Measuring temporal dynamics of functional networks using phase spectrum of fMRI data

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Introduction

Functional magnetic resonance imaging (fMRI) is a promising tool for studying neural networks because it provides researchers with the ability to image whole-brain activity with a fine spatial resolution (~3 mm, Kim et al., 1999). While the predominant method of analysis for fMRI data has been to identify which brain regions are involved in the performance of a specific task, researchers have recently begun to take advantage of the multivariate structure of fMRI data to monitor how brain regions interact to perform a task. One way to characterize these interactions is through the temporal correlation or coherence between regions. These types of interactions are referred to as functional connectivity. In a recent paper (Sun et al., 2004), we presented a spectral method using coherence of fMRI data to investigate functional connectivity. Here, we extend the method to detect relative latency differences between interacting regions.

The standard method of analysis of fMRI data is to estimate the relationship between the signal in each spatial subunit (voxel) and a reference function, which is based on the stimulus paradigm. This parameter estimate indicates the amount of task-related activity in each voxel. Statistical parametric maps for the entire brain volume are generated in this way by estimating the activity independently for each voxel. While there is often an implicit assumption that brain regions interact during the performance of a task, this method provides no means of measuring their relationship and therefore cannot provide a direct statistical measure of the inter-regional interactions. Moreover, this method is highly dependent on the reference function, which assumes a specific shape and timing of the hemodynamic response.

In an earlier paper, we presented a method to address these shortcomings using coherence, the magnitude component of coherency, which is a spectral measure of the linear time-invariant relationship between regions. We demonstrated that in this application, coherence is superior to correlation because correlation is sensitive to shape and temporal shift differences in the hemodynamic response, while coherence is invariant in these differences. Additionally, because coherence does not require a reference function or model of the response, the method can be extended to many types of experimental paradigms, including those with no specific stimuli, such as rest periods and delay periods. Here, we build upon the method and demonstrate how the phase-delay, derived from the phase component of coherency, can be used to investigate shifts in activation timing between regions. Measuring these temporal delays between regions is an important component in determining how regions within a network interact and
for providing valuable information about the sequence of cognitive processes within a network (Formisano and Goebel, 2003). Combined, coherence and phase-delay can be used to estimate the degree of linear relation and the relative difference in latency between brain regions.

In this paper, we apply these methods to fMRI data acquired during the performance of a bimanual task and during fixation to examine how the inter-regional dynamics of the motor network change between task and rest. During the task period, subjects are visually cued to execute a sequence of key presses that alternate between the left and right hands. The distributed network of motor cortical regions considered to be highly involved in such bimanual tasks includes the primary sensorimotor cortex (SI/M1), the dorsal premotor cortex (PMd), the supplementary motor area (SMA), and the posterior parietal cortex (PPC) (for a review, see Swinnen, 2002). During the rest phase, subjects are asked to maintain fixation and refrain from practicing or rehearsing motor sequences. While there are no "activations" during the rest period, fMRI studies have examined a distributed network of motor regions coupled to the primary motor cortex at rest. This network, similar to the network during task, includes M1 (contralateral to the reference region), SMA, and PMd (Biswal et al., 1995; Xiong et al., 1999).

While previous imaging and lesion studies have provided substantial information about each region’s functionality in the motor network, the inter-regional interactions, in particular the temporal dynamics of the network, are not well understood. The most extensively studied temporal relationship within the motor network has been between the SMA and M1. Previous imaging and electrophysiology studies have consistently shown that the activity in the SMA increases prior to the activity in M1 during the execution of a motor task (Ikeda et al., 1992; Kansaku et al., 1998; Menon et al., 1998; Weilke et al., 2001). However, little is known about the interactions between any other nodes in the network during task or how the temporal dynamics compare to that of the network during rest. Using the methods described above, we measure the functional coupling and temporal latencies of all regions in the motor network with the SMA as a reference region.

A number of studies have suggested that the SMA may play a central role in coordinating the motor network during the execution of this task. Electrophysiology and neuroimaging studies have shown that the SMA is highly active in tasks that require bimanual coordination, movement preparation, and motor sequencing (Roland et al., 1980; Kazennikov et al., 1999; Stephan et al., 1999a; Lee and Quessy, 2003). In addition, lesion studies have shown that bimanual coordination, particularly the temporal coordination between the left and right hands, is impaired in subjects with lesions that affect the SMA (Laplane et al., 1977; Halsband et al., 1993; Stephan et al., 1999b). Thus, by selecting the SMA as a reference region, we can compare our findings to previous measures of the SMA–M1 latency and gain insight in the dynamics of the bimanual network.

**Methods**

**Coherency**

**Magnitude and phase**

Coherency, a measure of the linear time-invariant relationship between two time-series, is a complex-valued function of frequency. The coherency, $R$, of time-series, $x$ and $y$, is defined as:

$$R_{xy}(\lambda) = \frac{f_{xy}(\lambda)}{\sqrt{f_{xx}(\lambda) f_{yy}(\lambda)}}.$$  (1)

where $f_{xy}(\lambda)$ is the cross-spectrum of $x$ and $y$ at frequency $\lambda$, and $f_{xx}(\lambda)$ and $f_{yy}(\lambda)$ are the respective power-spectra of $x$ and $y$ (Brillinger, 2001). In order to investigate specific features of the linear time-invariant relationship, we decompose the coherency function into its magnitude and phase components.

From the magnitude component of coherency, we derive coherence, which is a measure of the linear association between two time-series. The coherence, $Coh$, of $x$ and $y$ is defined as:

$$Coh_{xy}(\lambda) = \left| R_{xy}(\lambda) \right|^2 = \frac{|f_{xy}(\lambda)|^2}{f_{xx}(\lambda) f_{yy}(\lambda)}.$$  (2)

This real-valued function of frequency is bounded by 0 and 1, where 0 indicates that the two time-series have no linear relationship, and 1 indicates that one time-series can perfectly predict the other in a linear fashion. Note that the use of prediction here is not limited to causal prediction. In this case, prediction can be forward and/or backward.

From the phase component of coherency, we derive the phase-spectrum, which can be used to determine the relative timing between two coherent time-series. The phase-spectrum, $\phi$, is defined as:

$$\phi(\lambda) = \arg\{R_{xy}(\lambda)\} = \arg\{f_{xy}(\lambda)\},$$  (3)

where $\arg\{ \}$ represents the argument. The group delay, $\tau(\lambda)$, which is a measure of the linear delay between two time-series is defined to be proportional to the derivative of the phase-spectrum:

$$2\pi \tau(\lambda) = -\frac{d}{d\lambda} \phi(\lambda).$$  (4)

Thus, for a frequency band of interest, we can estimate a linear phase-delay as the average slope of the phase-spectrum within the band.

In summary, we extract two real-valued functions, coherence and phase-delay, from the magnitude and phase components of coherency. Coherence measures how well one time-series predicts another and phase-delay estimates the temporal lead or lag between them.

**Estimation**

To apply these spectral measures to fMRI data, we limit the frequencies of interest to those contained in the power-spectrum of the hemodynamic response, typically (0–0.15 Hz) (Aguirre et al., 1997; Sun et al., 2004). This band of frequencies enables us to measure the linear coupling and delay for a wide range of hemodynamic shapes, not just for the canonical HRF. The estimation of the band-averaged coherency was presented in Sun et al. (2004) and is summarized in Appendix A of this paper. Here, we present the estimation of the phase-delay from the phase-spectrum. From Eq. (3), we see that the phase-spectrum is simply the argument of the cross-spectrum. In order to minimize variance of the estimate, we find the cross-spectrum using Welch’s periodogram averaging method (see Appendix A). The phase-spectrum estimate is then simply the phase of the cross-spectrum estimate. The phase-delay is estimated by calculating...
the average slope of the unwrapped phase-spectrum. This can be described as:

$$\hat{\tau} = -\frac{1}{2\pi} \int_{\lambda_1}^{\lambda_2} \frac{d \varphi(\lambda)}{d \lambda} d\lambda,$$

which reduces to

$$\hat{\tau} = -\frac{1}{2\pi} \frac{\varphi(\lambda_2) - \varphi(\lambda_1)}{\lambda_2 - \lambda_1}.$$

In our example, we choose $\lambda_1 = 0$, and due to the mean centering of the time-series, $\varphi(\lambda_1)$ is also restricted to zero. Thus,

$$\hat{\tau} = -\frac{1}{2\pi} \varphi(\lambda_2),$$

which can be estimated by

$$\hat{\tau} = -\frac{1}{2\pi} \sum_{i} \varphi(i),$$

(choosing $i$ such that $\lambda_i$ is within the frequency band of interest) such that the estimate error is minimized.

In order to determine the goodness of the phase-delay estimate, we calculate the root mean squared error (RMSE) or residual, the most common evaluation for an estimated linear fit. The error in RMSE is defined to be the difference between the phase-spectrum values and the line whose slope was derived by Eq. (8) (Fig. 1D, shaded region). For a given false positive rate (alpha), NFFT, and frequency band, the confidence interval of the phase-delay estimate is proportional to the RMSE (Draper and Smith, 1981).

Notably, because the segments used in Welch’s periodogram-averaging method are mean centered, the value of the phase-spectrum at $\lambda = 0$ is defined to be either zero or $\pi$. Theoretically, the value is $\pi$ if one time-series is the inverse of the other – however, in practice, the value may flip due to noise in the signal. Therefore, in order to determine the most likely value at 0 Hz, we estimate the slope using both 0 and $\pi$ as values of the phase-spectrum at 0 Hz and select the value that results in the smallest RMSE for the estimate of the slope.

In Fig. 1, we present an example of these measures using simulated fMRI data. A model fMRI signal was generated by convolving an impulse train with the canonical hemodynamic response function (Josephs et al., 1997). This time-series was then replicated, and a delay of 1 s was introduced to one of the time-series (Fig. 1A). Independent Gaussian noise was added to both time-series, resulting in the two time-series displayed in Fig. 1B. Fig. 1C presents the coherence function of these two time-series. Because the hemodynamic response function only has power in the low-frequency band, we focus our analysis on the 0–0.15 Hz band (the shaded region in Figs. 1C and D). Within this band of frequencies, the coherence value is high, indicating that there is a linear relationship between the signals. The low coherence values in higher frequencies are due to the added noise, which spans all frequencies and is independent across the two time-series. Fig. 1D presents the unwrapped phase-spectrum. The phase within the low-frequency range exhibits a roughly linear relationship with frequency. The slope of the fitted line is the estimate of the linear phase-delay for the low-frequency range. Here, the slope is calculated to be .9954 s for a true delay of 1 s, and the RMSE of the fit is 0.0805, which results in a 95% confidence interval of ± 0.11 s.
Experimental methods

Subjects
Fourteen right-handed subjects (4 female; ages 19–29 years; mean age = 23.5) participated after giving informed consent according to procedures approved by the University of California. The subjects reported no history of neurological or psychiatric disorders and were taking no medications at the time of the study.

Experimental paradigm
In the MRI scanner, five 8-min functional runs were acquired for each subject using a mixed block/event-related paradigm (Visscher et al., 2003). The runs were composed of 4 types of condition blocks, each presented twice in a pseudorandom order. The condition types were a rest condition and three types of sequence conditions: “novel”, “learned”, and “random”. The “random” condition is presented in this report as the task condition. For each of the sequence blocks, five novel 8-item sequences were presented to the subject; sequences were separated with a pseudorandomized inter-trial interval (ITI) of 2.2, 4.4, or 6.6 s for a total block length of 58 s.

For each sequence, a series of eight consecutive visual cues were presented for a duration 725 ms each, resulting in a total sequence time of 5800 ms. Subjects were instructed to respond to each visual cue with the corresponding key within the time of the cue presentation (see Fig. 2). During the rest block, also of length 58 s, subjects were presented with a centered fixation cross. For this condition, subjects were instructed not to perform or rehearse any of the sequences. In total, there were 10 task blocks and 10 rest blocks, which result in 580 s per condition (Fig. 2).

Stimulus presentation
The stimuli were designed and presented using Eprime presentation software (http://www.pstnet.com). They were then back-projected onto a custom-designed non-magnetic projection screen that the subject viewed via a mirror. Responses were collected using a pair of five-fingered MR-compatible keyboards.

MRI data acquisition
All images were acquired with a 4 T Varian INOVA MR scanner (http://www.varianinc.com) and a TEM send-and-receive RF head coil (http://www.mrinstruments.com). Functional images were acquired using a 2-shot gradient-echo echo-planar image (GE-EPI) sequence with a repetition time (TR) of 543 ms per half k-space, an echo time of 28 ms, and flip angle of 20°, resulting in 432 total volumes acquired per run (864 after time-interpolation). Each volume, covering the top of the brain, consisted of ten 5-mm-thick axial slices with a 0.5 mm inter-slice gap. Each slice was acquired with a 22.4 cm² field of view with a 64 × 64 matrix size, resulting in an in-plane resolution of 3.5 × 3.5 mm. High resolution (.875 × .875 mm) in-plane T1-weighted anatomical images were also acquired using a gradient-echo multi-slice (GEMS) sequence for anatomical localization. Finally, MPFlash 3D T1-weighted scans were acquired so that functional data could be normalized to the Montreal Neurological Institute (MNI) atlas space.

![Experimental Design](image-url)  
Fig. 2. Task diagram. Sequences were presented to subjects using visual cues (see inset labeled Sequence Presentation). The stimuli were presented using four possible cue positions on either side of the fixation cross for a total of eight possible positions. Here, the horizontal dashes (‘_’) are placeholders representing finger position. During the sequence presentation, an ‘x’ appears in place of a dash, indicating to the subject the key to press. The ‘x’ changes position every 725 ms, for a total of eight different keys per sequence. During scanning, subjects are presented with five sequences per block, separated by an ITI of 2200, 4400, or 6600 ms. An example of the task condition is diagrammed. During the rest condition, a fixation cross was presented for the duration of the block. Two blocks of each sequence condition and two blocks of rest were presented in a pseudorandom order during each run.
MRI data analyses

Preprocessing. Functional images acquired from the scanner were reconstructed from k-space using a linear time-interpolation algorithm across shots of equal ordinal rank to double the effective sampling rate and corrected for slice-timing skew using temporal sinc-interpolation. Images were then corrected for movement using rigid-body transformation parameters and smoothed with an 8 mm full width at half maximum (FWHM) Gaussian kernel using SPM2 (http://www.fil.ion.ucl.ac.uk/spm).

Univariate analyses. Standard univariate analyses were performed to identify regions with high task-related activity. To model task-related activity, we used the canonical hemodynamic response function (HRF) (Josephs et al., 1997) convolved with independent variables for the onset and duration of each sequence. Here, the duration of each sequence was modeled as an epoch of 5800 ms. These covariates were entered into the modified general linear model for analysis. Parameter estimates, reflecting the percent signal change relative to baseline, were estimated for each covariate. T statistics of the parameter estimates were used to functionally identify the reference region and the regions of interest for the coherency analysis. All voxels selected for the reference region and regions of interest surpassed a threshold of $P < .05$, corrected for multiple comparisons using family-wise error (Nichols and Hayasaka, 2003).

Coherency magnitude and phase analysis. To identify networks of functional connectivity, we generated coherence, phase-delay, and residual (RMSE) maps by calculating the task-specific coherency between a reference seed located within the SMA and residual (RMSE) maps by calculating the task-specific estimate of the band-averaged coherence within the 0–0.15 Hz band (Sun et al., 2004). See Appendix A for a review of these estimates.

For each subject and each condition, we calculated a coherency magnitude map, phase-delay map, and residual map using a reference seed within the SMA. Examples of these maps are shown for a representative subject in Fig. 3. For the coherence map (Figs. 3A, D), high values (shown in yellow) represent regions that are functionally connected to the reference region. For this representative subject, the coherence map during the rest condition (Fig. 3A) reveals a network of regions highly coupled with the SMA; these include predominantly the medial frontal regions and precentral sulcus, anteriorly to the mid-line between the central and post-central sulcus, and dorsally and ventrally to include the primary motor hand area (Yousry et al., 1997). The dorsal PM mask extended from the mid-line between the central and precentral sulcus, anteriorly to the mid-line between the central and post-central sulcus, and dorsally and ventrally to include the primary motor hand area (Yousry et al., 1997). The PPC mask included cortex in the superior parietal lobe posterior to and inclusive of the post-central sulcus, and the cortex adjacent to and inclusive of the intraparietal sulcus at the junction of the two sulci (Simon et al., 2002). All masks were non-overlapping. Within each masked region, ROIs (for both the right and left hemispheres) were identified as the most significant voxel (based on univariate statistics) and all surrounding significant voxels within a 6 mm radius.

Results

Single subject example: coherence, phase-delay, and residual maps

For each subject and each condition, we calculated a coherency magnitude map, phase-delay map, and residual map using a reference seed within the SMA. Examples of these maps are shown for a representative subject in Fig. 3. For the coherence map (Figs. 3A, D), high values (shown in yellow) represent regions that are functionally connected to the reference region. For this representative subject, the coherence map during the rest condition (Fig. 3A) reveals a network of regions highly coupled with the SMA; these include predominantly the medial frontal regions and bilateral M1, but also bilateral PMd and PPC. During the task period (Fig. 3D), the network of regions highly coupled with the SMA is similar to those in the rest network; however, there are higher coherence values in the PPC along the intraparietal sulcus.

The phase-delay maps indicate the relative latency between the seed region and all other regions. On this map, blue indicates regions that are active prior to the seed, and red indicates regions that lag the seed. Note that the phase-delay map is based on a bivariate measure and therefore cannot be used to specify an ordering between two non-seed regions. Here, regions that have a 95% confidence interval of less than $\pm 0.5$ s are outlined in white. These confidence intervals are derived from the RMSE values displayed in the residual maps (Figs. 3C, F) (see Coherency section for details). High RMSE values (shown in yellow) indicate that the relationship between the reference voxel and the region is not...
modeled well by a linear delay, and therefore the estimation of the phase-delay is characterized by high variance. For this subject, during the rest condition (Fig. 3B), the right M1, bilateral PMd, right PPC, and precuneus (PreCu) lag the SMA, while the left M1 leads the SMA. In contrast, during the task condition, most regions in the motor network, including bilateral M1, bilateral PMd, and bilateral PPC lag the SMA, with a region in the left ventral PM leading the seed.

During the task condition, it is also possible to obtain the trial-averaged response for each region. From the phase-delay map (Fig. 4A), we selected voxels in the lPM (2), lM1 (3), and lPPC (4) that have increasing latency with respect to the SMA (1). The trial-averaged time-series for these regions (Fig. 4B) reflect these delays. We also chose a region in the right ventral PM (5) with a negative phase-delay (that is, region (5) leads region (1)). This lead is also reflected in the trial-averaged time-series. These trial-averaged responses illustrate that the phase-delay measure is less sensitive to differences in the shape of the response that may affect other latency measures such as time-to-peak, or onset (see for example time-series (2) and (3), which have similar peak times yet consistently delayed time-courses over their duration).

Group analysis: map-wise

In order to determine whether the phase-delays were consistent across subjects, we examined the group-averaged phase maps for both the task and rest conditions (Fig. 5). During the rest condition, regions that lag the SMA include the middle frontal gyrus, superior frontal gyrus, precuneus, inferior parietal lobule, and right precentral and post-central gyri (Fig. 5A). In contrast, during the task condition, we find that regions with a high latency with respect to the SMA were motor and premotor regions, as well as the frontal eye fields. Additionally, we find that left prefrontal regions lead the SMA in activity during task (Fig. 5B).

To quantify differences in the phase-delay between the task period and the rest period, we contrasted the phase-delay maps, using a nonparametric random-effects group analysis, with a threshold of $P < 0.05$, corrected for multiple comparisons (FWE). A nonparametric method is used here because the null distribution of the phase-delay values is unknown. Regions that have a
significant difference in the relative latency with the SMA across conditions are the left M1 ([44 – 18 64] MNI), the left middle frontal gyrus ([26 – 16 62] MNI), and medial superior frontal gyrus ([2 40 58] MNI). A change in latency suggests that the timing of information flow differs from rest to task. Fig. 6 shows the statistical map with a threshold of $P < .005$ (uncorrected) to present the significant regions as well as other regions that follow the same trend. The red indicates that the relative latency with SMA was greater during task than during rest. These regions include the left M1, left PMd, and bilateral PPC. Blue regions are those that have a decreased latency with SMA during task compared to rest. These regions include left middle frontal and superior frontal gyrus, the paracentral lobule and the left superior parietal lobule.

Group analysis: ROIs

In order to investigate the interactions between the SMA and specific nodes of the motor network, regions of interest (ROIs) were selected and defined a priori. These ROIs were located in bilateral S1/M1, bilateral PMd, and bilateral PPC. The coherency magnitude and phase-delay values for these regions are shown in Fig. 7. While all ROIs have significant coherence with SMA at rest, in all regions of interest, the coherency magnitude was significantly greater during task than at rest. The bar graph of phase-delays shows that delays also differ between task and rest. Specifically, the latency from SMA to the left PM, left M1, and bilateral PPC is significantly increased during task compared to rest. The phase-delay bar graph also reveals a trend from anterior to posterior regions during task. That is, the latency from SMA increases from PM to M1 to PPC. The group trial-averaged time-series for these ROIs, showing the same trend, are plotted in Fig. 7B.

Discussion

We have presented a novel method for evaluating the temporal relationship between functionally connected regions using phase-delay, a measure derived from the phase component of coherency. This bivariate spectral measure, in conjunction with the coherence, allows one to detect the linear relationship and to estimate the linear delay between regions. We applied these methods to functional imaging data acquired while subjects performed a motor task and during fixation to investigate the temporal dynamics of the same cortical motor network during task and at rest.

Phase-delay as a measure of network dynamics

The phase component of coherency was initially introduced to the neuroimaging field as a method to measure temporal properties
of highly localized regions for a periodic block design (Muller et al., 2003). Here, we extend this method to investigate latencies across a network of regions and to incorporate a variety of experimental designs beyond periodic designs. While there have been a number of other reported methods to measure the delay of the fMRI response (Menon et al., 1998; Rajapakse et al., 1998; Liao et al., 2002; Saad et al., 2003), phase-delay differs from these methods in several important ways. First, the phase-spectrum measures the overall linear delay between regions and is therefore not dependent on a specific feature of the hemodynamic response such as onset or time-to-peak. Because this measure takes into account the entire time-series and not just a small portion of the time-series, it may be less susceptible to noise (see also Saad et al., 2003). Other methods depend upon a model of the hemodynamic response function (HRF) (Rajapakse et al., 1998; Liao et al., 2002; Saad et al., 2003). Since the HRF has been shown to be highly variable across subjects and regions (Aguirre et al., 1998; Handwerker et al., 2004), estimated delays would be dependant

Fig. 6. Group statistical maps. These group statistical maps are generated by contrasting the task and rest delay maps. Red/yellow regions are those that have an increased latency (with respect to SMA) during the task period compared to the rest period. Blue/green regions have an increased latency during the rest period.

Fig. 7. ROI analysis of coherency magnitude and delay. (A) These bar graphs show group coherency magnitude and delay values with the standard error bars for each region of interest (ROI). The ROIs were selected within anatomical masks of M1, PM, and PPC (see Methods for details). The coherency magnitude graph shows significant coherence in all ROIs and a significant increase in coherence during the task compared to rest for all ROIs, excluding the SMA. The delay graph reveals a trend of increasing delay from anterior to posterior regions during the task period. Also note the significant delay between the SMA and right motor regions, whereas no significant delay was found between the SMA and left motor regions except for the left PPC. The group trial-averaged time-series for these voxels is plotted in panel (B) for the task condition.
on how well the model of the HRF fits the data. Furthermore, because these methods depend on a model of the stimulus paradigm, they cannot be used to measure latencies for conditions where no specific timing information is available, such as natural viewing epochs (Bartels and Zeki, 2004), delay periods during a memory task (Postle et al., 2000), or rest periods (Biswal et al., 1995).

Most importantly, however, the coherency method (coherence and phase-spectrum) allows one to measure the latency between functionally connected regions. The methods discussed above measure latency with only an implicit understanding of connectivity. Explicit measures of such temporal influences were recently presented by Goebel et al. (2003) using Granger causality. Granger causality allows one to measure influences between regions and to determine whether influence is causal (that is, the past events of one region predict the current event of another region) or instantaneous (the past and present events of one region predict the current event in another region). While this promising method incorporates both linear and non-linear influences, there is no direct measure of the latency between regions. Therefore, a second technique, such as the methods described above, or the phase-delay method would be necessary to quantify the temporal lead between regions with directed influence as measured by Granger causality.

Network dynamics during task and rest

Using phase-delay, we measured the relative latency differences between SMA and other motor regions during a bimanual sequence task. During the motor task, we found latency differences between SMA and M1 that were consistent with previous studies: Kansaku et al. (1998) and Weilke et al. (2001) found latency differences of 470 ms and 700 ms, respectively, for an externally cued motor task. In addition, we examined the latency differences between SMA and other motor regions such as PM and PPC. We found that activity in the SMA preceded all of the selected regions of interest with an increasing latency from anterior to posterior. This early activation suggests that the SMA may be involved in initiating and coordinating subsequent motor processes across these regions.

We also examined latencies in the motor regions during the rest condition. Functional networks during the resting or baseline state have recently gained interest in the neuroimaging field. Biswal et al. (1995) first identified a resting state network by measuring low-frequency correlations of the fMRI signal between the bilateral primary motor cortices. Following that study, resting state correlations were also reported between homologous primary motor, auditory, and visual cortices (Xiong et al., 1999; Cordes et al., 2000; Lowe et al., 2000), as well as non-primary brain regions such as the amygdala and hippocampus (Lowe et al., 1998), and Wernicke’s area and Broca’s area (Hampson et al., 2002). The high spatial and functional specificity of the correlated regions suggests that resting-state correlations are not a result of physiological artifacts such as breathing or cardiac pulsatility but instead are coupled to neuronal activity and driven by spontaneous cognitive or sensory processes.

We examined the motor network during rest using the same reference region and ROIs as for the task period. Our finding that the SMA is functionally connected to M1 at rest corroborates previous findings of correlations between M1 and SMA (Biswal et al., 1995; Xiong et al., 1999; Cordes et al., 2000). Using phase-delay, we were also able to examine the relative latencies between regions. To our knowledge, this study is the first to examine fMRI latencies during rest. In contrast to the anterior to posterior trend in the task period, an intra-hemispheric pattern dominated during the rest period. M1 and PM regions ipsilateral to the reference region had no significant phase-delay with respect to SMA, whereas M1 and PM contralateral were delayed by several hundred milliseconds. Our results suggest that during rest, there is a tighter temporal coupling within hemisphere than across hemispheres.

By contrasting task and rest periods, we were able to identify regions with significantly different latencies with respect to the SMA during task compared to rest. A change in latency may suggest a change in cognitive processing. For example, the relative latency between two regions may be near zero in one condition and significantly positive (or negative) in another condition, suggesting that some serial cognitive processing between the regions may be required during the second condition and not in the first. We observed this type of interaction between the left M1 and PM and the SMA. During the rest condition, there were no significant differences in the relative latencies of these regions with the SMA; however, during the task period, activity in the SMA preceded the activity in these regions, suggesting that sequential processing was present during the task period. In addition, because latency measures can be either negative or positive, a significant difference in latency may mean a change in the direction of information flow. For example, the relative latency between two regions, A and B, may be negative in one condition (B leads A) and positive in another condition (A leads B). This type of interaction was present in the left prefrontal cortex. From the group-averaged phase-delay maps, we can see that activity in the SMA precedes activity in the left PFC during the rest condition, but during the task condition, activity in the left PFC leads the SMA.

Do relative fMRI latencies reflect hemodynamic delays or neural delays?

There is still much discussion about whether the measured fMRI delay between regions is due primarily to hemodynamic differences or due to neural differences. While this method cannot distinguish between the two, evidence from our data suggests that the measured relative latencies are not solely governed by hemodynamic delays but instead may partially reflect latency differences of neural responses. First, we find that there are different latencies during the task period and the rest period. If the results were driven by hemodynamic latencies, then one would not expect the latencies to change with task. Second, we find differences in latency between homologous regions during task and rest. For example, during the task period, the latency of the right PPC was significantly shorter than the latency of the left PPC. During the rest period, the latency of left M1 and PM was significantly shorter than the latency of the right M1 and PM regions. One would expect that the physiological parameters that govern hemodynamic latencies would be comparable within homologous regions or especially between neighboring regions with common arterial supply or venous drainage.

Growing evidence from a number of studies has also suggested that while absolute delays have high variance and a significant hemodynamic contribution, relative latencies have a neural basis (for review, see Formisano and Goebel, 2003). Within the primary visual cortex, Menon et al. (1998) demonstrated that while the absolute latency of the hemodynamic response in the visual cortex was highly variable across subjects, the relative timing of the difference of the hemodynamic response between the left and right
visual cortex corresponded well to hemi-field stimulus offsets as short as 125 ms. Using a dynamic susceptibility contrast (DSC), Biswal et al. (2003) was able to decouple the hemodynamic delay from the task-induced (neural and vasomotor) delay. He found that during a bilateral finger-tapping task the hemodynamic delay was over 2 s, while the task-induced delay was 0.7 s. Biswal et al. also found that, during the task, the measured task-induced delay of SMA preceded M1 by 560 ms. This is in agreement with our latency measures between SMA and M1.

In summary, we have presented a novel method using the phase component of coherency to measure inter-regional latencies of fMRI data. Together, magnitude and phase components provide a measure of the dynamic interactions within a network. An important characteristic of these measures is that they do not require a reference function or model of the hemodynamic response and therefore can be used for a broad range of experimental designs. In this study, we applied coherence and phase-delay to fMRI data acquired from the motor network during rest and task periods. We were thus able to examine the temporal dynamics of this network. We found an anterior to posterior trend in the motor network during task and an intra-hemispheric left to right trend during rest. These results provide insight into the shift of information flow and cognitive processes that occur within the same network during two very different conditions. While much work remains, such as resolving hemodynamic from neural latencies, we feel that this method is a valuable addition to the currently limited set of tools for investigating inter-regional dynamics.

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Appendix A

To estimate coherency, we first estimated the cross-spectral and power-spectral densities using Welch’s modified periodogram averaging method. An estimate of the cross-spectrum can be obtained by multiplying the Fourier transform of x with the Fourier transform of y. Since the variance of this estimate is dependent on the power-spectrum and not on the length of the time-series, we transform of y. Since the variance of this estimate is dependent on averaging method. An estimate of the cross-spectrum can be power-spectral densities using Welch’s modified periodogram method is a valuable addition to the currently limited set of tools for resolving hemodynamic from neural latencies, we feel that this measure of the dynamic interactions within a network. An important characteristic of these measures is that they do not require a reference function or model of the hemodynamic response and therefore can be used for a broad range of experimental designs. In this study, we applied coherence and phase-delay to fMRI data acquired from the motor network during rest and task periods. We were thus able to examine the temporal dynamics of this network. We found an anterior to posterior trend in the motor network during task and an intra-hemispheric left to right trend during rest. These results provide insight into the shift of information flow and cognitive processes that occur within the same network during two very different conditions. While much work remains, such as resolving hemodynamic from neural latencies, we feel that this method is a valuable addition to the currently limited set of tools for investigating inter-regional dynamics.

Using these estimates of the cross-spectrum and the power-spectrum, we can estimate coherency:

\[
\hat{R}_{xy}^{(T)}(\lambda) = \frac{\hat{f}_{xy}^{(T)}(\lambda)}{\sqrt{\hat{f}_{xx}^{(T)}(\lambda) \hat{f}_{yy}^{(T)}(\lambda)}}. \tag{3}
\]

The band-averaged coherency is estimated using band-averaged estimates of the cross-spectrum and power-spectrum (Andrew and Pfurtscheller, 1996):

\[
\hat{\text{Coh}}_{xy}(\lambda) = \frac{|\sum \hat{f}_{xy}(\lambda)\sum \hat{f}_{xx}(\lambda)\sum \hat{f}_{yy}(\lambda)|}{\sqrt{\sum \hat{f}_{xx}(\lambda)\sum \hat{f}_{xy}(\lambda)\sum \hat{f}_{yy}(\lambda)}}. \tag{4}
\]

We can also derive a statistical measure of the difference between two coherency measures by using the arc-hyperbolic tangent transformation, where:

\[
\{\tanh^{-1}|R_{xy}(\lambda)| - \tanh^{-1}|R_{xy}(\tilde{\lambda})|\}
\]

is approximately normally distributed (Rosenberg et al., 1989).

References


