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Estimating Granger causality after stimulus onset: A cautionary note

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Abstract

How the brain processes sensory input to produce goal-oriented behavior is not well-understood. Advanced data acquisition technology in conjunction with novel statistical methods holds the key to future progress in this area. Recent studies have applied Granger causality to multivariate population recordings such as local field potential (LFP) or electroencephalography (EEG) in event-related paradigms. The aim is to reveal the detailed time course of stimulus-elicited information transaction among various sensory and motor cortices. Presently, interdependency measures like coherence and Granger causality are calculated on ongoing brain activity obtained by removing the average event-related potential (AERP) from each trial. In this paper we point out the pitfalls of this approach in light of the inevitable occurrence of trial-to-trial variability of event-related potentials in both amplitudes and latencies. Numerical simulations and experimental examples are used to illustrate the ideas. Special emphasis is placed on the important role played by single trial analysis of event-related potentials in experimentally establishing the main conclusion.

Keywords

Granger causality; single trial analysis; event related potentials; ASEO

Introduction

Invasively-recorded local field potential (LFP) and scalp-recorded electroencephalography (EEG) are widely used electrophysiological measures for investigating the neural mechanisms of cognition. In an event-related paradigm, single trial LFPs or EEGs are traditionally modeled as the linear superposition of a stimulus-locked waveform called event-related potential (ERP) and ongoing activity. Ensemble average is performed to obtain the average ERP which we will henceforth refer to as AERP. Subtracting the AERP from each single trial yields the ongoing brain activity which is further analyzed by time-frequency and functional connectivity methods (Kalcher and Pfurtscheller 1995). The problem with this simple approach is that it does not account for the influence of latency and amplitude variability of the evoked potential across individual trials. In particular, removal of the AERP from individual trials leaves a mixture of ongoing and evoked activities, and the analysis of those ongoing activities in the frequency range overlapping with that of the evoked potential is significantly affected. Truccolo et al.

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(Truccolo et al. 2002) have shown that statistical measures such as power spectral density and coherence evaluated as a function of time by a sliding window approach can exhibit temporal modulations that are artifacts due to the trial-to-trial variability of cortical evoked responses.

Granger causality has emerged in recent years as a useful tool to investigate the directions of neuronal interactions (Hesse et al. 2003; Brovelli et al. 2004; Roebroeck et al. 2005; Seth 2005; Lungarella and Sporns 2006). It can yield insights not possible with other techniques. For example, a time-frequency analysis of Granger causality promises to shed light on the debate regarding whether stimulus-response association is mediated by a pure feed-forward process (Fabre-Thorpe et al. 2001; Thorpe and Fabre-Thorpe 2001) or by an elaborate reciprocal computation involving multiple cortical areas (Ullman 1995; Grossberg 1999; Liang et al. 2000). To achieve a temporal function of Granger causality we fit multivariate autoregressive (MVAR) models to ongoing activity time series in short sliding windows (Ding et al. 2000). One requirement is that the time series in each window be generated by a zero-mean stationary stochastic process. Here zero-mean is defined with respect to an ensemble of realizations (trials). Since the AERP is the ensemble mean of the observed multi-trial data, the removal of AERP from single trial data meets the zero-mean requirement. However, the difference between the individual trial's ERP and the AERP remains in the data, and this difference is not uniform in time (Truccolo et al. 2002), leading to the violation of the stationarity assumption. In this paper, we show that Granger causality, like power and coherence, is adversely affected by the trial-to-trial variability of cortical evoked responses. In particular, without being cognizant of such adverse effects, the analysis result can easily be misconstrued as lending support to the view that stimulus processing in the brain involves reciprocal computation (Liang et al. 2000).

The main conclusion is established by several lines of evidence. First, based on the statistical meaning of Granger causality, we present arguments that predict the outcome of combining the simple AERP removal with the sliding window method in the presence of trial-to-trial evoked response variability. Second, numerical simulations mimicking actual neurophysiological recordings are created. We test the prediction on the simulated data where the correct answers are known. Third, we test the prediction on LFP data acquired from a monkey performing a visuomotor task. A novel single trial analysis method named Analysis of single trial evoked response and ongoing activity (ASEO) is used to separate the evoked response from the ongoing activity on a trial-by-trial basis (Xu et al. in press). This allows us to demonstrate that the observed temporal modulation of Granger causality may not reflect temporally resolved feedforward and feedback stimulus processing but may be the result of incomplete removal of evoked activity which varies from trial to trial.

Methods

MVAR model and Granger causality estimation

Granger causality is based on the idea of prediction. For two simultaneously measured jointly stationary time series, one series can be called causal to the other if we can better predict the second by incorporating past knowledge of the first (Wiener 1956; Granger 1969). Granger causality analysis can be performed in the time-domain as well as in the frequency-domain. We summarize the basic steps here. For more details see Ding et al. (2006). Let $\mathbf{W}_t = [\mathbf{X}_t, \mathbf{Y}_t]'$ be a two dimensional stationary time series, where the prime denotes matrix transposition. Under fairly general conditions, $\mathbf{W}_t$ could be represented by the following bivariate autoregressive process:

$$W_t + \sum_{i=1}^{\infty} A_i W_{t-i} = \varepsilon_t \tag{1}$$

where $\mathbf{A}_i$ are 2 by 2 coefficients matrices. Equation (1) can be recast in component form,

$$X_t + \sum_{j=1}^{\infty} a_{2\,j} X_{t-j} + \sum_{j=1}^{\infty} b_{2\,j} Y_{t-j} = \varepsilon_{2t}$$

$$Y_t + \sum_{j=1}^{\infty} c_{2\,j} X_{t-j} + \sum_{j=1}^{\infty} d_{2\,j} Y_{t-j} = \eta_{2t}$$

where $\boldsymbol{\varepsilon}_{2t}$ and $\boldsymbol{\eta}_{2t}$ are uncorrelated over time with contemporaneous covariance matrix $\boldsymbol{\Sigma}$:

$$\sum = \begin{pmatrix} \sum_2 & \Upsilon_2 \\ \Upsilon'_2 & \Gamma_2 \end{pmatrix}$$

With finite data the above infinite series representation must be truncated to finite order. The correct model order is usually determined by minimizing the Akaike Information Criterion (AIC) (Akaike 1974). Standards techniques, such as the Levinson, Wiggins, Robinson (LWR) algorithm, can be used to estimate $\mathbf{A}_i$ and $\boldsymbol{\Sigma}$ (Ding et al. 2000). Once an autoregressive model is adequately determined, i.e. $\mathbf{A}_i$ and $\boldsymbol{\Sigma}$ are known, we obtain the spectral matrix as

$$S(\omega) = \begin{pmatrix} S_{xx}(\omega) & S_{xy}(\omega) \\ S_{yx}(\omega) & S_{yy}(\omega) \end{pmatrix} = H(\omega) \sum H^*(\omega)$$

where $H(\omega) = \begin{pmatrix} H_{xx}(\omega) & H_{xy}(\omega) \\ H_{yx}(\omega) & H_{yy}(\omega) \end{pmatrix} = \left(\sum_{j=0}^{m} A_j e^{-i\omega j} \right)^{-1}$ and $\mathbf{A}_0$ is the identity matrix.

The total interdependence between $\mathbf{X}_t$ and $\mathbf{Y}_t$ at frequency ω is defined as

$$f_{X,Y}(\omega) = \ln \frac{S_{xx}(\omega)\, S_{yy}(\omega)}{|S(\omega)|}$$

The causal influence from $\mathbf{Y_t}$ to $\mathbf{X_t}$ at frequency ω is defined as

$$f_{Y \to X}(\omega) = \ln \frac{S_{xx}(\omega)}{\underset{\sim}{H}_{xx}(\omega) \sum_2 \underset{\sim}{H}^*_{xx}(\omega)}$$

where $\tilde{H}_{xx}(\omega) = H_{xx}(\omega) + \frac{\Upsilon_2}{\Sigma_2} H_{xy}(\omega)$.

Likewise, the causal influence from $\mathbf{X_t}$ to $\mathbf{Y_t}$ at frequency ω is defined as

$$f_{X \to Y}(\omega) = \ln \frac{S_{yy}(\omega)}{\tilde{H}_{yy}(\omega)\, \Gamma_2 \tilde{H}^{*}_{yy}(\omega)}$$

where $\tilde{H}_{yy}(\omega) = H_{yy}(\omega) + \frac{\Upsilon_2}{\Gamma_2} H_{yx}(\omega)$. These spectral functions can be integrated over the entire frequency domain to obtain their respective time-domain counterparts.

ASEO single trial analysis

A number of techniques for the trial-by-trial estimation of event-related potentials have been developed, including the Woody matched filter method (Woody 1967), the frequency domain maximum likelihood method (Jaskowski and Verleger 1999; de Munck et al. 2004), the wavelet method (Demiralp et al. 1999), the fragmentary decomposition approach (Melkonian et al. 2001), and Bayesian inference based methods (Truccolo et al. 2003; Knuth et al. 2006). The Analysis of Single-trial Evoked response and Ongoing activity or ASEO method differs from the past approaches in that it models the evoked responses and the ongoing activity simultaneously (Xu et al. in press). As shown in equation (2), the starting point of the ASEO method is the Variable Signal Plus Ongoing Activity (VSPOA) model of single trial time series recordings (Truccolo et al. 2003; Chen et al. 2006),

$$x_r(t) = \sum_{n=1}^{N} \beta_{rn}\, s_n(t - \tau_{rn}) + z_r(t) \tag{2}$$

where $x_r(t)$ ($r = 1, 2, \cdots R$ and $t = 0, 1, \cdots T - 1$) is the observed LFP or EEG discrete-time signal of the rth trial (R and T being the number of trials and the number of data samples for each trial, respectively), $s_n(t)$ ($n = 1, 2, \cdots N$) is the unknown ERP component waveform (N being the total number of components) with a trial-to-trial variable amplitude scaling factor and latency shift given by β_{rn} and τ_{rn}, respectively, N is the total number of components, and $z_r(t)$ is ongoing activity which includes all the non-phase-locked signals and is assumed to be a zero mean AR random process,

$$z_r(t) = \sum_{k=1}^{K} a_k z_r(t - k) + e_r(t) \tag{3}$$

where a_k ($k = 1, 2, \cdots K$) is the kth unknown AR coefficient, K is the AR model order, and $e_r(t)$ is a white noise with zero-mean and variance σ^2 to be estimated from data.

By applying the discrete Fourier transform (DFT) to (2), we obtain its frequency-domain representation as,

$$X_r\ (\omega) = \sum_{n=1}^{N} \beta_{\mathrm{rn}} e^{-j\omega\tau_{\mathrm{rn}}} S_n\ (\omega) + Z_r\ (\omega)$$

where $X_r\ (\omega)$, $S_n\ (\omega)$ and $Z_r\ (\omega)$ stand for the Fourier transforms of $x_r\ (t)$, $s_n\ (t)$ and $z_r\ (t)$, respectively. We know that $Z_r\ (\omega)$ for different values of r and ω are independently and identically distributed (i.i.d.) circularly symmetric complex Gaussian random variables with zero-mean and unknown variance $f\ (\omega)$ where

$$f\ (\omega) = \frac{\sigma^2}{\left| 1 - \sum_{k=1}^{K} a_k e^{-jk\omega} \right|^2}$$

is the power spectral density (PSD) of the ongoing activity in (3).

The negative log-likelihood function of the LFP or EEG data is:

$$L = \sum_{r=1}^{R} \sum_{\omega=0}^{\lceil \frac{T}{2} \rceil \omega_0} \left\{ \ln f\ (\omega) + f^{-1}\ (\omega) \left| X_r\ (\omega) - \sum_{n=1}^{N} \beta_{rn} e^{-j\omega\tau_{rn}} S_n\ (\omega) \right|^2 \right\} \quad (4)$$

Minimizing (4) with respect to $S_n\ (\omega)$, β_{rn}, τ_{rn}, a_k and σ^2 yields the maximum likelihood estimates of the unknown parameters. However, in general, the minimizer of (4) cannot be produced in closed-form. Consequently, the ASEO algorithm used an iterative approach to solve this problem. The algorithm includes two main steps, the Frequency-step or F-step and the Time-step or T-step, which are iterated. In the F-step, using the most recently available estimate of the PSD of the ongoing activity, the waveforms of the ERP components $S_n\ (\omega)$ and their single-trial latency shifts (τ_{rn}) and the amplitude scaling factors (β_{rn}) are estimated in the frequency domain by the maximum likelihood method. In the T-step, the AR model parameters of the ongoing activity are estimated in the time domain based on the most recently estimated ERP parameters using an approximate maximum likelihood method. These two steps are iterated until no further improvement is seen in the estimated quantities.

Estimation of ongoing activity

In this work we contrast two ways of extracting the ongoing activity $z_r\ (t)$ during the time period in which sensory stimulus is being processed. The traditional way is to calculate AERP by averaging $x_r\ (t)$ with respect to the trial index r and then subtract the AERP from $x_r\ (t)$. We refer to the result obtained this way as the residual. It is clear from equation (2) that this residual is a mixture of ongoing activity and event-related potentials (Truccolo et al. 2002). The other way, which is a more principled way according to the VSPOA model in equation (2), is to estimate the event-related potentials $\sum_{n=1}^{N} \beta_{rn} s_n\ (t - \tau_{rn})$ on a trial-by-trial basis and subtract it from $x_r\ (t)$.

Experimental data

Experiments involved a highly trained macaque monkey performing a visual-motor pattern discrimination task at the Laboratory of Neuropsychology, National Institute of Mental Health (Bressler et al. 1993; Ledberg et al. 2007). Animal care was in accordance with institutional guidelines. Event-related local field potentials (LFPs) were simultaneously recorded from multiple surface-to-depth bipolar teflon-coated platinum electrodes, chronically implanted in the cerebral hemisphere contralateral to the monkey's preferred hand. Data from up to 16 channels (sites) were analog filtered (-6 dB at 1 and 100 Hz, 6 dB per octave falloff) and digitized at 200 samples/second. The monkeys initiated each trial by depressing a lever with the preferred hand. Data collection began about 90 ms prior to stimulus onset and continued until 500 ms post-stimulus. Each stimulus consisted of four dots arranged as a (left- or right-slanted) line or diamond on a display screen. Monkeys responded (Go condition) to one visual pattern type (line or diamond), and withheld response (No-Go condition) to the other. Only Go trials from a striate channel and a prestriate channel are considered in the present study.

Results

Theoretical consideration

To establish the specific manner in which trial-to-trial variability of event-related potentials adversely affects the time-frequency analysis of Granger causality, we consider a simple conceptual model. The goal is to generate predictions that can be tested on both simulated and experimental data. Figure 1(a) and (b) show event-related potentials simulated by sinusoids from two channels. By construction, channel 2 (Fig. 1(b)) lags behind channel 1 (Fig. 1(a)) by 20 ms, and the amplitudes of the two channels are assumed to be correlated on a trial-by-trial basis. Physiologically, one may view channel 1 as arising from a primary sensory area while channel 2 from an association area. To calculate Granger causality between these two channels, we follow the traditional approach by first obtaining the AERP through averaging and then subtracting AERP from each trial to produce the residual data (Figures 1(c) and 1(d)), which are then subjected to a sliding window analysis. For the 50 ms window between the two solid lines, the strong activity in channel 1 temporally precedes that in channel 2. Since these activities are correlated, we will see a causal influence from channel 1 to channel 2 by the definition of Granger causality. As the window is moved to between the dashed lines, the opposite occurs. Specifically, the temporal precedence of strong activity in channel 2 over that in channel 1 will result in a causal influence from channel 2 to channel 1. In general, as the analysis window is moved through the entire trial, one may observe multiple episodes of causal influence reversals, depending on the morphology of the ERPs. Such intricate temporal patterns of Granger causality modulations are clearly artifactual and are the result of three factors. First, the event-related potentials from two different channels are of a similar shape and have a distinct temporal offset. Second, the two event-related potentials have correlated trial-to-trial variability. Third, the time-frequency analysis of Granger causality is carried out by employing a small moving window. It is worth noting that an analysis with a long time window extending over the entire evoked response will result in a predominantly unidirectional driving from channel 1 to channel 2.

Simulation

We first tested the above theoretical prediction on simulated data. The event-related potentials were produced by one cycle of 12 Hz sinusoidal waves which were then combined with ongoing activities. The single-trial amplitudes of the sinusoidal wave for the first channel were drawn independently from a uniform distribution between 2 and 12. The single-trial amplitude for the second channel was the amplitude of the first channel plus standard Gaussian noise. This ensures that the amplitudes of the two channels are correlated. For added realism we also included single-trial latency shifts for the ERP components and they were uniformly distributed

random variables between 0 and 10 ms. An ensemble of 500 trials of LFPs, each with 120 data points, was generated. At a sampling rate of 200 Hz, each trial was 600 ms long, 100 ms of which occurred prior to stimulus onset (0 ms). As in the conceptual example, the ERP for the first channel started about 50 ms after the stimulus onset, while the ERP from the second channel was delayed by about 20 ms. The ongoing activity for both channels was Gaussian white noise processes with zero mean and 0.05 standard deviation. These two noise processes were uncorrelated with each other. Figure 2 (a) and (b) showed the 500 simulated realizations (trials) (channel 1 (a) and channel 2 (b)).

Following the traditional approach, the AERPs for both channels were calculated and removed, and an analysis window of 50 ms in duration moving with a 10 ms increment was applied to the residuals. Figure 2(c) showed the power as a function of time and frequency for channel 1. Consistent with the analysis of Truccolo et al. (Truccolo et al. 2002), increased power in the band of 10 to 20 Hz coincided with the occurrence of the event-related potential and is the consequence of the mixture of ongoing activity and ERPs left in the residual by the AERP removal method. Choosing the middle of the frequency band underlying the power burst we estimated Granger causality at 15 Hz as a function of time and the result was shown in Figure 2(d). From the construction of the signals, it is clear that the ongoing activities from these two processes were independent and the event-related potential in channel 2 is a time-delayed version of that in channel 1. The figure, however, revealed an intricate causal influence pattern where channel 1 first exerted a causal influence on channel 1 starting around 80 ms post stimulus, which was followed by a reciprocating causal influence from channel 2 to channel 1 starting around 100 ms. Further causal interactions ensued between 110 ms and 140 ms. This alternating causal influence pattern was as predicted by the conceptual model and the three essential factors for its occurrence were present here by construction. We note that the reciprocal causal influence pattern seen here is not the property of the selected frequency. Similar findings existed for the time–domain Granger causality which was obtained by integrating spectral Granger causality over the entire frequency domain (0-100 Hz).

Experiment

Two channels of LFP recordings, one from the striate cortex (channel S) and the other from the prestriate cortex (channel P) were considered. The superposition of 1429 trials of LFPs was shown in Figure 3(a) and (b). Figure 3(c) displayed the AERPs from both channels. It is clear that the two AERPs are of a similar shape and there is a delay of about 15 to 20 ms between them. Physiologically, the striate cortex precedes prestriate cortex in the anatomical organization of the visual system (Felleman and Van Essen 1991). Thus, the delay may reflect the latency difference in stimulus information arrival at the two recording sites. The residuals after AERP removal for channel S and P were shown in Figure 3(d) and (e), respectively. Choosing a 50 ms window and sliding this window 10 ms each time, the coherence function at 15 Hz was evaluated on the residuals and was shown in Figure 3(f). The strong coherence between the two channels in the interval from 80 and 180 ms, according to Truccolo et al. (Truccolo et al. 2002), is attributable to the correlated single trial responses from the two channels. These observations suggest that the three factors discussed in the context of the conceptual example were present in this experiment, and we thus predicted that reciprocal causal influences existed between channel S and channel P, with channel S initiating the exchange. Figure 3(g) confirmed this prediction by showing Granger causality at 15 Hz as a function of time. Again, the frequency chosen here was not a determining factor. Similar results were found for the time-domain Granger causality.

Unlike the simulation example, the true answer in experimental data was not known *a priori*. To establish that trial-to-trial variability of event-related potentials underlined the observed temporal modulation of causal influences, we applied the ASEO method to extract the event-

related potential on a trial-by-trial basis. Two components were modeled (N=2 in equation (2)) (Xu et al. in press). Here the value of N was chosen in the following way. First, inspection of AERP revealed two major components (Fig 3(c)), one being a negative potential peaking around 100 ms and the other being a positive potential peaking between 200~300 ms. Second, ASEO was applied with this initial choice of N=2 to separate ERPs from ongoing activity. The accuracy of the estimation was assessed by comparing the average of single trial ERPs with that of the raw LFP recordings (see below). Third, nearby N values (N=1 and N=3) were used to check whether N=2 yielded optimal performance. Figure 4 (a) and (b) showed 1429 trials of recovered single trial event-related potentials for both channels. Ongoing activities recovered by removing event-related potentials on a trial-by-trial basis were displayed in Fig. 4(c) and (d). It is worth noting that the LFP data in Fig. 3(a) and (b) are the linear superposition of the single trial event-related potentials in Fig. 4(a) and (b) and the ongoing activities in Fig. 4(c) and (d). To assess the veridicality of the ASEO method, in Fig. 4(e), ensemble averages (AERPs) of the raw LFP data in Fig. 3(a) and (b) were compared with ensemble averages of recovered single trial ERPs in Fig. 4(a) and (b). The excellent agreement between the two averages was taken as evidence that the ASEO method accurately extracted single trial event-related potentials from raw LFP time series data.

After the separation of evoked responses from ongoing activity we proceeded to obtain two additional results. First, coherence and Granger causality at 15 Hz as functions of time was calculated on the ongoing activity (Fig. 4(c) and (d)) and shown in Fig. 5(a) and (b), respectively. It can be seen that both coherence and Granger causality were greatly reduced in the period of 80 to 180 ms post stimulus onset compared with those shown in Fig. 3(d) and (e). Second, to further demonstrate that the alternating pattern of causal influence in Fig. 3(g) is the consequence of trial-to-trial variability of the ERPs, we analyzed the single-trial event-related potential data in Fig. 4(a) and (b) in a way similar to that used to analyze the conceptual model in Fig. 1, where simulated single-trial ERPs were considered. After the ensemble averages were calculated for the data in Fig. 4(a) and (b) they were removed from the individual traces to yield residuals. This is analogous to the steps leading from Fig. 1(a) and (b) to Fig. 1 (c) and (d). The residuals in this case represented the differences between individual trials' ERPs and their ensemble AERP. As expected, a moving window analysis performed on the so-obtained residuals revealed a reciprocal causal influence pattern as shown in Fig. 5(c). These findings suggested that the patterns in Fig. 3(g) were largely the result of trial-by-trial correlated variability of two event related potentials with a time offset between channels S and P.

Discussion

The classical approach to cognitive neuroscience views the event-related potential as the signal and the ongoing activity as noise to be eliminated with averaging. Extensive research over the past two decades shows that this view is overly simplistic. Ongoing processes, rich in oscillation and synchronized activity, provide another powerful index of cognitive operation (Singer 1993; Herrmann and Knight 2001; Liang et al. 2002). In light of this revelation, how to recover the ongoing activity during the post-stimulus time period is a question of practical importance. The naïve method of simply removing ensemble average (AERP) from single trial recordings is not always viable. Truccolo et al. (Truccolo et al. 2002) has performed detailed analysis to demonstrate that power as well as functional connectivity measures such as coherence can exhibit temporal modulations that is artifactual caused by the trial-to-trial variability of event-related potentials. Without being cognizant of this underlying reason one may erroneously attribute physiological significance to such temporal modulations.

In this work we extend the previous work to the domain of Granger causality analysis. Granger causality has emerged in recent years as a leading empirical method for determining the direction of neural information transmission among different brain areas (Ding et al. 2006).

Applied to ongoing activity in the absence of sensory stimulation, it has revealed insights into the organization of large-scale cortical networks not possible with other methods (Brovelli et al. 2004; Chen et al. 2006). Currently, attempts are being made to examine cortical sensorimotor processing with this method. The accurate recovery of ongoing activity during the post-stimulus time period, however, presents a challenge. In this paper, we showed, with both simulated and experimental data, that trial-to-trial variability of stimulus-elicited event-related potentials can adversely impact a time-frequency analysis of Granger causality. In particular, the temporally alternating patterns of causal influence between a lower and higher sensory areas, while artifactual, may be misconstrued as evidence contributing to the debate regarding the manner with which the brain processes sensory input leading to motor output (Ullman 1995; Grossberg 1999; Liang et al. 2000; Fabre-Thorpe et al. 2001; Thorpe and Fabre-Thorpe 2001). Three factors are identified as essential in generating the observed temporal modulation. First, the event-related potential from one channel leads that from the second channel, and these potentials have similar waveforms. Second, the amplitudes and/or latencies from the two event-related potentials are correlated. Third, a small moving window is employed for the time-frequency analysis of Granger causality. Being cognizant of these factors and their effect on Granger causality analysis is crucial in the proper interpretation of experimental data. It should be noted that if a time window long enough to encompass all the main components of the ERP trace is utilized, the temporal alternation pattern in Granger causality will be replaced by a predominantly unidirectional driving from the early evoked activity to the late evoked activity, a result that is again artifactual.

ERP studies became feasible in the 1960s with the advent of computer technology. From the outset, the trial-to-trial variability issue was being noticed, and sometimes made use of. In conjunction with simple stimulus-response paradigms, Morrell and Morrell (Morrell and Morrell 1966) proposed to divide the total collection of trials into subensembles according to the level of response time (RT). Averages were performed for each subensemble and the resulting ERP waveforms were then compared. This technique, referred to as *subensemble averaging*, opens the possibility of examining the brain's activation patterns as a function of a behavioral variable (e.g. RT) and is still in use today (Liang et al. 2002). The first method dealing with evoked potential data on a single-trial basis was Woody's adaptive matched filter technique (Woody 1967). Here, a grand average (AERP) is first performed and a component of interest is identified whose waveform is used as a template. Cross correlation between this template and the single-trial time series is calculated over a pre-specified time interval that is stepped through the entire trial to yield latency and amplitude for each trial. While the original goal is to get a better ERP by adjusting for latency variability, recent work has shown that latency and amplitude on a trial-by-trial basis can be interesting physiological variables in their own right (Truccolo et al. 2003; Knuth et al. 2006). Since these early studies numerous other statistical methods for estimating single trial ERPs have appeared (Jaskowski and Verleger 1999; Melkonian et al. 2001; Truccolo et al. 2003; de Munck et al. 2004; Knuth et al. 2006). For the purpose of this work a proper model of single trial recordings is an important starting point. Recognizing that the ERP is comprised of time-resolved components and these components can vary with respect to one another from trial to trial, Truccolo et al. (2003) and Knuth et al. (2006) have developed the differentially Variable Component Analysis (dVCA) method, based on the VSPOA model in equation (2). The dVCA method is formulated in the time-domain and treats the ongoing activity as white noise. The Analysis of Single-trial Event-related potential and Ongoing activity (ASEO) (Xu et al. in press) used here is a further improvement over the dVCA method in that it is formulated in the spectral domain, which allows for a more accurate estimate of latency, and treat the ongoing activity as an autoregressive process to be estimated from data. The effectiveness of this method has been demonstrated in Xu et al. (in press), and is also evidenced in Fig. 4(e), where the AERPs calculated from the raw LFP data are seen to be nearly identical to that calculated by averaging the single trial ERPs estimated by ASEO. The work presented here shows that the use of an

effective single trial method is essential in experimentally establishing that trial-to-trial variability of event-related potentials underlies the observed temporal patterns of Granger causal influences.

In the absence of stimulation the state of the brain is characterized by ongoing neural activity. The distinction between the analysis of this state and that of the stimulus processing state has not escaped the notice of an early pioneer. In an article entitled “The theory of prediction,” which laid the conceptual foundation of the modern Granger causality estimation, Wiener (1956) wrote: “Or again, in the study of brain waves we may be able to obtain electroencephalograms more or less corresponding to electrical activity in different parts of the brain. Here the study of the coefficients of causality running both ways and of their analogues for sets of more than two functions may be useful in determining what part of the brain is driving what other part of the brain in its normal activity. This is the key phrase, as the method does not intrinsically involve the introduction of artificial stimuli into different parts of the brain. The danger of introducing such stimuli is that by their intensity and brusqueness they may tear new paths through the brain which are followed by its normal activity and which may be considered in a certain sense artifacts.”

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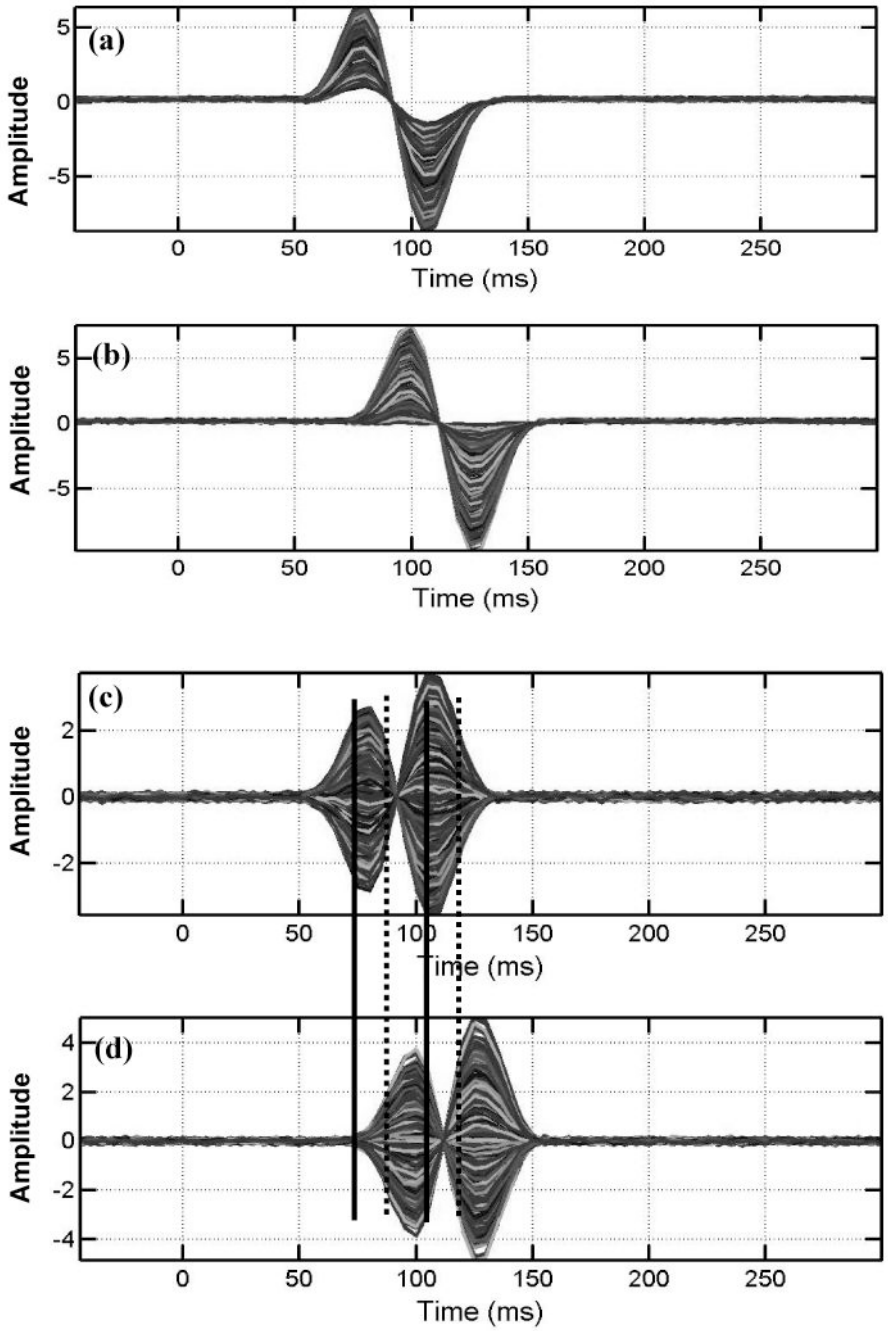


Figure 1.
A conceptual model. (a) and (b): 500 trials of simulated data from channel 1 and 2, respectively. (c) and (d): residuals after subtracting the ensemble averages. Two analysis windows are delineated by the interval between the two solid lines and that between the two dashed lines. Vertical axis: arbitrary unit.

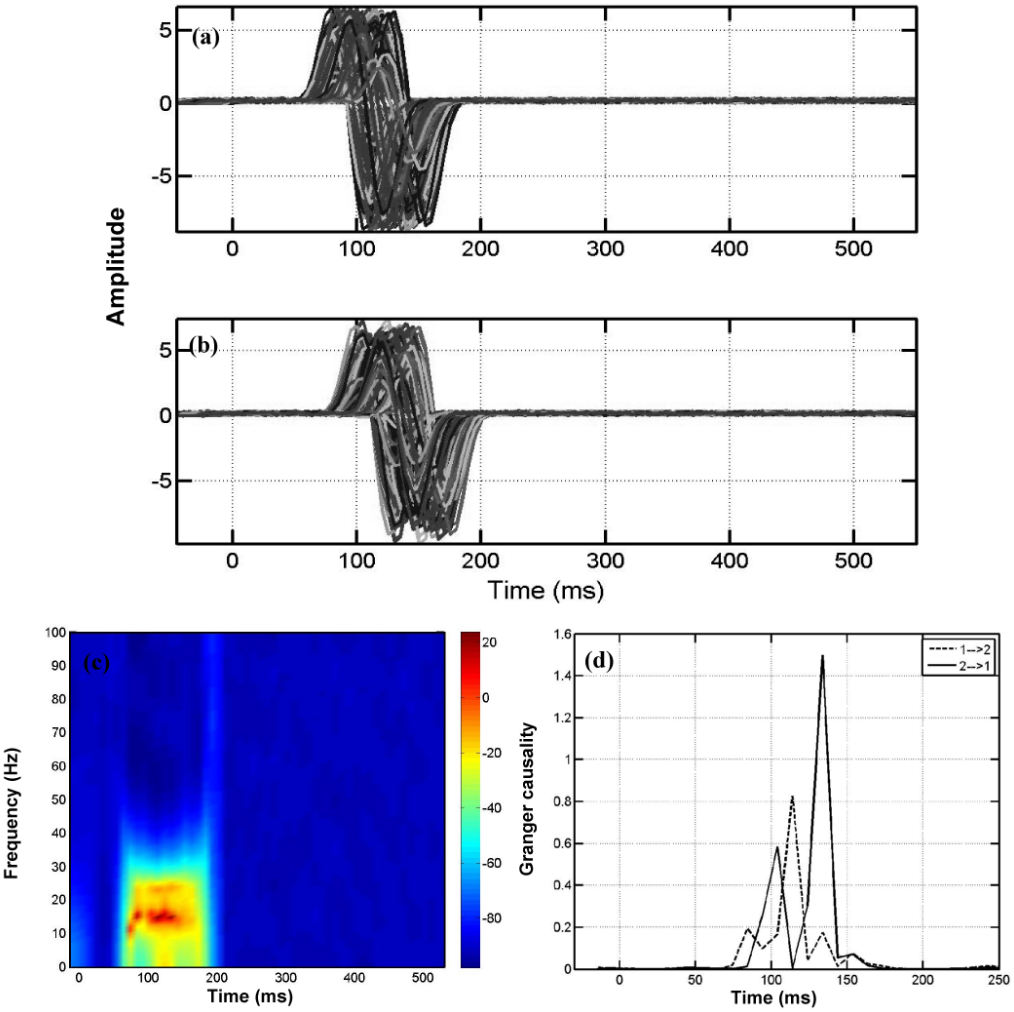
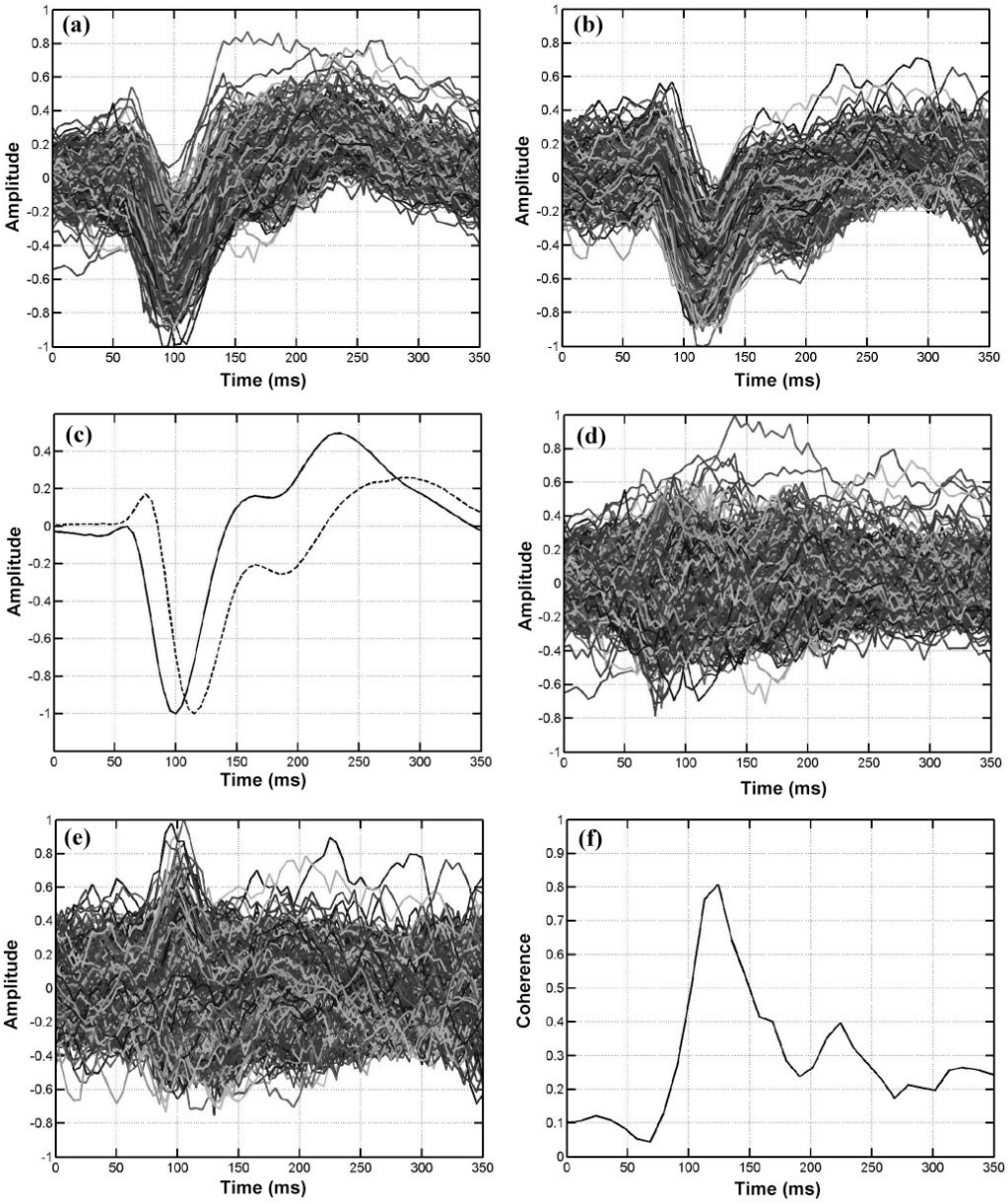


Figure 2.

500 realizations of simulated data from channel 1 (a) and channel 2 (b). Both latency variability and amplitude variability are considered. Vertical axis: arbitrary unit. (c) Time-frequency plot of power for channel 1. (d) Granger causality at 15 Hz as a function of time. Dashed line: channel 1 → channel 2. Solid line: channel 2 → channel 1.



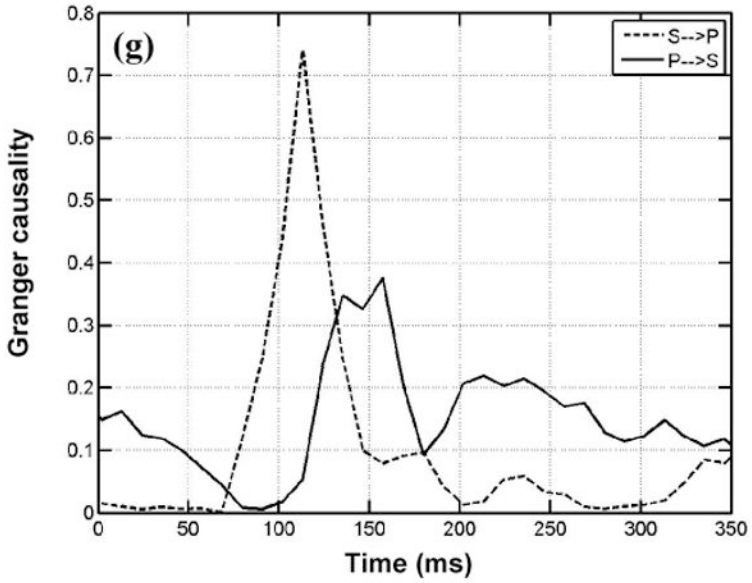


Figure 3.
(a) and (b): single trial LFPs from channel S (striate cortex) and channel P (prestriate cortex), respectively. The amplitudes are normalized. (c) AERPs for channel S (solid line) and channel P (dashed line). (d) and (e): residuals obtained by removing AERP from single trial LFPs. (f) Coherence at 15 Hz as a function of time between the two channels using the residuals after AERP removal. (g) Granger causality at 15 Hz as a function of time between the two channels using the residuals after AERP removal. Dashed line: channel S → channel P; solid line: channel P → channel S.

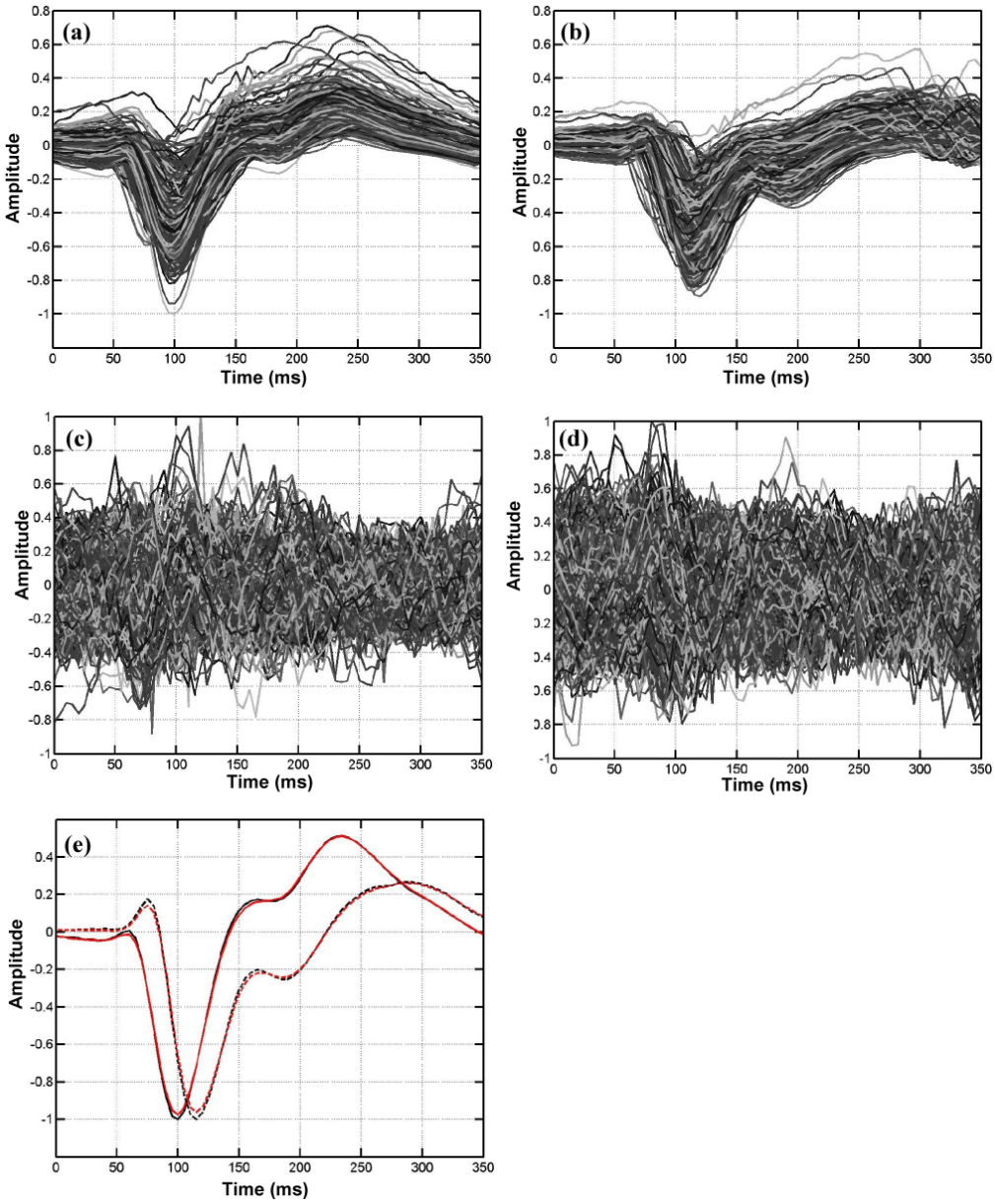


Figure 4.

Single trial event-related potentials for (a) channel S and (b) channel P extracted by the ASEO method from data in Fig. 3(a) and (b). (c) and (d): ongoing activities obtained by removing single trial event-related potentials in Fig. 4(a) and (b) from data in Fig. 3(a) and (b). (e): AERPs from data in Fig. 4(a) and (b) (red) plotted together with AERPs (black) from data in Fig. 3(a) and (b) for channel S (solid line) and channel P (dashed line).

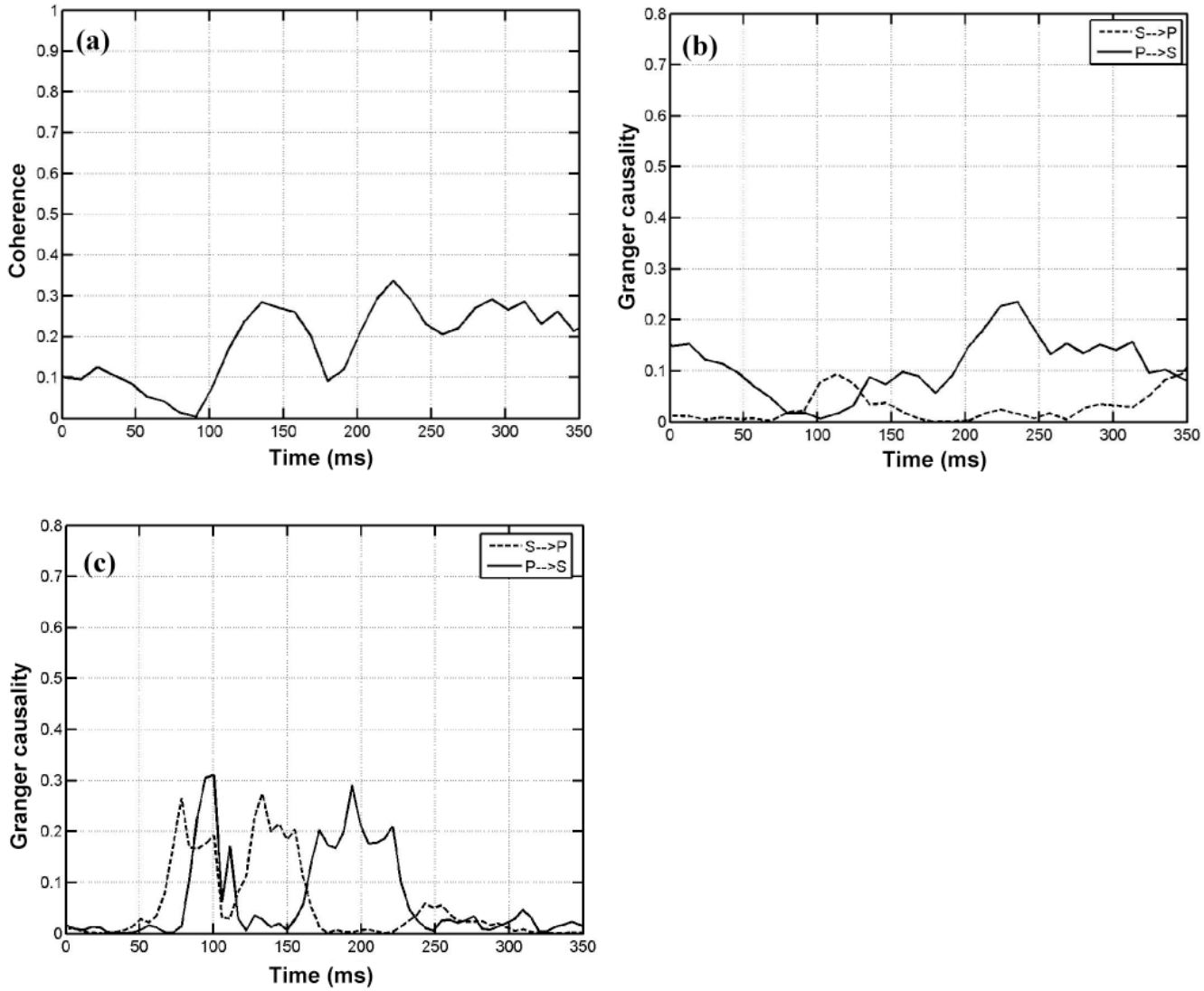


Figure 5.

(a): Coherence at 15 Hz as a function of time between channels S and P using the ongoing activity in Fig. 4(c) and (d). (b): Granger causality at 15 Hz as a function of time between channels S and P using the ongoing activity in Fig. 4(c) and (d); dashed line: channel S → P; solid line: channel P → S. (c): Granger causality at 15 Hz as a function of time for data in Fig. 4(a) and (b). Dashed line: channel S → P; solid line: channel P → S.