assuming the noise components, m(t) and n(t), are mutually uncorrelated and uncorrelated with x(t), the term R_{ns}(0) = \alpha R_{mx}(\tau - \Delta t) = R_{ns}(0) = 0. Consequently, R_{rs}(\tau) is reduced to

\[ R_{rs}(\tau) = \alpha R_{xx}(\tau - \Delta t). \]  

Thus the cross-correlation function between r(t) and s(t) is reduced to a scaled and time-shifted version of the auto-correlation function of x(t). Since R_{xx}(\tau) is maximal at τ = 0, R_{rs}(\tau - \Delta t), and, consequently, R_{rs}(\tau) are maximal at τ = Δt. Thus, by determining the maximum of the cross-correlation function, we can estimate the time delay between the reference and FMRI response signals.

In FMRI studies, the cross-correlation coefficient is widely used (Bandettini et al., 1993) for detecting activated voxels. Voxels are considered activated if the correlation between their FMRI response and a reference signal exceeds a predetermined threshold. The cross-correlation coefficient function, defined by Eq. (3) and under the same assumptions used to derive Eq. (2), is maximal at τ = Δt:

\[ \rho_{rs}(\tau) = \frac{R_{rs}(\tau)}{\sqrt{R_{xx}(0)R_{ss}(0)}}. \]  

By computing the cross-correlation function and estimating the magnitude and location of its peak, we can estimate both the maximal cross-correlation coefficient and the time delay between the reference and FMRI response signals.

Given that different voxels respond to the stimulus with different response delays (Lee et al., 1995; Saad et al., 1995), the cross-correlation coefficient estimated at a single value of τ is not maximal for all voxels. As a result, the more the delay at a single voxel differs from that of the reference function, the lower is the cross-correlation coefficient estimate and the less likely the voxel is to be considered activated. To avoid such a bias in the detection of activated voxels, it is important to estimate, for each indi-
individual voxel, the maximum cross-correlation coefficient that occurs at the response delay, $\Delta t$, for that specific voxel.

In practice, the time series, $r(t)$ and $s(t)$, are discrete series defined only at integer multiples of the sampling period. Consequently, $R_{rs}(\tau)$ is also discrete; thus the true maximum of $R_{rs}(\tau)$ typically occurs between known samples and must be estimated using higher order interpolation.

The estimation of the maximum of $R_{rs}(\tau)$ and, consequently, $\Delta t$, can be simplified using the envelope function $|Z_{rs}(\tau)|$ of $R_{rs}(\tau)$ (Bendat and Piersol, 1986). The envelope function is the amplitude of the analytic function $Z_{rs}(\tau)$ defined as

$$Z_{rs}(\tau) = R_{rs}(\tau) + jH[R_{rs}(\tau)],$$

where $H[.]$ denotes Hilbert Transform. When $\tau$ equals the time delay, $\Delta t$, $|Z_{rs}(\Delta t)|$ is equal to $R_{rs}(\Delta t)$. Hence $H[R_{rs}(\Delta t)]$ is equal to 0. Thus the Hilbert Transform of the cross-correlation function goes to zero when the cross-correlation function is maximal. Therefore, finding the peak of $R_{rs}(\tau)$ reduces to finding the location of the zero-crossing of $H[R_{rs}(\tau)]$, which, in turn, involves one linear interpolation about $0$. Fig. 1 details the computationally efficient algorithm for estimating response delay and maximal voxel cross-correlation coefficient using the Hilbert Transform.

Impact of finite-duration time series

For discrete, finite-duration FMRI signals, estimation of time delay and cross-correlation coefficient using the Hilbert Transform is susceptible to error associated with the Discrete Fourier Transform (DFT), constraints on sampling FMRI time series, and noise. The delay estimate error $e$, the difference between the true delay and the estimated delay, is the resultant of noise and artifacts of the algorithm.

DFT artifacts

DFT artifacts that require correction when implementing the Hilbert-based estimate are circular convolution, the ramp bias, or “Bow-tie” effect (Bendat and Piersol, 1993), and spectral leakage. Circular convolution and Bow-tie artifacts are easily corrected for using zero-padding and Eq. (4), respectively,

$$R_{rs}(\tau) = \frac{T}{T - \tau} R_{rs}^b(\tau),$$

where $R_{rs}(\tau)$ is the corrected cross-correlation function; $R_{rs}^b(\tau)$ is the cross-correlation function with the Bow-tie artifact; $T$ is the sampling duration; and $\tau$ is the lag.

Spectral leakage

The effects of spectral leakage and Common Time Base are more difficult to reduce and require careful examination when estimating delays at a high temporal resolution. Spectral leakage arises from the use of a finite-length time window, $w(t)$, to represent a time series, $e(t)$, with an unlimited time history. The sampled time series, $x(t)$, defined over the time interval $(0 < t < T)$, is equal to the product, $w(t)e(t)$, where $w(t)$ is a rectangular function defined by $w(t) = 1$ for $(0 < t < T)$ and 0 for all other $t$. The use of such a window introduces significant amplitude and phase distortions into the Fourier Transform estimate of $e(t)$. These distortions are especially pronounced for sinusoidal and narrow band signals (Bendat and Piersol, 1993), such as FMRI time series. Moreover, noise and commonplace pre-conditioning operations such as zero-padding and removal of linear trends may further complicate spectral leakage. Spectral leakage effects can be reduced with alternate windows, such as the Hanning window or alternate spectral estimation techniques such as Multi Taper Methods (MTM) (Percival and Walden, 1993).

To illustrate the effects of spectral leakage on cross-correlation and time delay estimates, we created a set of time series that are pertinent to the experimental stimuli and data analysis commonly used in the FMRI experiments. We modeled the FMRI response with a sinusoid, having a 40 s period and a phase (delay) $\phi$. The sinusoid was sampled at 0.5 Hz for a sampling period, $T = 200$ s. This signal simulated the FMRI response to a visual stimulus having a square wave time course of the same fundamental period. In blocked design stimulation, a sinusoid model is correlated at 0.97 with the average FMRI response (Saad et al., 2001). A set of sinusoids that varied only in delay ranging from 0 to 38 s, in increments of 0.1 s, were used to represent FMRI responses at various time delays. Using the algorithm outlined in Fig. 1, we estimated the cross-correlation coefficient and time delay between each sinusoid and the reference sinusoid (time delay = 0). For each sinusoid, the leakage-induced time delay estimate error ($e_{lb}$) was computed by subtracting the estimated delay ($\Delta t$) from the true delay used to create the sinusoid. Delay estimation was performed using both rectangular and Hanning windows.

For errors and artifacts occurring in the presence of noise, we created another set of simulated FMRI responses by adding Gaussian noise to sinusoids with the same signal characteristics as described in the previous paragraph. Noise sequences were generated using Matlab’s (1999) random number generator, and each sinusoid was paired with a unique noise sequence. The signal-to-noise ratio was defined as the variance of the overall signal amplitude divided by the variance of the noise amplitude. Five hundred time series were generated at each signal-to-noise ratio (SNR) level between $-40$ and 40 dB.

Fig. 2 shows $e_{lb}$, the delay estimate error versus true delay using rectangular (dashed–dotted line) and Hanning windows (solid line). The error, $e_{lb}$, is a bias error that changes with the true delay difference between stimulus and response and with different signal types. For this reason, we express the estimate bias using both its mean and standard deviation (or variance), and we seek to minimize both aspects of error with our delay estimate. Note how $e_{lb}$ varies as a function of the true delay. For the rectangular window
Fig. 1. Flowchart for the Hilbert Transform estimate of the response delay (Δt) and cross-correlation coefficient $\rho_{rs}(\Delta t)$ between the fMRI signal $s(t)$ and the reference signal $r(t)$. From the top, RLT, removal of linear trend (*, only when present in time series); ZP 2$^{n+1}$, zero-pad to a length of 2$^{n+1}$ ($n$ is defined in (A)); $\mathcal{F}$, Fast Fourier Transform; $i\mathcal{F}$, inverse $\mathcal{F}$; *, complex conjugate; $\times$, multiplication; $R_s(\tau)$, correlation function; $S_s(f)$, power spectrum; $H[.]$, Hilbert Transform. (A) Remove the linear trend from $s(t)$ and $r(t)$. Zero-pad to a length of 2$^n$ to avoid circular convolution effects (Bendat et al., 1993) where $n$ is such that $2^{n+1} < N \leq 2^n$ and $N$ is the number of samples in $s(t)$ or $r(t)$. Compute the Fast Fourier Transform $s(f)$ and $r(f)$ of the padded series of $s(t)$ and $r(t)$, respectively. (B) Use $s(f)$ and $r(f)$ to compute the cross-power spectrum $S_{rs}(f)$ and the autospectra $S_{rr}(f)$ and $S_{ss}(f)$. (C) Inverse Fast Fourier Transform of $S_{rr}(f)$ and $S_{ss}(f)$ to obtain the autocorrelation functions $R_{rr}(t)$ and $R_{ss}(t)$ of $s(t)$ and $r(t)$, respectively. Note that $R_{ss}(0)$ and $R_{rr}(0)$ are used in Eq. (3). (D) Multiply $S_{rs}(f)$ by 2 for positive frequencies and 0 for negative frequencies. The inverse Fast Fourier Transform of the modified $S_{rs}(f)$ is a complex series having the cross-correlation function $R_{rs}^b(\tau)$ and its Hilbert Transform $H[R_{rs}^b(\tau)]$ as its real and imaginary parts, respectively. The $b$ superscript indicates the presence of the “Bow-tie” artifact in these estimated functions. (E) To remove the “Bow-tie” artifact multiply each element of $R_{rs}^b(\tau)$ and $H[R_{rs}^b(\tau)]$ by $T/(T-\tau)$, where $T$ is the sampling duration and $0 \leq \tau \leq T$. (F) Interpolate $H[R_{rs}(\Delta t)]$ around the first 0 crossing to estimate the response delay $\Delta t$ such that $H[R_{rs}(\Delta t)] = 0$. Interpolate $R_{rs}(\tau)$ around $\Delta t$ to estimate $R_{rs}(\Delta t)$. (G) Estimate the
the largest $e_{lb}$ was 0.303 s with a mean and standard deviation of 0.073 and 0.103 s, respectively. In contrast, for the Hanning window, the largest $e_{lb}$ was reduced to 0.023 s and the mean and standard deviations were reduced to 0.006 and 0.003 s, respectively. Note that the spectral leakage artifacts are due to basic DFT operations and not the other steps in the HT algorithm. Ideally, to reduce the effect of spectral leakage on correlation functions, the time interval over which a signal is sampled should be lengthened.

While the Hanning window reduces spectral leakage effects on delay estimates, it also reduces the contribution of the data that lie at the ends of the window to the estimate of cross-correlation and time delay. This reduced contribution is akin to a loss of information, which results in more delay estimate variance in the presence of noise. Given the imminent presence of noise in FMRI time series, it is important to consider the confounding effects of noise on time delay estimates obtained via the Hanning window. Spectral leakage can be reduced with MTM without necessarily increasing the variance of spectral estimates. However, MTM requires more computation and does not reduce the Common Time Base errors, which we discuss in the next section.

Common Time Base

Constraints on sampling the FMRI data introduce a bias to the cross-correlation coefficient and result in an increased variance in the time delay estimates. This bias occurs when both the reference time series and the delayed FMRI response are sampled over a common time period. For voxels with long response delays, the Common Time Base\(^1\) introduces noise to the cross correlation estimate because the FMRI response exhibits no signal (only noise) until a time $t$ equal to the delay between the stimulus and the response. Fig. 3 illustrates this problem. The larger the delay with respect to the sampling period $T$, the larger the bias error in the cross correlation estimates and the variance of estimated delays. Note that Common Time Base errors occur only when noise is present in the signals. The correlation coefficient bias can be corrected for white noise stimuli using equations developed in Seybert and Hamilton (1978) and Schmidt (1985); however, these equations are inadequate for the narrow bandwidth signals obtained in FMRI and they do not reduce the variance of the delay estimate.

Another method for correcting Common Time Base errors consists of shifting the two time series by the estimated time delay and reestimating the correlation and delay between the two shifted signals. By shifting the two time series to reduce the Common Time Base error, we also reduce the spectral leakage errors since the delay difference and, consequently, the leakage-induced errors $e_{lb}$ are minimized. This requires the estimation of the delay between reference and FMRI time series and the shifting of the time series to bring them in temporal alignment before a new estimate of the delay difference is obtained. For discrete-time reference and FMRI time series, shifting can be performed by discarding samples at the beginning of the reference time series and samples at the end of the FMRI time series. The iterative Shifted Time Base algorithm shown in Fig. 4 illustrates how response delay estimates can be obtained with minimal Common Time Base errors and spectral leakage artifacts without windowing.\(^1\)

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1 In the signal processing literature, Common Time Base is termed time delay bias. Since this bias affects the cross-correlation coefficient, we changed its appellation to avoid confusion with the bias error of the time delay estimate ($\Delta t$) that is introduced by spectral leakage artifacts.
Onset estimator: comparison to Phase estimator

Recently, a response delay estimator using only the onset time of the rising phase of the FMRI response, \( s(t) \), has been proposed to yield less variability than a delay estimator using the entire FMRI response such as the Hilbert transform estimator. The differences in variability between the two estimators are thought to be of physiologic nature, possibly due to nonstationarity in the latter part of the neuronal or FMRI response. However, the methodologies of the two estimators are different and may not be equally sensitive to noise. The effects of estimator methodology on the variability of the delay estimate were investigated using both simulated and empirical data.

The Onset estimator fits a line to the data points in the rising edge of the FMRI response. The response delay is then determined from the intersection between the fitted line and the baseline that precedes the rising edge. The rising phase of the FMRI response is defined by those sampled data points with amplitude between 20 and 80% of the peak.
amplitude in the response. The estimated FMRI delay is defined as the intercept between the baseline and a straight line fit to the rising phase.

**Simulated data**

The contribution of estimate methodology to the variability in estimated response delay, \( \Delta t \), was investigated with simulated FMRI time series shown in Fig. 5. The simulated FMRI signals consisted of an ideal FMRI response with additive white noise. Fig. 5A shows the ideal (no noise) FMRI response modeled as a 2-s square pulse (ON period) followed by a 25-s baseline (OFF period) convolved in entirety with a gamma variate function (Cohen, 1997). The gamma variate function is an estimate of the linear, time-invariant response of FMRI to a visual stimulus activated by the visual stimulus, we estimated the cross-correlation coefficient between each voxel time series and the reference time series shown in Fig. 6 (dashed). The reference time series were generated by convolving the time course of the stimulus (square wave, dashed–dotted) with the gamma-variate function (Cohen, 1997). The cross-correlation coefficient threshold for detecting activated voxels was 0.23, which has a significance level of \( P < 0.0001 \) (with correction for repeated sampling (Johnson et al., 1992)). The cross-correlation coefficient along with the response delay, between the reference time series and the FMRI response, was computed using the Hilbert Transform algorithm. To be consistent with the delay estimation methods reported by Menon et al. (1998), we retained only those

![Fig. 5. Creation of simulated FMRI responses. (A) Convolve Stimulus Time Course (gray) with gamma variate function representing the FMRI transfer function to obtain an ideal FMRI response (solid). (B) Add white noise to create simulated FMRI response (black) and filtered FMRI response with FIR filter (1/27 Hz–4/27 Hz) to create \( s(t) \) (gray).](image-url)
FMRI responses that were delayed by no more than 5 s with respect to the reference time series. Note that when comparing results across scans of different ON periods, we retained only the voxels that were activated in all scans. The activated voxels were split into two pools of left and right occipital cortex according to their location. Time series from activated voxels were bandpass-filtered bidirectionally using the same filter applied to the simulated time series. For each of the left and right voxel pools, the activated time series were filtered and averaged together, and the linear trend was removed. The average time series were split into 11 epochs (one for each stimulus presentation). For each epoch, the Onset and Phase estimators were used to estimate the FMRI response delay. The variance for a specific delay estimator was obtained from the delay estimates from all 11 epochs.

Results

Shifted Time Base and leakage corrected Hilbert delay estimates

In the absence of noise, the spectral leakage error is effectively the bias error of the time delay estimate. The use of the Shifted Time Base method reduced this error to a mean of −0.005 s and a standard deviation of 0.009 s. This bias error is practically null when compared to the sampling period of 2 s. Fig. 7 summarizes the reduction in spectral leakage and Common Time Base errors that results from the Shifted Time Base correction and the Hanning window modification for signals of varying SNR. The dotted curve shows the variability of estimated response delays due to both leakage-induced and Common Time Base errors. The gold standard for examining the variance in estimated delay as a function SNR, referred to as “Noise Only,” is represented here by the square markers. Noise Only time series were generated with a constant phase and an identical time base; thus the variance of the delay estimator was due to the presence of noise alone and not algorithm artifacts. Results from delay estimation without the Shifted Time Base correction are represented with the dashed line for the rectangular window and the solid line for the Hanning window. Results using Shifted Time Base corrections are shown with the circular markers. For SNR > 15 dB, the Hanning window produced less variance in \( \varepsilon \) than the rectangular window. However, for SNR less than 15 dB, the Hanning window actually resulted in more variance in the delay estimate than the rectangular window. This difference illustrates the trade-off that occurs between leakage-induced errors and noise-induced errors when a Hanning window is used. Note how the use of a rectangular window with no correction for leakage or Common Time Base resulted in the highest variance of the delay estimation methods over all SNR levels.

Phase versus Onset delay estimator

Simulated data

As illustrated in Fig. 8, the variance in the estimated response delays using the Onset method was consistently and significantly \((P < 0.001)\) larger than the variance obtained using the Phase method. The inset is an enlargement
of the graph corresponding to an SNR range between 40 and
−5 dB. The ratio of the variances of the two estimators
increased nonlinearly with decreasing SNR. This indicates
that the variance of the Onset estimator increases at a faster
rate than the variance of the Phase estimator.

**Empirical data**

For each length of stimulus ON period, Fig. 6 shows the
stimulus time course (dashed–dotted), the ideal FMRI re-
sponse and the filtered, average, measured FMRI response
across voxels activated at all ON periods. Recall that the
ideal response is obtained by convolving a rectangular wave
(dashed–dotted, representing stimulus time course) with a
gamma variate function. Note that for all ON periods, the
ideal response (dashed) is narrower than the response ob-
served experimentally (solid). The same discrepancy be-
tween the empirical FMRI response and the predicted re-
sponse using a linear model was reported by Vasquez and
Noll (1998), who report nonlinear FMRI responses to short
ON periods.

For each length of stimulus ON period, the average
FMRI time series was divided into 11 consecutive epochs
(one for each stimulus presentation) and the response delay
of each epoch was estimated using each of the Phase and
Onset estimators. Assuming that the true response delay to
each of the 11 stimuli is fixed from one stimulus presenta-
tion to the next, this analysis allows us to compare the
variability in delay estimate from both methodologies.

Fig. 9 illustrates, for one subject and an ON period of 2 s,
the delay variance for each estimator and for each of the 11
ON–OFF epochs. Each row shows, in black, one of the 11
epochs of the average FMRI response. Shown in gray is the
reference time series used by the Phase estimator. The
dashed lines show the straight line fit to the rising edge of
the FMRI response used by the Onset estimator, and the
plus symbol indicates the intercept between the straight line
and the preceding baseline. The numbers and corresponding
bars on the left side of the graph illustrate the difference
between the delay estimate for each individual epoch and
the mean delay computed from all epochs. The bars graph-
ically represent the variability of each of the delay estima-
tors. Note how the Onset estimator (black) varies more than
the Phase estimator (gray).

Fig. 10 summarizes the results from three subjects. The
graph on the left shows the variance of FMRI delay for the
Onset estimator (gray) and the Phase estimator (black) as a
function of stimulus ON period. The right graph is an
enlargement of that portion of the left graph corresponding
to FMRI delay variance between 0 and 2.5 s². The symbols
codify the three subjects used in the study and the solid lines
connect the mean variance for each estimator computed
across subjects. Note that the delay variance obtained with
the Phase estimator is significantly smaller ($t$ test, $P <
tor was significant across subjects and ON periods. In the bottom graph, the delay estimate variance for the Phase estimator decreased significantly than that obtained with the Onset estimator. Moreover, as indicated on the left graph, the delay estimate variance is less consistent for the Onset estimator than the Phase estimator. For the Onset estimator, the variance changed significantly (f test, $P < 0.001$) between subjects and between ON period duration. Conversely, as seen on the bottom graph, that delay estimate variance for the Phase estimator is more consistent across subjects and ON periods.

For ON periods of 2 s, the variance of the Phase estimator was significantly smaller than the variance of the Onset estimator (f test, $P < 0.001$). The delay variance for the Phase estimator decreased significantly (f test, $P < 0.001$) with longer duration ON periods. The smallest delay variance of 0.20 s$^2$ (average across subjects 0.29 s$^2$) was obtained with the Phase estimator and an ON period of 14 s. With such small variance, delay changes of 100 ms are detectable on a voxel-wise basis ($P < 0.01, N = 60$). In contrast, the variance of the Onset estimator increased with longer duration ON periods because of increasing variance in the baseline estimate.

**Discussion**

We proposed a computationally efficient algorithm, using the Hilbert Transform, to simultaneously detect activated voxels and estimate, with high temporal resolution, their response delays with respect to a reference time series. The model assumes that the signal is a scaled and time-shifted version of the reference signal and noise. The delay is estimated from all of the signals’ spectral components instead of only the phase of the response’s fundamental frequency (Sereno et al., 1995). Furthermore, the algorithm directly estimates the delay difference $\Delta t$ between reference and FMRI signals rather than a first-order approximation of it (Henson et al., 2002). In addition to estimating delay and cross-correlation coefficient, the algorithm estimates the covariance between the FMRI response signal and the reference time series. The covariance is a measure of the linear association between the reference time series and the FMRI signal (Johnson and Wichern, 1992). In the event that the FMRI response is different from the reference model, the covariance, cross-correlation coefficient and delay represent the best linear fit of the response, in the least square sense, to the reference time series (Bendat and Piersol, 1986). This may result in a biased delay estimate, which would affect estimates of delay differences across voxels with differing BOLD response characteristics. For such cases, computationally expensive models that allow for both response width and delay estimation should be used (Kruggel and von Cramon, 1999; Miezin et al., 2000).

We have demonstrated that both noise and spectral leakage impact time delay estimates when using the Hilbert method or other techniques requiring DFT operations. It is important to note that filtering the FMRI time series does not affect the impact of noise on the variability of the delay estimates obtained via the Hilbert Transform. This lack of effect is attributed to the inherent filtering that occurs when using the cross correlation function to estimate time delays. Only frequency components that are common to both the reference time series and the empirical FMRI signal will contribute to the cross correlation function that is used to estimate the response delay. Thus choosing a reference time series with little or no noise is akin to filtering the FMRI signal prior to cross correlation estimation.

**Common Time Base and spectral leakage correction**

Because the Hilbert estimator relies on the DFT, the estimation of delays in the FMRI response is subject to spectral leakage and Common Time Base artifacts. These artifacts introduce bias and variance to the estimates of the response delay between reference time series and FMRI response. Consequently, the variance in delay estimates is increased at all SNR levels. However, the increases are most noticeable at higher SNR, where errors from these artifacts exceed errors caused by noise alone. Thus it is imperative to consider spectral leakage and Common Time Base artifacts when high-resolution response delay estimates with minimal bias and variance are required. Such requirements arise in FMRI when estimating delays of averaged FMRI responses.

To reduce leakage-induced artifacts on the delay estimate, we used windowing and Shifted Time Base corrections. We found that windowing reduced the leakage artifacts; however, it increased the sensitivity of the delay estimates to noise. Conversely, Shifted Time Base correction methods reduced leakage errors without increasing the estimate’s sensitivity to noise. The Shifted Time Base correction requires no separate analysis of the reference time series and is easily applied to all types of time series. Furthermore, the Shifted Time Base method reduces Com-
mon Time Base errors in both delay and cross-correlation estimates.

**Phase and Onset delay estimators**

It has been proposed (Menon et al., 1998) that the latter part of the BOLD response is more variable than its onset. Larger variance in the postonset response could be neuronal, cognitive, or hemodynamic in origin. For example, fluctuations in the subject’s attention during the ON period of a stimulus would introduce larger variability in the latter parts of the BOLD response and that variability might also differ across multiple presentations of the same stimulus. If such a postonset variability is large enough, it is possible that the Phase estimator, which uses the entire FMRI response, exhibits higher variance than the Onset estimator, which only uses the rising portion of the FMRI response. However, since the Onset estimator utilizes a portion of the time series, and consequently less information, its variance could be larger than that of the Phase estimator despite postonset variability.

For the empirical data used in this study, with time courses mimicking those used by Menon et al. (1998), we found that the Onset estimator yielded more variance than the Phase estimator. Moreover, for longer duration ON periods, the variance of the Phase estimator decreased or remained constant. This observation contradicts the notion that increased variability is present in the plateau and descent stages (or phases) of the FMRI response. For longer duration ON periods, where variability in the plateau and descent stages may be more pronounced, one would expect more variability in the delay estimates obtained with the Phase estimator. For our data, the delay variance for the Phase estimator decreased with increasing stimulus ON period. This was the result of an increase in FMRI signal amplitude, and consequently SNR, with longer ON periods. This increase in SNR resulted in less delay estimate variance because of the relative decrease of noise contribution.

We conclude that in contrast to the Onset estimator, the Phase estimator is consistent and less sensitive to noise. Thus, one needs to carefully consider whether the postonset variability, if any, in the FMRI response warrants the use of the Onset estimator instead of the Phase estimator. Moreover, experimental protocol permitting, the use of longer duration ON periods is recommended as SNR is increased, and consequently variance in the delay estimate is reduced.

**References**


