Dynamics of Event-Related Causality in Brain Electrical Activity

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Abstract: A new method (Event-Related Causality, ERC) is proposed for the investigation of functional interactions between brain regions during cognitive processing. ERC estimates the direction, intensity, spectral content, and temporal course of brain activity propagation within a cortical network. ERC is based upon the short-time directed transfer function (SDTF), which is measured in short EEG epochs during multiple trials of a cognitive task, as well as the direct directed transfer function (dDTF), which distinguishes direct interactions between brain regions from indirect interactions via brain regions. ERC uses new statistical methods for comparing estimates of causal interactions during prestimulus “baseline” epochs and during poststimulus “activated” epochs in order to estimate event-related increases and decreases in the functional interactions between cortical network components during cognitive tasks. The utility of the ERC approach is demonstrated through its application to human electrocorticographic recordings (ECoG) of a simple language task. ERC analyses of these ECoG recordings reveal frequency-dependent interactions, particularly in high gamma (>60 Hz) frequencies, between brain regions known to participate in the recorded language task, and the temporal evolution of these interactions is consistent with the putative processing stages of this task. The method may be a useful tool for investigating the dynamics of causal interactions between various brain regions during cognitive task performance. *Hum Brain Mapp* 29:1170–1192, 2008. © 2007 Wiley-Liss, Inc.

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INTRODUCTION

Analyses of neuroimaging data from PET and fMRI have recently progressed beyond the anatomic localization of brain activation to the study of relationships between different brain regions using measures such as effective connectivity [Penny et al., 2004] and directed interactions [Goebel et al., 2003]. However, the temporal resolution of these metabolic measures of brain activation is not sufficient for capturing either the detailed temporal dynamics of brain activation, or the rapid changes in functional brain

interactions that are thought to occur during most cognitive tasks. In contrast, the temporal resolution of electrophysiological measures of brain activity, i.e. EEG, electrocorticography (ECoG), and MEG, is sufficient for these purposes. For example, analyses of electrophysiological recordings for event-related potentials (ERPs) and event-related power changes [Durka et al., 2001; Lachaux et al., 2005; Miwakeichi et al., 2004] have demonstrated regional brain activation on time scales of tens to hundreds of milliseconds. To measure interactions between recorded brain regions, investigators have studied temporal fluctuations in coherence [Andrew and Pfurtscheller, 1996; Bullock et al., 1995], brain electrical source analysis coherences [Hoechstetter et al., 2004], and oscillatory synchrony [Tallon-Baudry et al., 2001, 2004]. In addition, attention has recently focused on the directionality of interactions between brain regions. For this purpose various approaches have been adopted, such as calculations of evoked potential covariances [Gevins et al., 1995], the imaginary part of coherency [Nolte et al., 2004], adaptive phase estimation [Schack et al., 1999], and methods based on Granger causality [Baccala and Sameshima, 2001a,b; Bernasconi and Konig, 1999; Brovelli et al., 2004; Freiwald et al., 1999; Ginter et al., 2001; Hesse et al., 2003; Kaminski and Blinowska, 1991; Sameshima and Baccala, 1999].

The concept of Granger causality [Granger, 1969] originated in econometrics, and there are several statistical testing procedures for assessing its significance [Lutkepohl, 1993]. According to Granger causality, an observed time series $x_l(t)$ causes another series $x_k(t)$, if knowledge of $x_l(t)$'s past significantly improves prediction of $x_k(t)$. In light of this definition, causal relationships between EEG signals can be evaluated, and statistical analyses can be used to infer the direction, intensity and spectral characteristics of the transfer of activity between brain regions during cognitive tasks. A measure of brain activity related to Granger causality is the directed transfer function (DTF). In the case of two time series DTF is equivalent to the Granger causality measure, but DTF extends the causality concept to multichannel data [Kaminski et al., 2001]. The advantages of this approach over pair-wise approaches to multichannel electrophysiological data have been widely discussed. Pair-wise treatments of these signals can lead to errors in the estimation of mutual influences between channels [Blinowska et al., 2004; Kus et al., 2004]. Comparisons of DTF with other estimators of causality have also been widely discussed [Baccala and Sameshima, 2001a,b; Blinowska et al., 2004; Ginter et al., 2005; Kus et al., 2004]. The DTF method has been successfully applied to the localization of epileptic foci [Franaszczuk et al., 1994], the evaluation of EEG propagation during sleep and wakefulness [Kaminski et al., 1997], the estimation of information transfer in behaving animals [Korzeniewska et al., 1997], the investigation of EEG-EMG coupling mechanisms [Mima et al., 2001], and the estimation of human functional cortical connectivity [Astolfi et al., 2005; Babiloni et al., 2005].

Unfortunately, nonzero values of DTF between two recording sites do not necessarily imply that the causal influences between them are direct. DTF represents a linear combination of causal influences along all causal pathways—direct and indirect—originating from one site and terminating at another. The influence may be mediated by another site or by several sites, or by sites that are not even recorded. For this reason a new measure was proposed, the direct directed transfer function (dDTF). This measure differentially enhances direct causal influences over indirect ones [Korzeniewska et al., 2003]. However, dDTF is not designed to analyze very short data epochs, and thus it cannot be used to study interactions that occur on brief time scales, such as during cognitive tasks. This particular limitation may be overcome when multiple trials of a particular cognitive task are available for analysis. In this case, another algorithm should be used for MVAR coefficient estimation [Ding et al., 2000]. The application of this algorithm to electrophysiological data is known as the short-time directed transfer function (SDTF) [Ginter et al., 2001, 2005].

To combine the benefits of dDTF and SDTF we introduce a new estimator, the short-time direct directed transfer function (SdDTF). This function evaluates the directions, intensities, and spectral contents of direct causal interactions between signals and is also adapted for examining short-time epochs. These properties of SdDTF are expected to make it an effective tool for analyzing nonstationary signals such as EEG activity accompanying cognitive processes. In this study, we applied SdDTF to ECoG signals recorded during multiple trials of a simple word production task in order to examine the functional connectivity of cortical regions responsible for this task, as well as changes in their interactions over time, depending on different stages of task performance.

To evaluate the statistical significance of event-related changes in SdDTF, i.e. event-related causality (ERC), new statistical methodology was developed for comparing prestimulus (baseline) with poststimulus SdDTF values. The main difference between this methodology and other statistical methods [Durka et al., 2004; Ginter et al., 2005; Tanji et al., 2005; Zygierevicz et al., 2005] is that both the baseline and poststimulus epochs are treated as nonstationary. To construct a joint 95% confidence interval, bivariate smoothing was applied using a penalized thin-plate spline model [Ruppert et al., 2003], while the Family-Wise Error Rate (FWER) was controlled using the Bonferroni correction.

The development of ERC and its application to human EEG are motivated by a growing awareness that oscillatory neuronal activity plays an important organizing role in large-scale neural networks responsible for cognition and other brain functions [Buzsaki and Draguhn, 2004; Engel et al., 2001; Varela et al., 2001]. Furthermore, the event-related response characteristics and functional significance of oscillatory EEG activity appears to depend on its spectral characteristics [Crone et al., 1998a,b, 2006;

Pfurtscheller and Lopes da Silva, 1999]. For example, functional activation of sensorimotor cortex is accompanied by suppression of EEG activity in alpha (8–12 Hz) and beta (13–25 Hz) bands, and by increased activity in higher, i.e. gamma, frequencies (>30 Hz). Invasive EEG recordings in patients undergoing epilepsy surgery have discovered that event-related increases in signal energy are not limited to the traditionally defined 40-Hz gamma band, but also occur in higher gamma frequencies, i.e. >60 Hz [Crone et al., 1998a, 2001a]. These “high gamma responses” consist of a broadband increase in signal energy with a reactive frequency range that may extend from 60 Hz up to 200 Hz [Canolty et al., 2006; Crone et al., 2001a; Lachaux et al., 2005; Leuthardt et al., 2004; Tallon-Baudry et al., 2005]. Event-related high gamma activity has been observed in humans performing a variety of experimental tasks activating sensorimotor [Crone et al., 1998a; Leuthardt et al., 2004; Ohara et al., 2000; Pfurtscheller et al., 2003], auditory [Crone et al., 2001a; Edwards et al., 2005; Ray et al., 2003], visual [Crone et al., 2001b; Lachaux et al., 2005; Tanji et al., 2005], and language cortices [Crone et al., 2001b; Sinai et al., 2005], suggesting that it may provide a relatively general index of regional cortical processing [Crone and Hao, 2002; Crone et al., 2006].

Because oscillatory activity in gamma frequencies has been proposed as a mechanism for dynamically organizing the activity of neuronal assemblies in large-scale brain networks [Engel et al., 2001; Singer, 1993], it seems reasonable to hypothesize that during a functional task engaging such a network, gamma activity arising from one part of the network may have a causal influence on gamma activity arising from other part of the network, and that these causal influences may occur with different strengths and directionalities, reflecting the changing functional demands on the network during task performance. Because ERC is designed to evaluate the directions, intensities, and spectral characteristics of event-related causal interactions between signals, it appears to be well suited for testing this hypothesis. Our previous observations of event-related high gamma activity during language tasks led us to focus our current application of ERC on the causal interactions between signals in high gamma frequencies during a word production task, auditory word repetition.

MATERIALS AND METHODS

Time Series Analysis With SdDTF

Granger causality assumes that time series $x_i(t)$ causes another time series $x_k(t)$ if knowledge of $x_i(t)$'s past significantly improves prediction of $x_k(t)$. To evaluate the causality between more than two time series, as in multichannel ECoG data, a multivariate autoregressive (MVAR) model is fitted to the recorded signals. The model assumes that the value of the x at a time t depends on its p previous values and the random component e . Analyzed signals (from K channels) are treated as realizations of one multi-

variate stochastic process. The MVAR process can be expressed as:

$$\mathbf{x}(t) = - \sum_{j=1}^p \mathbf{A}_j \mathbf{x}(t-j) + \mathbf{e}(t) \quad (1)$$

or

$$\sum_{j=0}^p \mathbf{A}_j \mathbf{x}(t-j) = \mathbf{e}(t) \quad (2)$$

where $\mathbf{A}_0$ is equal to the $K \times K$ identity matrix, $\mathbf{A}_j$ is a $K \times K$ MVAR coefficients matrix, $\mathbf{e}(t)$ is a zero mean uncorrelated residual noise vector with covariance matrix $\mathbf{V}$, and p is the model order. Estimation of the $\mathbf{A}_j$ coefficients and matrix $\mathbf{V}$ can be obtained by multiplying Eq. (2) on the right by $\mathbf{x}^T(t-r)$ (T denotes vector transposition, $r = 1, \dots, p$) and taking the expectation of both sides, which gives the Yule-Walker equation:

$$\sum_{j=0}^p \mathbf{A}_j \mathbf{R}(-r+j) = 0 \quad (3)$$

where $\mathbf{R}(n)$ is $\mathbf{x}(t)$'s covariance matrix at lag n , for the single realization $\mathbf{x}(t)$ ($t = 1, \dots, N_s$) of the stochastic process $\mathbf{x}$. For a single realization of the stochastic process, the unbiased estimate of covariance matrix can be computed from:

$$\bar{\mathbf{R}}(n) = \frac{1}{N_s - n} \sum_{t=1}^{N_s-n} \bar{\mathbf{x}}(t) \bar{\mathbf{x}}^T(t+n) \quad (4)$$

where $\bar{\mathbf{x}}$ is the vector of recorded data.

The statistical properties of $\bar{\mathbf{R}}(n)$ depend on the length of the data record—the longer the record the better the estimate. If N_s is small, it is impossible to get a good estimation of $\mathbf{R}(n)$, and as a consequence, it is difficult to obtain a good MVAR model. But if multiple realizations of the same process (multiple trials of a task) are available, the above quantity can be computed for each realization and averaged over realizations to obtain a final estimate of the covariance matrix. In this approach, a single task repeated many times may be treated as a realization of a nonstationary stochastic process with locally stationary segments. This makes it possible to analyze data epochs that are short enough to be treated as locally stationary.

The estimated residual noise covariance matrix can be obtained through

$$\bar{\mathbf{V}} = \sum_{j=0}^p \bar{\mathbf{A}}_j \bar{\mathbf{R}}(j) \quad (5)$$

where $\bar{\mathbf{A}}_j$ is the estimate of MVAR coefficients computed by substituting estimates $\bar{\mathbf{R}}$ to Yule-Walker Eq. (3).

To determine the correct value of model order p , the Akaike Information Criterion [Akaike, 1974] was used.

Because EEG (and ECoG) activity may be understood in terms of rhythms and oscillations, it is useful to describe the spectral properties of their signals. For this purpose the MVAR equation may be transformed to the frequency domain [Marple, 1987]. Then

$$\mathbf{X}(f) = \mathbf{H}(f)\mathbf{E}(f) \quad (6)$$

where

$$\mathbf{H}(f) = \left(\sum_{j=0}^p \mathbf{A}_j e^{-i2\pi j f \Delta t} \right)^{-1} \quad (7)$$

$\mathbf{H}(f)$ is the transfer function of the multi-channel system, f is frequency, and Δt is the sampling interval.

The element h_{kl} of the matrix $\mathbf{H}(f)$ describes the transfer function between the k -th output and the l -th input of the system. If the element h_{kl} of $\mathbf{H}$ is equal to zero, the hypothesis that $x_l(t)$ causes $x_k(t)$ can be rejected. The matrix is not symmetric, meaning that transfer from channel k to channel l is different from that in the opposite direction. In this way, the directional properties of a multi-channel system may be obtained and interpreted as causal relationships, signal flows, or activity transfers. The $\mathbf{H}$ matrix has been used to calculate SDTF. In this method, electrical brain activity propagation is expressed as $\theta_{kl}(f) = |H_{kl}(f)|^2$.

As mentioned above, a nonzero value of the transfer matrix $\mathbf{H}(f)$, does not indicate that the causal relationship between recording sites is direct; the influence may be mediated by other recording sites. To distinguish direct causal relationships from indirect ones, we have used partial coherence [Korzeniewska et al., 2003]. Partial coherence [Bendat and Piersol, 1971; Jenkins and Watts 1968] represents the linear dependence between spectral components of time series $x_k(t)$ and $x_l(t)$ when the influence of all other $(K - 2)$ time series of the multichannel recording is removed. Its value is normalized between 0 and 1, and it is nonzero only when the relationship between channels k and l is a direct one at the given frequency. Spectral matrix can be obtained from $\mathbf{H}$ and $\mathbf{V}$ by:

$$\mathbf{S}(f) = \mathbf{H}(f)\mathbf{V}\mathbf{H}^*(f) \quad (8)$$

where the asterisk denotes transposition and complex conjugation. Diagonal elements of the matrix are power spectral densities of corresponding signals; off-diagonal elements are cross-spectral densities. Multivariate spectral quantities like ordinary and partial coherence can be obtained from a spectral matrix $\mathbf{S}$ by calculating as follows. Ordinary coherence:

$$\eta_{kl}(f) = \frac{s_{kl}(f)}{\sqrt{s_{kk}(f)s_{ll}(f)}} \quad (9)$$

where s_{kl} is an element of spectral matrix $\mathbf{S}(f)$. Partial coherence can be given in the form:

$$\chi_{kl}(f) = \frac{c_{kl}(f)}{\sqrt{c_{kk}(f)c_{ll}(f)}} \quad (10)$$

where c_{kl} is an element of the inverse of spectral matrix $\mathbf{S}(f)$.

$$\mathbf{C}(f) = \mathbf{S}^{-1}(f) \quad (11)$$

Since partial coherence describes *direct* relationships between signals, and the transfer matrix $\mathbf{H}(f)$ measures the *directed* relationships between them, a combination of the two measures results in a measure of direct causal interactions between signals in a multi-channel recording. We propose this combination, called SdDTF, in the form:

$$\zeta_{kl}(f) = \frac{|h_{kl}(f)||\chi_{kl}(f)|}{\sqrt{\sum_f \sum_{kl} |h_{kl}(f)|^2 |\chi_{kl}(f)|^2}} \quad (12)$$

The SdDTF function shows whether a signal component at a given frequency in channel k is shifted in time with respect to a signal component of the same frequency in channel l , and whether the shifted components are coherent and are not explained by components of other channels. For this function a new normalization procedure was applied in which SdDTF was normalized to all direct transfers between channels, i.e. to all estimated SdDTF values (12). SdDTF takes values from 0 to 1. Zero indicates a lack of direct causal relationships. The nonzero values of SdDTF are interpreted as a flow of activity from one channel to another one, i.e. $\zeta_{kl}(f) > 0$ indicates flow of activity from channel l to channel k ($l \rightarrow k$). The temporal evolution of causality estimates can then be obtained by calculating them in a short window that is shifted along the signal of interest. The windows are overlapped resulting in a smoothed SdDTF estimate.

Considerations for Application of SdDTF

Application of the SdDTF method to EEG time series requires careful attention to the choice of parameters in the analysis. First, a sufficient number of data samples should be used. A sufficient amount of data is necessary for the MVAR model to fit the recorded data well. The length of the time window should be small enough to treat the data as stationary, yet large enough to take into account the jitter of the recorded signal interactions across trials. It is generally agreed that the number of parameters should be $< 10\%$ of the available data samples. The number of data samples should also be a few times greater than the number of channels K . The sufficient number of data samples can be estimated by the inequality:

$$\frac{K(p+1)}{N_s n_t} < 0.1 \quad (13)$$

where N_s denotes the length of the moving window (number of samples per epoch) and n_t denotes the number

Figure 1.

AIC criterion for a sample of epochs (windows) in one data set. Each line illustrates the relationship between AIC and model order in one data epoch (window). Horizontal axis—model orders; vertical axis—value of AIC.

of trials used. If the data are not stationary given the window length, the window length may be shortened, but this will require that the number of trials is increased or that the number of channels is reduced.

The chosen model order p should yield a well-fit MVAR model. For this purpose only values indicated by an AIC criterion can be taken (see Fig. 1). If there is no minimum in AIC despite a sufficient number of data samples, some preprocessing steps may be undertaken to improve the fit. Signals may be filtered to include only the frequency range of interest or a collection of frequency ranges within a larger frequency range of interest. However, it is important to ensure that the filter does not change the phase properties of the signals being analyzed. The filter's impulse response should be short even if its spectral characteristics are not sharp.

Statistical Testing Framework

Because SdDTF is an explicit function of the MVAR model parameters, its estimator for each time-window can be obtained by substituting the estimators of the MVAR model parameters into Eq. (12). All trials are used to provide a point estimator for SdDTF within each time-window. The windowing strategy can be viewed as a first step in smoothing the time-dependent SdDTF function. However, some of the noise inherent in the original signal is resistant to the smoothing method described in the previous section. For example, the circles in Figure 2 represent the estimated SdDTF function in each time window (in this case ranging from 1 to 243) for the flows from channel E9 to channel E3 (top), and from E3 to E9 (bottom) in fre-

quency 86 Hz. These plots suggest sizeable residual noise around a smooth temporal trend and show that the baseline SdDTF function is nonstationary. This is probably due to the nonstationarity of the original ECoG signals. The statistical testing procedure described in this section takes this nonstationarity into account by comparing the mean SdDTF value of each baseline window with the mean SdDTF value of each poststimulus window. A similar pattern is observed at any given time point as a function of frequency, with significant variability around a smooth frequency trend. Thus we have employed a formal bivariate smoothing model that takes into account both the frequency f , and the temporal window t , which is defined as:

$$Y_{ft} = g(f, t) + \varepsilon_{ft} \quad (14)$$

where $g(f, t)$ is an unspecified function representing the actual SdDTF function and ε_{ft} are independent $N(0, \sigma_\varepsilon^2)$ random variables capturing the white noise around the signal. There are many nonparametric approaches to bivariate smoothing, but here we use a penalized thin-plate spline model for $g(\cdot, \cdot)$ (e.g. [Ruppert et al., 2003]). A thin-plate

Figure 2.

Estimated SdDTF values for flows between two channels (E3 and E9 in Fig. 5) at frequency 86 Hz. X axis—sequentially numbered time windows in which SdDTF values were estimated. Y axis—values of SdDTF estimates.

Figure 3.

Time-frequency plots of SdDTF (left panels) and of splined/smoothed SdDTF (right panels) for flows between two channels (E3 and E9 in Fig. 5), showing the entire analyzed frequency range.

spline function can be viewed as spatial plates joined at a number of knots. We used a mesh of 240 knots generated by 6 equally spaced frequencies between the minimum and maximum frequency and 40 equally spaced temporal windows between the minimum and maximum temporal windows. The maximum complexity of the $g(\cdot, \cdot)$ surface is 243 degrees of freedom. It can be shown that a bivariate penalized spline estimator can be obtained as an estimator in a particular mixed model. Estimation is based on the Restricted Maximum Likelihood (REML) criterion, which is based on the maximum likelihood principle by exploiting the link between the penalized criterion and mixed models (for technical details, see [Ruppert et al., 2003]). Figure 3 shows the original SdDTF estimates (left panel) and the penalized thin-plate spline (right panel) for the flows from channel E9 to channel E3 and from E3 to E9.

To introduce our testing framework, we first introduce some notations. Denote by $f_1, \dots, f_m$ the frequencies where f_m is the number of analyzed frequencies ($f_m = 41$ in this application). Also, denote by $t = t_1, \dots, t_n$ the time index corresponding to one window in the baseline, where t_n is the total number of baseline windows ($t_n = 43$ in this application). In Figure 3 the baseline starts from the beginning of the plot and the end of the last baseline window coincides with the first vertical marker “s”, which denotes stimulus onset. Similarly, denote by $T = T_1, \dots, T_n$ the time index corresponding to one window in the poststimulus period, where T_n is the total number of poststimulus windows ($T_n = 152$ here). In Figure 3 the poststimulus period begins at the vertical marker “s”.

Our goal was to test for every frequency f , and for every baseline/stimulus pair of time windows (t, T) , whether $g(f, t) = g(f, T)$. More precisely, the implicit null hypothesis was that

$$H_{0,f,T} : g(f, t_1) = g(f, T) \quad \text{or} \quad g(f, t_2) = g(f, T) \\ \text{or} \dots \text{or} \quad g(f, t_n) = g(f, T) \quad (15)$$

with the corresponding alternative

$$H_{A,f,T} : g(f, t_1) \neq g(f, T) \quad \text{and} \quad g(f, t_2) \neq g(f, T) \\ \text{and} \dots \text{and} \quad g(f, t_n) \neq g(f, T) \quad (16)$$

To test these hypotheses we constructed a joint 95% confidence interval for the differences $g(f, t) - g(f, T)$ for $t = t_1, \dots, t_n$. Let $\hat{g}(f, t)$, $\hat{\sigma}_g(f, t)$ be the penalized spline estimator of $g(f, t)$ and its associated estimated standard error in each baseline time window. Similarly, let $\hat{g}(f, T)$, $\hat{\sigma}_g(f, T)$ be the penalized spline estimator of $g(f, T)$ and its associated estimated standard error in each poststimulus time window. Since residuals are independent at points well separated in time, the law of large numbers applies and we can assume that for every baseline/stimulus pair of time windows (t, T)

$$\frac{\hat{g}(f, t) - \hat{g}(f, T) - g(f, t) + g(f, T)}{\sqrt{\hat{\sigma}_g^2(f, t) + \hat{\sigma}_g^2(f, T)}} \sim N(0, 1) \quad (17)$$

approximates a standard normal distribution. A joint confidence interval with at least 95% coverage probability for $g(f, t) - g(f, T)$ is

$$\hat{g}(f, t) - \hat{g}(f, T) \pm m_{0.95} \sqrt{\hat{\sigma}^2(f, t) + \hat{\sigma}_g^2(f, T)} \quad (18)$$

where $m_{0.95}$ is the 97.5% quantile of the distribution

$$\text{MAX}(t_n, T_n) = \max_{t_1 \leq t \leq t_n, T_1 \leq T \leq T_n, f_1 \leq f \leq f_m} |N_{t,T,f}| \quad (19)$$

where $N_{t,T,f}$ are independent $N(0,1)$ random variables. This is equivalent to a Bonferroni correction for $t_n T_n f_m = 267,976$ tests leading to a value of $m_{0.95} = 5.21$. This value is much larger than 1.96, which corresponds to the 97.5% quantile of a normal distribution and is typically used when testing multiplicity is not an issue. The Bonferroni correction is exact when the independence assumption holds and is conservative when it does not. More precisely, the FWER, or the expected fraction of false positive results, is at most $\alpha = 0.05$, irrespective to the degree of correlation of the $N_{t,T}$ variables. This test rejected $H_{0,f,T}$ if zero was not contained in any of the corresponding confidence intervals. Figure 11 indicates by yellow-red and green-blue areas the time-frequency windows, in the post-stimulus phase for which $H_{0,f,T}$ was rejected.

The testing strategy is illustrated in Figure 4 using a schematic representation. Each rectangle represents a window either in baseline or poststimulus periods while S indicates the stimulus onset time. Panel A indicates that the first window immediately after the stimulus (black filled rectangle) is compared to each window in the baseline. Panels B and C indicate the same procedure for the second and third poststimulus windows, respectively. The procedure is, of course, continued until the last poststimulus window. The left and right distributions (smooth bell-shaped curves) are the distributions of SdDTF corresponding to baseline and poststimulus windows, respectively. Each pair of baseline/poststimulus windows is compared based on the t -test described in Eq. (17)–(19) whose null distribution is well approximated by a standard normal distribution. The t -test was designed for the null hypothesis of zero differences between the SdDTF means. The normalizing standard error is the standard deviation of the estimated mean difference. To account for multiple testing, the FWER was controlled using the Bonferroni correction. This ensured that our statistical approach was conservative. Because the application of ERC to our data represents an exploratory analysis and is not testing a priori hypotheses about specific activity flows based on previous studies, we were more concerned about assigning significance to small, irrelevant flows than we were about missing relevant flows.

By definition, the ERC method gives an estimate of the directions and magnitudes of statistically significant, event-related changes in direct activity propagation between brain sites, as a function of frequency. In other

Figure 4.

Schematic representation of the statistical testing methodology for comparing baseline with poststimulus SdDTFs. Each rectangle represents a window either in baseline or poststimulus periods while the vertical line labeled “S” indicates the stimulus onset time. Panel A indicates that the first window immediately after stimulus onset (black filled rectangle) is compared to each window in the baseline. Panels B and C indicate the same procedure for the second and third poststimulus windows. The left and right distributions (smooth bell shaped curves) are the distributions obtained from bivariate smoothing of the SdDTF values corresponding to baseline and poststimulus windows respectively.

words, ERC (Event Related Causality) corresponds to SdDTF, but masked according to statistical significance. The activities analyzed by this method are considered

together as a multichannel system. Thus, the magnitudes of event-related changes in activity propagation between any pair of recording sites are relative to those among all other pairs of channels in the system.

Experimental Data

ECoG data was obtained in a subject who had undergone surgical implantation of subdural electrode arrays for the surgical management of intractable epilepsy and had given informed consent for research testing that was approved by the Institutional Review Board in compliance with the Declaration of Helsinki. Anatomical localization of the implanted subdural electrodes (see Fig. 5) was accomplished by co-registration of preimplantation MRI with postimplantation CT using anatomical fiducials, and by surface renderings of preimplantation MRI to visualize cortical gyral anatomy [Sinai et al., 2005].

The subject performed a simple word production task, auditory word repetition, which has been detailed elsewhere [Crone et al., 2001b]. The subject responded to a series of auditory word stimuli ($N = 116$) by repeating them aloud. The mean duration of the auditory stimuli was 750 ms, and the mean response latency was 1,340 ms. These times were later used to categorize the time course of SdDTF results according to three approximate stages of task performance: (1) stimulus processing from stimulus onset (s) to stimulus offset (o), i.e. 0–750 ms poststimulus-

onset, (2) response preparation from stimulus offset (o) to response onset (r), i.e. 750–1,340 ms, and (3) response production from response onset (r) to the end of signal analysis, i.e. 1,340–2,500 ms.

ECoG signals were digitally recorded (300 Hz lowpass at 3 dB/oct, 1,000 Hz sampling), and a common average reference was used with all analyzed channels to obtain reference-independent spatial maps of spectral measures [Crone et al., 2001b]. This was done to de-emphasize more global activity unrelated to the functional task without introducing systematic biases from the reference electrode. Selection of ECoG channels for SdDTF analyses were based upon the results of previous power spectral analyses [Crone et al., 2001b] demonstrating event-related power augmentation in high gamma frequencies (80–100 Hz) during the same or similar language tasks. The rationale for this procedure was that interpretation of causal interactions between ECoG signals were expected to be more plausible in high gamma frequencies if an event-related increase in signal energy had already been demonstrated at these frequencies. Because the common average reference had been used in previous power spectral analyses, it was important to use it here so that the spatial dependencies would be preserved in the current study. Individual stimulus response trials were visually inspected and those with artifacts were excluded from subsequent analysis. Raw ECoG recordings were downsampled to 333.33 Hz and then digitally band-pass-filtered.

Each sample of the raw ECoG time series was averaged across trials, and this was subtracted from the raw ECoG signal of each individual trial (for each window and each channel). In addition, the mean of data points in each window for each trial was computed and subtracted from the signal. These procedures achieved one of the requirements for fitting the MVAR model, that the time series x in Eq. (1) has a zero mean. To normalize the amplitudes of ECoG signals across channels, the signal in each window was also divided by its standard deviation computed over all samples in the window. This normalization allows the comparison of flow changes between different stages of task processing and different channel pairs [Ding et al., 2000]. The first step in these preprocessing procedures also had the effect of removing phase-locked activity from the signals being analyzed. The resulting nonphase-locked activity, which had previously been considered “noise” in computations of ERPs, has been increasingly recognized as containing rich task-relevant information [Ding et al., 2000; Kalcher and Pfurtscheller, 1995] and in some cases to reflect task-related cortical activity that cannot be inferred solely from the ERP [Crone et al., 2001a; Senkowski and Herrmann, 2002; Senkowski et al., 2007]. Perhaps more importantly, in a recent comparison of causality analyses with and without subtraction of the ensemble average [Oya et al., 2007], spurious causality responses were observed when the subtraction was not done.

For each window the MVAR model order was found by using the AIC—Akaike Information Criterion [Akaike,

Figure 5.

Positions of electrodes for ECoG recording. White discs indicate electrodes implanted for clinical purposes. Numbered discs indicate recording sites analyzed for this study.

1974]—for each epoch (window) separately. For most cases, the orders indicated by AIC were the same for epochs within a data set (see Fig. 1). A common model order was thus applied for all windows in each data set. The chosen order was 10. In the next steps the MVAR model of the chosen order was fitted to signals in each epoch separately, and its spectral quantity (SdDTF) was found as a function of time in windows that were 120 samples wide (360 ms), shifted successively by 5 samples (15 ms) to cover the entire task time (including pre and poststimulus epochs).

To test the null hypothesis that task-related poststimulus SdDTF values did not differ from those in the baseline, bivariate smooth SdDTF estimates in the prestimulus (baseline) and poststimulus windows were compared (43 prestimulus windows, baseline duration = 710 milliseconds; 152 post-stimulus windows covering 2,500 ms) using the statistical testing procedures described above. The FWER was 0.05. Because of the multiple comparisons between SdDTFs for all baseline and poststimulus windows, a Bonferroni correction [Fisher and van Belle, 1993] was applied ($\alpha = 0.05/(43 \cdot 152 \cdot 41)$).

RESULTS

Methods estimating causal relations between time series, including methods based on DTF, have been evaluated using simulated signals [Baccala and Sameshima, 2001a,b; Blinowska et al., 2004; Kaminski and Liang, 2005; Kaminski et al., 2005; Kus et al., 2004; Sameshima and Baccala, 1999; Schelter et al., 2006; Winterhalder et al., 2005]. As dDTF combined the well-described methods of partial coherence and DTF [Korzeniewska et al., 2003], the SdDTF approach introduced here combines partial coherence and SDTF. Since the elements of this approach have been well known and/or studied with simulations, in this study we have concentrated on demonstrating the advantages of the combined approach (SdDTF) in a simple simulation, as well as the application of SdDTF to complex human ECoG signals.

The advantages of SdDTF over SDTF are illustrated by a simple simulation of signals in three different channels changing over time. A schematic of the simulation is presented in Figure 6, and the results are shown in Figure 7. The signals were simulated in such a way that there was no flow (no causal relations) between channels during the first second. During the next second, flows from channel 1 to 2 ($1 \rightarrow 2$), and from 2 to 3 ($2 \rightarrow 3$) were simulated. There was again no flow during the third second, and during the last second flows $3 \rightarrow 2$ and $2 \rightarrow 1$ were simulated. These signals were created as follows. During the first second all signals contained the same spectral components between 86 and 96 Hz, but white noise was added separately to the signals in each channel. During the next second, when flows $1 \rightarrow 2$ and $2 \rightarrow 3$ were simulated, channel 1 contained the same signal used during the first second. Channel 2

Figure 6.

Schematic of simulated model of activity flows. Horizontal axis represents time. Below are indicated the frequencies (~ 90 Hz or ~ 110 Hz) of simulated activity flows in different time periods. Numbers within circles represent channels (recording sites). Arrows represent direct flows only.

contained the signal used in channel 1, albeit shifted later by 6 ms, and white noise of different mean and variance was added to it. Channel 3 contained the signal used in channel 2, albeit shifted later by 12 ms, with additional white noise of different mean and variance than was added to all of the previously used signals. During the third second all channels contained the same frequency components between 105 and 114 Hz, and different components of white noise as in the first second of the simulation. During the last second, when flows of opposite directions were simulated ($3 \rightarrow 2$ and $2 \rightarrow 1$), channel 2 contained the signal used in channel 3, shifted by 6 ms, with additional white noise of different mean and variance than the previous ones. Likewise, channel 1 contained the signal used in channel 2, shifted by 12 ms, with additional white noise.

In the cross-spectra shown in Figure 7a and defined in Eq. (8), there is activity around 90 Hz during the first 2 s and activity around 110 Hz during the next two seconds for each pair of channels. Ordinary coherences depicted in Figure 7b (above the diagonal) and defined in Eq. (9), are also similar for each pair of channels. They show relationships for 86–96 Hz and 105–114 Hz components during the first and third epochs, as well as for noise components during the second and fourth epochs, when noise components were propagated across channels. However, partial coherences—below the diagonal—show relationships only between channels 1 and 2 and between channels 2 and 3 during the second and fourth epochs, when signals were directly related between these channels. Partial coherence is close to zero during the first and third epochs because the spectral components are common to all three channels and noise components are independent; thus no direct

relationships should be observed between channels. Partial coherence is close to zero for channels 1 and 3 during the second epoch because a noise component added to channel 2 was not present in channel 1, and it is also close to zero during the fourth epoch because a noise component added to channel 2 was not present in channel 3. Thus there were no direct relationships between signals 1 and 3. The small yellow patches in the plots of partial coherence for channels 1 and 3 are edge effects from analyzing windows with concatenated signals.

SDTF (Fig. 7c) does not differentiate direct flows and indirect ones. There are visible flows 1→2 and 2→3 (direct flows), as well as 1→3 (indirect flow), during the second epoch, and flows 3→2 and 2→1 (direct flows), as well as 3→1 (indirect flow) during the fourth epoch. SdDTF plots (Fig. 7d) illustrate the effect of multiplying SdTF by partial coherence. Only direct flows 1→2 and 2→3 are observed during the second epoch, and only direct flows 3→2 and 2→1 are observed during the fourth epoch. The indirect flows 1→3 and 3→1 seen in SdTF are eliminated in the SdDTF plots (thin patch in 3→1 is an edge effect from concatenated signals), yielding a more precise estimate of the changing relationships between signals.

Application of SdDTF to human ECoG signals yielded a number of interesting observations that were generally consistent with the putative functional neuroanatomy and dynamics of the word repetition task. Raw plots of SdDTF during auditory word repetition are illustrated in Figure 8. There are prominent activity flows to and from E3 and E9 in many time-frequency points (SdDTF values are high for pairs of sites including E3 or E9). This finding is consistent with the expected activation of cortical regions during the

Figure 7.

Cross-spectra, coherences, SdTFs and SdDTFs of three-channel MVAR model of simulated signals. In each plot the horizontal axis represents time in seconds (relative to the beginning of the shifted window), the vertical axis represents frequency, and the color scale (at right of each set of plots) represents the value of calculated functions from minimum (blue) to maximum (red): (a) cross-spectrum, (b) coherence, (c) SdTF, and (d) SdDTF. (a) plots on the diagonal are power spectra for channels named at the top of the picture; plots off the diagonal are cross-spectra for pairs of channels (one of them is named above and the other is named to the left of the time-frequency plot). (b) ordinary coherences are plotted above the diagonal and partial coherences below the diagonal (both of these symmetric matrices are shown in the same array of plots), again for pairs of channels (named at the top and to the left). (c) SdDTFs for pairs of channels. This matrix is not symmetric; each plot shows SdTF for flows from the channel named above the plot to the channel named to the left of the plot. (d) activity flows measured by SdDTF. Each plot shows SdDTF for direct flows from the channel named above the plot to the channel named to the left of the plot.

Figure 8.

SdDTF of twelve-channel MVAR for ECoG signals recorded during auditory word repetition. Organization of the figure is the same as for Figure 7d. Each plot shows time-frequency-specific values of SdDTF for flows from the electrode site named above the plot to the site named to the left of the plot. Horizontal axis is time with vertical lines demarcating stimulus onset (s), stimulus offset (o), and response onset (r). Maximum SdDTF values are red; minima are green-blue.

word repetition task, which requires the subject to hear a spoken word and then speak it aloud. E9 (see Fig. 5) is located over the lateral surface of the posterior superior temporal gyrus, likely within Brodmann's area 22 (BA22) and Wernicke's area [Bogen and Bogen, 1976]. E3 is located over inferior precentral gyrus, likely within mouth/tongue area of premotor/motor cortex (BA4/BA6). Moreover, the timing of SdDTFs is consistent with the expected timing of cortical activation during the task. There are prominent flows between E3 and E9 for time-points between onset of the auditory stimulus (vertical marker "s" in Fig. 8) and its offset (vertical marker "o"). These reciprocal flows between auditory association cortex and mouth/tongue area of motor cortex occur at a stage in the task when the spoken word is being heard. There are also flows into E3 from other sites at this stage. In addition, during the baseline period before stimulus onset (prior to the vertical marker "s") there are large flows

between E12 and other sites. E12 is located over fusiform gyrus (BA37), likely within visual association and basal temporal language areas [Luders et al., 1991]. These flows appear to decrease after onset of the auditory stimulus.

It should also be noted that for channels in which SdDTFs are high, there may also be visible changes in the power spectrum (see Fig. 9). For example, there is a visible change in the power spectrum of the E9 signal in the epoch between stimulus onset and offset. A similar power change, somewhat less visible, occurs in channel E3. However, SdDTF also enables the determination of activity flows between channels for which the power spectra appear to be unchanged. This is illustrated in Figure 10 by plots of statistically significant event-related changes in SdDTF, referred to here as ERC. In particular, there is a large increase in activity flow during the spoken response (following marker "r") from E2 over pars opercularis (BA44, part of Broca's area) to E4 over inferior precentral

Figure 9.

Power spectra for the same signals used in Figure 8. Time-frequency axes as in Figure 8.

gyrus (BA4/6, mouth/tongue area of premotor/motor cortex); however, there are no visible changes in the spectra for channels E2 and E4 (see Fig. 9).

Like the activity flows suggested by the raw plots of SdDTF (see Fig. 8), the statistically verified event-related changes in flow revealed by ERC (see Fig. 10) also appear to correspond to different stages of the language task. For example, increases in activity flow between sites E3 and E9 are limited to the duration of the auditory stimulus (word perception stage between “s” and “o” in Fig. 10). This is illustrated in greater detail in Figure 11. Note that following this word perception stage (after “o”) there are decreases in flow between these two sites. Other event-related increases in flow are also observed during the word perception stage (see Fig. 10), including: (i) flow from E7 (auditory association cortex in superior temporal gyrus) to E3 (mouth/tongue area of premotor/motor cortex), (ii) flows among sites overlying auditory association cortices in lateral superior temporal gyrus (E8→E9, E9→E7, and E9→E8), and (iii) from E11 in supramarginal gyrus (BA40, likely part of Wernicke’s area) to E3 in mouth/tongue motor/premotor cortex.

Other examples of the correspondence of ERC to stages in the experimental task (see Fig. 10) can be seen in flows E2→E5 and E5→E4, and in bidirectional flow between E7 and E2. During the word perception stage (between markers “s” and “o”) there are no increases, but during the response preparation stage (between “o” and “r”) flow increases appear bidirectionally between E7 in auditory association cortex of superior temporal gyrus and E2 in pars opercularis (BA44, part of Broca’s area), from E2 to E5 in mouth/tongue area of motor cortex (adjacent to E2), and among sites within mouth/tongue premotor/motor cortex (E5→E4). These results suggest cooperation between auditory association cortex, Broca’s area and mouth/tongue motor areas during preparation of the spoken response. ERC increases also appear during the verbal response itself, in the immediate time frame after marker “r”. Most of the large flow increases are directed into E4 in mouth/tongue motor cortex, suggesting a convergence into cortex responsible for articulation of the spoken word response: E1→E4 and E2→E4 (BA44 and BA45, i.e. Broca’s area); E3→E4, E5→E4, and E6→E4 within mouth/tongue sensorimotor cortex; and E10→E4 and E11→E4 from supramarginal gyrus (BA 40, part of Wernicke’s area). Some of these flows, especially E2→E4, are detailed in Figure 12. At the same time, there are also flow increases within auditory association cortex (E7→E8) and from auditory association cortex to mouth/tongue motor cortex (E7→E4), which may correspond to the subject hearing and verifying his spoken response [Crone et al., 2001a].

Relationships between the stages of language task performance and event-related activity flows are also illustrated in Figure 13. Each arrow represents an integral of activity flow changes over a particular stage, normalized to the duration of that stage. The value of this integral is represented by the width and color of the arrow. Colors

Figure 10.

ERC of ECoG signals recorded during auditory word repetition, as in Figure 8. Plots arrayed as in Figure 8 with similar axes. Prestimulus baseline is not shown because ERC represents statistically significant changes in SdDTF from baseline. Color scale of ERC values (min to max) is shown to right of array. Black indicates time-frequency points with no significant difference

between SdDTF after stimulus and SdDTFs for baseline. Time-frequency points colored yellow-green-blue show event-related decreases of poststimulus SdDTF in reference to baseline SdDTF. Points colored orange-red-brown show event-related increases of SdDTF.

Figure 11.

Greater details of ERC plots from Figure 10 of reciprocal flows between site E9 (auditory association cortex) and site E3 (mouth/tongue area of premotor/motor cortex) during auditory perception, i.e. between onset (s) and offset (o) of the auditory word stimulus. Axes and color scale as in Figure 10.

Figure 12.

Greater details of ERC plots from Figure 10 for flows between sites E1 and E2 in Broca's area, and E4 (mouth/tongue motor cortex). Axes, color scale, and organization of plots as in Figure 10.

eration because the physiological interpretation of flow decreases during task performance is less clear.

During the word perception stage of word repetition (Fig. 13a) the predominant increase in ERC for 82–100 Hz is observed from auditory association cortex to mouth/tongue motor cortex ($E9 \rightarrow E3$), as described above (see also

Figs. 10 and 11). In addition, there are other, less prominent flows from auditory association cortex to mouth/tongue motor cortex ($E9 \rightarrow E5$, $E9 \rightarrow E4$, $E7 \rightarrow E3$, and $E8 \rightarrow E3$). Furthermore, there are also increases in flows from auditory association cortex to mouth/tongue motor cortex “via” supramarginal gyrus (BA40/Wernicke's area):

Figure 13.

Integrals of ERC for frequency range 82–100 Hz calculated for three stages of auditory word repetition task. (a) auditory perception stage (between “s” and “o” markers in Figures 8 and 10), (b) response preparation (between “o” and “r”), (c) verbal response (following “r”). Arrows indicate directionality of ERC. Width and color of each arrow represent the value of ERC integral. Color scale at the left. For clarity, only integrals for event-related flow increases are shown.

Figure 14.

ERC averaged over all pairs of channels and over all time-points, for increases of SdDTF only. Horizontal scale—frequency, vertical scale—averaged ERC value. Vertical markers indicate frequency range taken for further calculations of integrals.

E9→E11→E3. During the second stage—“response preparation” (Fig. 13b) there are flow increases between auditory association cortex and Broca’s area (E7→E2, E2→E7), from Broca’s area to mouth/tongue motor cortex (E2→E5), among sites in Wernicke’s area (E7→E11, E9→E11), and between Wernicke’s area and mouth/tongue motor cortex (E11→E5, E4→E11). The third stage, i.e. during the spoken response (Fig. 13c), is characterized mainly by flow increases from Broca’s area to tongue/mouth motor cortex (E2→E4, E1→E4), but also by smaller flow increases from Wernicke’s area to mouth/tongue motor cortex (E7→E4, E11→E4) and from mouth/tongue motor cortex to Broca’s area (E4→E2 and E3→E2), perhaps reflecting the activation of feedback pathways while the patient speaks and hears his own spoken response.

It is important for a multichannel model to consider the full set of brain regions that are responsible for the analyzed task. Partial observation of these brain regions can lead to spurious estimates of causality [Eichler, 2005; Krichmar et al., 2005]. However, in the clinical setting where human ECoG recordings are possible, the sampling of brain regions is solely determined by diagnostic or therapeutic needs or limitations. To investigate the robustness of ERC under these circumstances, i.e. the degree to which ERC results depend on the set of recording sites included in the SdDTF model, we repeated the ERC analysis for the previously considered system, but with one electrode site removed, added, or replaced. Results for the first stage of the task are shown in Figure 15. Note that the recording sites that were removed, added or replaced excluded those that had the greatest event-related gamma activity according to our previous power spectra analysis [Crone et al.,

2001b] or that had the greatest signal flows according to our current ERC analysis (see Fig. 13). Removing or replacing such crucial recording sites would have been more likely to produce artificial causalities [Eichler, 2005].

Figure 15a shows the integrals of ERC after removal of one recording site (top—E6 removed, bottom—E8 removed). In both of these 11-channel systems (11 recording sites) the largest increase in flow (the largest arrow) is still between Wernicke’s area and mouth/tongue motor cortex (E9→E3), as it was in the original 12-channel system (Fig. 13a). The less prominent flow increases (e.g. E7→E3, E3→E7, E11→E3, and E10→E3) were largely unchanged. Although their magnitudes (width of arrows) relative to each other changed to a small degree, none achieved any greater prominence in the overall set of flows. Because we did not plot the smallest 10% of the ERC integrals, small changes in the magnitudes of lesser flow increases sometimes led to their disappearance (e.g. E9→E11 and E9→E4) or appearance (e.g. E6→E9 and E8→E9) from one system to another.

Figure 15b shows integrals of ERC for two cases with one added recording site (13-channel systems; top—electrode near electrode E1 is added to the analysis; bottom—electrode near E12 is added). In this case, the largest increase in flow (the largest arrow) is again between Wernicke’s area and mouth/tongue motor cortex (E9→E3), and there are relatively small changes in the magnitudes of the lesser flows.

Similar results are also obtained for systems with one electrode replaced by another electrode. Figure 15c shows two cases in which one electrode has been replaced (12-channel system; top—electrode E12 replaced by electrode near E1, bottom—electrode E12 replaced by electrode near E12). The greatest increase in flow remains the same (E9→E3), and there are relatively small changes in the magnitudes of lesser flows. To summarize, removing, adding or replacing electrodes results in relatively modest changes in ERC magnitude, but the overall pattern of ERC results is stable, suggesting that the ERC method is robust.

DISCUSSION

Estimating Functional Brain Interactions

The cognitive processes responsible for language are likely to require complex, time-dependent interactions between the brain regions that are responsible for different components of task processing [Mesulam, 1990; Salmelin, 2007; Salmelin et al., 1994]. To understand the brain networks participating in language and other cognitive tasks, it is therefore necessary to identify not only the time and place of task-related brain activation, but also the dynamic interactions between activated brain regions. Electrophysiological recordings (EEG, MEG, and intracranial EEG) are ideal for this purpose because of their excellent temporal resolution, and a variety of approaches have been taken to exploit the temporal resolution of electrophysiological signals in order to study the brain regions engaged by human

Figure 15.

Integrals of ERC for the word perception stage of the task in the frequency range 82–100 Hz, after removal ((a) left panel), adding ((b) middle panel) and replacing ((c) right panel) of one recording site. (a) ERC integrals after removing channel E6 (top) or E8 (bottom). Sites removed from analysis are marked by black X's. (b) ERC integrals with one added recording site (13-channel systems), top-electrode near electrode E1 added to the analysis, bottom-electrode near E12 added. Sites added to the analysis are marked by green-filled circles. (c) ERC integrals in which one electrode has been replaced (12-channel system), top-electrode E12 replaced by electrode near E1, bottom-electrode E12 replaced by electrode near E12. Signals recorded from sites marked by black X's were replaced by signals marked by green-filled circles.

cognitive processes, including language. Based on the putative role of brain oscillations in the binding of perceptual information [Basar-Eroglu et al., 1996] and of distributed oscillatory systems in the formation of neural networks [Basar et al., 2001a,b], researchers have used time-frequency analyses to study event-related changes in electrophysiological signals. In both humans and animals, using scalp EEG, MEG, and intracranial EEG, these studies have demonstrated time- and frequency-dependent changes in signal energy (power) during a variety of cognitive tasks [Bertrand and Tallon-Baudry, 2000; Brovelli et al., 2005; Hagoort et al., 2004; Hald et al., 2006; Lachaux et al., 2000, 2005; Miwakeichi et al., 2004; Palva et al., 2002; Pesaran et al., 2002; Ray et al., 2003; Rodriguez et al., 1999; Tanji et al., 2005].

Although frequency-specific changes in signal energy appear to reflect the dynamics of brain oscillations associated with cognitive processing in functionally specialized brain regions, neurophysiological studies in animals have suggested that synchronization between these oscillations

plays a key role in the integration of processing within distributed cortical networks. In particular, synchronization of oscillatory activity in gamma frequencies has been observed during processing in both local and distributed cortical networks and has been proposed as a general mechanism of transiently connecting neural assemblies [Engel and Singer, 2001; Varela et al., 2001]. For this reason, a number of methodological approaches have been used to measure phase synchronization of oscillatory activity in gamma and other frequency bands during a variety of experimental paradigms, including visual short-term memory [Tallon-Baudry et al., 2001, 2004], declarative memory formation [Fell et al., 2001], word recognition [Mormann et al., 2005] verbal memory encoding of recalled vs. not-recalled nouns [Schack and Weiss, 2005], and syntactic processing of sentences [Braeutigam et al., 2001]. Among the various approaches for studying synchronization, a number of studies have used coherence as a frequency-dependent measure of functional cooperation between the cortical components of neural networks. In

addition, several studies have attempted to study the temporal course of this functional cooperation during a variety of experimental paradigms, including word and sentence processing [Weiss and Mueller, 2003; Weiss et al., 2005] and finger movement [Nolte et al., 2004].

Using coherence and its phase, investigators have inferred not only functional cooperation between network components, but also information transfer between brain regions with coherent activity during cognitive tasks [Schack et al., 1999, 2003]. In order to study the directionality and intensity of interactions between different neural populations and the electrophysiological signals they generate, the concept of Granger causality may also be invoked. Methods based on this concept may be designed to determine the sources and targets for interactions among brain regions, allowing one to study the dynamic architecture of brain networks involved during cognitive tasks. To measure causality during cognitive tasks, it is important to consider the full set of brain regions that might be responsible for the task. However, Granger causality is defined for a bivariate model and thus can only determine the directionality and intensity of interactions within pairs of signals. Applying this as such to multichannel recordings of brain activity would necessarily result in interactions within each pair of signals, without a clear indication of which interactions are relevant among all recorded sites. If a multivariate approach is used instead, the directionality and intensity of causal interactions can be determined from the global perspective of the whole network. The success and versatility of this approach for measuring causality has been illustrated not only in analyses of simple simulated circuits [Ginter et al., 2005; Kus et al., 2004; Schelter et al., 2006], but also in studies of more complicated systems. For example, multivariate Granger causality has been used to identify functional pathways in a brain-based device modeling cortical-hippocampal interactions during spatial navigation [Krichmar et al., 2005]. This approach has also been used to predict the functional consequences of lesions to a neural network modeling sensorimotor integration of head and eye movements during target fixation [Seth, 2005]. Multivariate causality has also been used in the time-frequency plane by SDTF analysis of multichannel human EEG recorded during motor tasks [Ginter et al., 2001, 2005; Kaminski et al., 2005].

Direct vs. Indirect Causal Interactions

An important problem to be solved by multivariate causality analysis is whether causal interactions are direct and/or indirect. The directness of interactions may be inferred by combining the results of DTF, phase spectrum, and cross-correlogram analyses [Cassidy and Brown, 2003], by using partial direct coherence (PDC) [Baccala and Sameshima, 2001a,b; Sameshima and Baccala, 1999], or by using dDTF [Korzeniewska et al., 2003]. DTF does not distinguish between direct and indirect interactions. Partial coherence does, but does not provide information about

the direction of interactions [Winterhalder et al., 2005]. By combining DTF and partial coherence, dDTF provides information about the directionality of direct interactions [Korzeniewska et al., 2003; Kus et al., 2004]. In this study, we introduce SdDTF, which combines the advantages of dDTF and SDTF in order to elucidate the temporal evolution of exclusively direct causal relationships during multiple trials of an experimental cognitive task. Moreover, the normalization used in SdDTF enables one to compare particular causal relations, e.g. occurring in a particular frequency range, to all the others occurring in an investigated system. In contrast, DTF and PDC are normalized in each frequency separately, which can provide misleading results [Korzeniewska et al., 2003]. Furthermore, DTF and dDTF are normalized to “inflows” only (flows into a particular recorded site), while PDC is normalized to “outflows” only. SdDTF is normalized to all flows (both inflows and outflows) appearing within the studied system, among all studied frequencies.

When using methods based on Granger causality, it is important to remember that the concept is probabilistic rather than deterministic. When the neural network responsible for a cognitive process is only partially observed, it can lead to spurious causalities [Eichler, 2005; Krichmar et al., 2005]. This consideration can be addressed in part by approaches such as PDC, dDTF, and SdDTF, that emphasize direct flows or interactions, as well as by use of a larger number of channels. Nevertheless, it is important to have a relatively comprehensive coverage of the investigated system. This is why for our application of SdDTF to real data, we selected a patient with electrodes covering most of the cortical sites likely to be crucial for language processing. For the same reason we chose all recording sites at which previous analyses of event-related power spectra demonstrated activation during the task. In particular, we studied sites where we had previously observed event-related augmentation of high gamma (80–100 Hz) power in the same ECoG recordings of the same or similar language tasks [Crone et al., 2001b; Sinai et al., 2005]. Our current analyses used a wider high gamma frequency range (80–120 Hz) because studies in our lab and in others [Crone et al., 2001a; Tanji et al., 2005] have shown that high gamma responses are often greatest in this frequency range, though they may extend into even higher frequencies [Crone et al., 2001a]. It is important to acknowledge, however, that in spite of our attempts to include as many potentially relevant brain sites in the MVAR model used for SdDTF and ERC, the possibility remains that our ECoG recordings did not capture all the brain regions responsible for our language task. This potential limitation is not unique to language and will be an important consideration in most functional-anatomic systems. Thus, the interpretation of ERC results in future studies of human brain mechanisms should probably be based upon the commonalities observed among a variety of subjects and recording arrays and should always acknowledge the possibility of relevant activity flows outside of the observed system.

Special Considerations for Multi-Channel ECoG Signals

As mentioned above, using a large number of channels in a multivariate analysis of causality helps to avoid spurious causalities. However, a compromise between the number of channels and the time resolution of analysis must be made in view of the aforementioned inequality (13). SdDTF shows direct flows between recording sites in the time-frequency plane, and the time resolution of the plane depends on the moving window length N_s . For twelve channels ($K = 12$), a model order of ten ($p = 10$), and a hundred repetitions or trials of a task ($n_t = 100$), the window length $N_s > 10K(p + 1)/n_t$ should be $N_s > 13$ samples ($N_s > 39$ ms for sampling frequency 333.33 Hz). Additionally, the number of samples in the window (window length) should be a few times greater than the number of channels. Therefore, we took $N_s = 120$ (360 ms), i.e. 10 times greater than the number of channels. This resulted in a well-fit AR model. For almost all epochs (windows) of the ECoG dataset, the AIC criterion had the same minimum and thus the same model order (see Fig. 1). This indicated that the length of the shifting window (in samples) used in this study was sufficient for our ECoG data. Since the current study focused on the dynamics of signal flow in relation to broadly defined stages of task processing, a higher time resolution was not required. The dependency between the number of channels and the time resolution would be an important consideration for experiments and analyses requiring more precise timing.

Studying the causal interactions among multiple cortical sites is a challenging statistical problem due to the nonstationary nature of ECoG, the expected variation of interactions within baseline and post stimulus periods, and the large number of tested hypotheses. We addressed these problems by assuming *local* stationarity of signals within short time windows and used a large number of trials to reduce the variability of MVAR parameter estimates. Using a moving window approach the procedure estimated SdDTF values between channels as a continuous and smooth function of time. Variability of the SdDTF estimate at every time point (the beginning of the moving window) was estimated using a bivariate smoothing approach. The joint confidence intervals for the differences between the smoothed SdDTF function at each pair of baseline/poststimulus times was obtained by augmenting the pointwise confidence intervals by the corresponding Bonferroni correction. This ensured that the FWER was no larger than a fixed level, in our case $\alpha = 0.05$. If tests are independent, then the FWER is exactly 0.05.

Nonlinear Interactions

It is important to acknowledge that causal interactions can be both linear and nonlinear in brain systems. Several investigators have suggested that nonlinear mechanisms may play a important role in the functional connectivity of

large-scale neural networks [Bekisz and Wrobel, 1999; Breakspear and Terry, 2002a,b; Friston, 1997; Schanche and Eckhorn, 1997; Senkowski et al., 2007]. For example, low frequency oscillations could organize higher frequency ones [Canolty et al., 2006; Friston, 1997]. SdDTF is a linear method and does not give any information about the nature (linear or not) of the causality. Nevertheless, linear methods may be sensitive to both linear and nonlinear causal interactions [Chavez et al., 2003; Freiwald et al., 1999; Gourevitch et al., 2006]. Indeed, MVAR models can be used to describe nonlinear systems [Fraszczuk and Bergey, 1999]. The detection of dependencies by linear methods does not necessitate that the dependencies are of linear nature [Freiwald et al., 1999]. Thus, the ERC method cannot determine if the observed activity flow changes are due to linear vs. nonlinear dynamics. In our subject's data (see Fig. 10), for example, significant changes in activity flow are observed simultaneously for two frequency bands within the analyzed frequency range for flows $E7 \rightarrow E3$ and $E10 \rightarrow E3$ during the "word perception" stage (between markers "s" and "o"), and for flow $E4 \rightarrow E2$ during the "spoken response" stage (after marker "r"). However, we cannot determine whether these simultaneous changes represent separate, independent linear causalities in two frequency bands vs. nonlinear causalities between these two frequencies. It is also possible that ERC reveals nonlinear dependencies between frequencies but shows it for only one of the interrelated frequency bands. A recent study using a nonlinear Granger causality approach [Gourevitch et al., 2006] showed that functions similar to SdDTF (directed coherence and PDC) appear to correctly identify linear linkages even if the autoregressive parts are nonlinear. On the other hand, the nonlinear Granger causality yields some interesting results for complex systems but remains dependent on the parameters of the method (order and scale chosen). This study concluded that if the results are heavily dependent on frequency, methods similar to SdDTF (PDC and directed coherence) may be preferred.

Time-Frequency Characteristics of ERC Flows

Evident in the time-frequency plots of SdDTF, and even more so in those of ERC (see Fig. 10), changes in flows are mostly limited to certain frequency bands, and very rarely do they occur in the entire frequency range of the analysis. This is also illustrated in Figure 14, where ERC is averaged over all channels and over all time points. Five or six overlapping frequency bands are apparent in the figure, with boundaries demarcated by local minima at 89, 95, 100, 106, and 113 Hz. In Figure 10, for example, there is a prominent increase in $E2 \rightarrow E4$ flow in the 82–100 Hz band during the word production stage, an increase in $E5 \rightarrow E4$ flow in the 95–113 Hz band during the response preparation stage, and an increase in $E3 \rightarrow E9$ flow in the 95–120 Hz band during the word perception stage. The finding of flows in a variety of gamma bands is not surprising given the

observations by other investigators of gamma responses in a variety of frequency ranges during language and other cognitive tasks [Bertrand and Tallon-Baudry, 2000; Braeutigam et al., 2001; Ford et al., 2005; Pulvermüller et al., 1997; Tallon-Baudry and Bertrand, 1999; Weiss et al., 2005]. It is intriguing, however, that after exploring a wide range of gamma frequencies without any arbitrary choice of frequency bands, we observed distinct patterns of flow in different, naturally occurring frequency bands during different stages of processing. These findings may complement previous findings in subdural ECoG of a broadband event-related synchronization (ERS, i.e. power increase) over a wide range of high gamma frequencies (60–200 Hz) [Crone et al., 2001a, 2006]. This broadband high gamma activity may represent the spatial and temporal summation of narrower band gamma responses generated by overlapping neuronal networks oscillating at different frequencies [Crone and Hao, 2002; Crone et al., 2006; Pfurtscheller et al., 2003]. Although the current application of ERC to ECoG indicates that significant flows may occur without any apparent power changes, it is at least plausible that both the broadband high gamma ERS and the ERC flows observed in different subregions of the high gamma band reflect the activity of distinct neuronal assemblies that occupy adjacent or identical cortical territory and therefore cannot be resolved without taking into account their interactions with neuronal assemblies in different cortical regions. These interactions, manifesting as ERC flows, could occur at different frequencies according to the local and global resonant properties of the neural networks in which the interacting assemblies are participating, and at different times according to the functional demands of the task. Thus, compared with previous ECoG power spectral analyses, the multichannel approach introduced here may provide additional insights into the functional role of high gamma activity during cortical processing.

Spatial Characteristics of ERC Flows

It is important to note that ERC analyses demonstrated not only local flows in high gamma frequencies within functionally specialized cortical regions, but also long-range flows between putative language regions in frontal, parietal, and temporal lobes (see Fig. 13). The observation of long-range flows is in agreement with the putative role of synchronization across large-scale brain networks during cognitive processes [Bressler and Kelso, 2001; Miltner et al., 1999; Rodriguez et al., 1999; Singer, 1999; Varela et al., 2001]. Cognitive functions such as language likely require the active participation of multiple widely distributed and segregated cortical regions, as well as their cooperative interaction [Matsumoto et al., 2004; Mesulam, 1990; Price, 2000; Vigneau et al., 2006; Weiss and Mueller, 2003; Weiss et al., 2005]. The propagation of oscillatory activity evident in our ERC analyses may reflect the integration of processing in spatially distributed nodes of functionally specialized, e.g. language, networks.

The distributed neural networks involved during cognitive tasks such as language are also expected to interact over short-time intervals. For example, in the word repetition task that was used with our subject, information about speech sounds decoded in auditory association cortex must be rapidly translated into motor commands for spoken responses in premotor and motor cortex. Synchronization of neural activity at gamma frequencies could provide an efficient means of rapidly coupling these spatially disparate cortical regions [Palva et al., 2002; Pfurtscheller and Lopes da Silva, 1999; Schack et al., 2003; Singer, 1993], and synchronization at high-gamma frequencies might provide higher temporal resolution than at lower frequencies [Tanji et al., 2005]. Indeed, we observed many rapid changes in ERC in high gamma frequencies during word repetition. The most striking of these changes occurred at the transitions between putative stages of task processing, often resulting in distinct patterns of ERC for different stages.

We also observed ERC flows in different sub-bands within the high-gamma range. These might reflect interactions within and among networks synchronized at multiple different frequencies, processing information in parallel [Basar-Eroglu et al., 1996]. Processing at different levels of cognitive representation may be instantiated by different distributed cortical networks [Bressler and Kelso, 2001], and a plausible mechanism for this large-scale integration is the formation of dynamic links mediated by synchrony over multiple frequency bands [Varela et al., 2001]. Additionally, interruption of this synchrony, i.e. uncoupling, is necessary to proceed from one cognitive state to another [Rodriguez et al., 1999]. The transitions between cognitive states, e.g. stages of a cognitive task, may require that distributed networks coordinated at one or more frequencies are replaced by new networks coordinated at different frequencies. During different stages of stimulus processing, transitions may occur very rapidly such that a cortical system rapidly breaks functional couplings within one set of areas and establishes new couplings within another set [Bressler and Kelso, 2001]. The changes we observed in ERC flows occurred in multiple discrete frequency bands with temporal courses that appeared to be delimited by the putative stages of task performance, and it seems plausible that these features reflect transitions between distinct cooperating networks.

Functional-Anatomic Correlations With ERC Flows

The spatial-temporal patterns of ERC flows observed in the human ECoG data were generally consistent with the expected topography and timing of activation within and cooperation between cortical language areas during the different stages of word production [Binder et al., 1997; Price, 2000]. There were prominent increases in ERC flow from, within and into auditory association cortex in posterior superior temporal gyrus during the stimulus perception stage of auditory word repetition (see Fig. 13a). Flows

among posterior superior temporal gyrus and inferior parietal lobule, presumably within Wernicke's area, occurred during auditory stimulus perception, as well as during response preparation stages. This area is known for its involvement during auditory processing of spoken words [Binder et al., 1997; Bookheimer et al., 2000]. Moreover, during response preparation, increases in flows were widespread among all the studied cortical areas (auditory association cortex, Wernicke's area, Broca's area and mouth/tongue area of motor cortex) (see Fig. 13b). During this stage there were also flows to mouth/tongue area of motor cortex from Broca's area, known to be involved in different aspects of speech production, e.g. word generation, phoneme discrimination, and semantic processing [Price, 2000]. However these flows were even more prominent during the spoken responses (see Fig. 13c).

We also observed changes in ERC flows between basal temporal cortex, particularly fusiform gyrus, and other cortical language areas. In a previous study we observed event-related increases in high gamma power (80–100 Hz) in the same region during three word production tasks, including word repetition, word reading, and picture naming [Crone et al., 2001b]. Similar high gamma activity (80–120 Hz) was observed in this area by Tanji et al. [2005] during picture naming and lexical decision, with variable responses for different lexical semantic categories (tools vs. animals). Accounts of the function of basal temporal cortex in language typically refer to its role in lexical semantic representations that are probably bilaterally distributed, perhaps explaining why its resection during epilepsy surgery usually does not result in significant language impairment [Krauss et al., 1996; Luders et al., 1991]. Nevertheless, electrocortical stimulation mapping in this area frequently interrupts a number of different language tasks [Schaffler et al., 1994], including the word repetition task used in this study, and the function of this area in this task is expected to depend on dynamic interactions with perisylvian language areas in the dominant hemisphere.

CONCLUSIONS

The SdDTF methods introduced herein were designed to measure direct causal interactions between brain sites with nonstationary activity and to statistically evaluate their evolution in time. For signals in which event-related changes are visible in their spectrograms, there may also be visible changes in ERC during the same timeframe. However, ERC may also reveal changes in the pattern of activity flow between signals for which power spectra remain unchanged. In human ECoG signals, changes in the pattern of ERC depend on the stage of task performance. These changes are in agreement with the expected involvement of particular cortical regions during word production in response to auditory word stimuli. ERC is a sensitive method of determining the directions and intensities, as well as the spectral contents, of changing activity flows during direct interactions between cortical areas.

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