

## EVENT-RELATED POTENTIALS

STEVEN L. BRESSLER  
Florida Atlantic University  
Boca Raton, Florida

MINGZHOU DING  
University of Florida  
Gainesville, Florida

### 1. ELECTROMAGNETIC BRAIN ACTIVITY

#### 1.1. Genesis

Electromagnetic activity is generated by neurons in the cerebral cortex and subcortical structures of the brain. Neurons generally differ from other cell types of the body by being specialized for the reception, integration, and conduction of excited states. The shape of the neuron is related to its specialized function. Two types of branching extension of the cell body, the dendrite and the axon, allow the neuron to receive excited states from, and transmit them to, other neurons.

The dendrites are specialized to receive excited states (and inhibition) from other neurons at synapses, where the release of chemical transmitter from the presynaptic axon terminal causes postsynaptic ion channels gated by ionotropic receptors to open. Transmembrane current flow through the open ion channels ensues, driven by the electromotive force across the postsynaptic membrane (1). The electromotive forces at synaptically opened ion channels distributed over the branches of a neuron's dendritic tree drive current flow in closed loops. Excitatory synapses create loop currents consisting of net positive charge that flows inward across the postsynaptic dendritic membrane, passes through the intracellular compartment, flows outward across passive membrane with a strength that decreases with distance from the sites of influx, and finally completes the loop through the extracellular space. The excitatory postsynaptic potential is a depolarization of the dendritic transmembrane potential due to this net inward flow of positive current across the postsynaptic membrane. Loop currents created by inhibitory synapses flow in the opposite direction (1,2). The net outward flow of positive current across the postsynaptic membrane at inhibitory synapses produces a hyperpolarization called the inhibitory postsynaptic potential.

Loop currents establish a gradient of transmembrane potential that continuously varies in time and spatially along the dendrites as a function of current strength. The sum of currents contributed by all the active synapses on the dendritic tree produces a resultant transmembrane potential at the cell body and the initial segment of the axon. A critical effect of the loop currents occurs when this resultant potential exceeds the firing threshold and the initial segment responds by generating a train of pulses (action potentials). Each pulse, with a relatively fixed amplitude and duration, actively propagates along the axon, diverging into axonal branches and reaching all the branch terminals, at whose synapses chemical transmitters are released.

In the extracellular space, loop currents generated by neighboring neurons summate when they flow in the same direction, and cancel otherwise. The passage of current across the resistance in this space is manifested by an extracellular electrical field of potential, or field potential. The field potential recorded by an electrode in the extracellular space represents the sum of potentials associated with the loop currents generated by a set of active neurons. The intracellular components of the same closed-loop currents that give rise to the field potential are primarily responsible for the closely related magnetic field (3).

The magnitude of the field potential recorded by an extracellular electrode (with respect to a neutral reference) at any instant in time depends on multiple factors, including the number of active nearby neurons, the strength and directions of their currents, their morphology and alignment, and the position of the electrode in the field. For a population of neurons to generate a strong field potential, it is not sufficient that the neurons actively generate strong extracellular currents. The morphology and alignment of those neurons must also promote the summation of the currents in the extracellular space. For example, the field potential generated by a population of neurons in which the orientations of the dendrites are uniformly distributed in all directions is zero, on average, due to cancellation of extracellular currents, even if the individual dendrites are all maximally excited. On the other hand, parallel alignment of the dendrites promotes extracellular current summation if the same portion of each dendrite, e.g., the distal end, is excited. However, cancellation may still occur if the location of the excitation is randomly distributed along the dendrites.

In general, populations in which the neurons each have a single long dendrite aligned in parallel across the population, and concurrently receive either excitation or inhibition at the same dendritic locale, e.g., distal or proximal end, tend to generate extracellular currents that maximally summate and augment the field potential. This type of population is called a dipole generator and the field it generates is a distributed dipole field, meaning that the summated loop currents which emerge from one end (pole) of the dendrites are detected by an extracellular electrode there as a current source, and the currents that enter into the other end (pole) are detected by an extracellular electrode there as a current sink (1). An important property of such a dipolar source-sink population geometry is that it generates an open field, meaning that the currents spread in the volume of the brain and can be detected at a distance from the generating population (4). A superficial cortical sink is recorded as a negative potential, and a superficial source as a positive potential, by an electrode in the superficial cortical layers, at the cortical surface, or at the scalp (5).

The question of what causes field potentials to change over time is central to understanding the relation of ERPs to brain function. Although the determinants of temporal variation of the field potential are diverse, and their effects are not well understood, some basic aspects of neuronal population activity that bring about temporal variation of its generated field potential may be identified (6). One

important aspect is the number of unitary generators contributing to the population activity and the magnitudes of the currents that they generate. Another crucial aspect is synchrony, the tendency for the outputs of the unitary generators in the population to similarly change in time. Factors such as inputs from other populations and intrinsic changes in the excitability of the population can affect both the total magnitude of currents generated by the neurons of the population and their degree of their synchrony. These factors thus influence the time course of the population field potential and ultimately determine the dynamics of Event-Related Potential (ERP) generation in relation to brain function.

## 1.2. Measurement

Electrical field potentials of the brain may be recorded from a variety of different types and sizes of electrode, placed at a variety of locations within or outside the head. The nature, size, and location of both the indicator and reference electrodes are important for determining the spatial scale of integration of the field potential that is represented by a recorded voltage trace, as well as the recorded voltage range. Microelectrodes placed directly within the brain record field potentials, integrated on a submillimeter scale, that are predominantly generated by local neuronal populations. In order to truly localize the field potential to a restricted population, two closely spaced electrodes are inserted into the same brain region and the potential difference between the two is recorded as the local field potential (LFP). Although the amplitude range can vary considerably, intracortical field potentials are generally no larger than 1,500 microvolts in peak-to-peak amplitude.

Electrodes placed on the surface of the brain integrate over a larger submillimeter to millimeter scale. Since the cerebral cortex makes up most of the brain's surface, and the noncortical surfaces are difficult to access, the intracranial brain surface field potential is almost always recorded from the cortex as the electrocorticogram (ECoG). The ECoG recording may be bipolar, i.e., the difference in field potential activity recorded from two nearby cortical surface electrodes, or monopolar, i.e., from one cortical surface electrode with respect to a distant neutral reference electrode. ECoG amplitudes are normally in the range of several hundred microvolts. Integrating over an even greater spatial extent, the extracranial electroencephalogram (EEG) is recorded from the surface of the head, again either bipolarly or monopolarly. Scalp-recorded EEGs are greatly attenuated due to the high resistivity of the skull and scalp, and peak-to-peak amplitudes usually lie between 10 and 50 microvolts in the adult human. Finally, the magnetoencephalogram (MEG) records the magnetic field with sensors located just outside the head surface. MEG records from a third-order gradiometer are commonly less than 1 to 2 picoTesla in peak-to-peak amplitude. Both the EEG and MEG integrate over a centimeter spatial scale.

The cerebral cortex is uniquely positioned to make the principal contribution to brain activity recorded extracranially as the EEG and MEG. The cortex is also a common

target of intracranial recording, in the form of the cortical LFP and ECoG, because cortical population activity is thought to be fundamentally related to cognitive processes. The cortical pyramidal cell is an important class of excitatory neuron that is critically involved in the generation of cortical electrical field potentials and the corresponding magnetic fields. The pyramidal cells have long apical dendrites, aligned in parallel, perpendicular to the cortical surface. They are densely interconnected with each other and with neighboring neuron types, both excitatory and inhibitory, to form local neuronal circuits that are complex but similarly organized throughout the cortex. Pyramidal cells are also targets for synaptic inputs from other cortical and subcortical areas, and likewise send long, myelinated axons to those areas. A local population of pyramidal cells that are densely interconnected and have common input sources can generate an open dipole field that is recordable either locally or at a distance from the population. Synchronously active dipole fields of multiple local populations tend to summate and thus be detectable at a greater distance than those of the individual local populations alone, unless cancellation occurs due to surface folding (5).

Measurement of ERPs at the cortical surface or scalp involves the detection of summated dipole fields of extracellular currents generated by cortical pyramidal cell populations that have become synchronously active as a result of an external sensory event or an internal motor or cognitive event. Measurement of the Event-Related Field (ERF) involves detection of magnetic fields generated by intradendritic current flow of cortical pyramidal cell populations (3). The generator populations that are detected by the ERP and ERF generally overlap, but are not identical because of differences between the two measures in sensitivity to generator orientation and depth. The time-varying ERP or ERF waveform is commonly treated as a signal to be detected in the presence of noise. The following discussion deals explicitly with the ERP, but similar considerations also apply to the ERF.

Noise refers to any contribution to the potential difference (voltage) recorded from two electrodes that is not from the signal source. Common sources of noise in brain electrical recordings include (1) potentials from the brain (cephalic noise), (2) potentials from the head muscles and skin, eyes, and tongue (extracephalic cranial noise), (3) potentials from parts of the body other than the head, such as the heart (extracranial physiological noise), (4) random microscopic fluctuations at the electrodes (thermal noise), (5) noise from movement of the person or animal (movement artifact), (6) fluctuations introduced by electronic recording components (electronic noise), (7) radiated contamination from other electrical equipment (environmental noise), and even (8) fluctuations due to imprecision in the discrete digitization of the continuously varying voltage from the electrode for storage in a digital computer (quantization noise).

The ability to detect the ERP waveform signal in the presence of noise depends on the relative strengths of signal and noise, as measured by the ratio of signal power (magnitude squared) to noise power. If this signal-to-noise ratio is large, then the signal may be observable in the

digitized time series of just a single voltage trace. If it is small, however, some procedure is required for signal detection. A simple and effective signal detection technique is to average over an ensemble of realizations of the voltage time series. This is a reasonable procedure if each individual time series realization is registered to a common time marker representing the occurrence of an event.

The cortical sensory evoked potential is an example of a signal that is commonly detected by ensemble averaging. Repeated stimuli, e.g., flashes of light or brief tones, are presented to a subject while voltages are recorded from arrays of monopolar or bipolar electrodes placed within or near the corresponding region of sensory, e.g., visual or auditory, cortex. The voltage records are digitized and broken into time segments corresponding to the successive stimulus presentations, called trials. The resulting time series segments from the individual trials are collected, temporally registered with respect to the time of each stimulus, and averaged separately for each electrode.

When using ensemble averaging to detect the cortical sensory evoked potential, it is generally considered that a dipole generator population of pyramidal cells in the sensory cortex responds to each stimulus in a characteristic manner by generating a reproducible waveform signal. This waveform may not be detectable in the single-trial time series if the signal-to-noise ratio is too small. It is further considered that, although there may be variations in signal amplitude from trial to trial, the signal is time-locked to the stimulus and any variation in signal latency is small. The noise, on the other hand, is deemed to be temporally unrelated to the stimulus. From these premises, which embody the standard signal-plus-noise model (7), ensemble averaging of the single-trial time series is predicted to maintain the magnitude of the stimulus-evoked signal while decreasing the magnitude of the noise by destructive waveform cancellation. The signal-to-noise ratio increases in proportion to the square root of the number of trials averaged. Thus, ensemble averaging is a straightforward method for ERP signal detection by enlargement of the signal-to-noise ratio. It may be used to detect ERPs related to motor and cognitive events, as well as sensory, as long as the premises of the model hold.

## 2. EVENT-RELATED BRAIN ACTIVITY

### 2.1. Identification

ERPs have engendered a great deal of interest because of their potential for revealing the dynamics of cognitive processing by the brain. Temporal variation of the ERP occurs on a subsecond time scale that is conducive to measurement of the rapidly changing dynamics of cognition. Thus, an abiding theme in the ERP literature is the identification of *components* spanning brief periods of time before or after a measurable event, and the understanding of these components in terms of sensory, motor, or higher-order cognitive processes of the brain.

The ERP waveform consists of a series of positive and negative wavelike components that are identified by their time of occurrence and polarity. Thus, for example, the

P300 component occurs as a positive wave that peaks at or near 300 ms after a stimulus event. Components sometimes also are designated simply according to their serial order, so that the P300 component might also be called the P3 component, meaning the third positive wave following the stimulus. Other components are named based on event properties. The Contingent Negative Variation (CNV), for example, is a slow negative wave that appears in the interval between two stimuli after a contingency of the second stimulus on the first has been established.

### 2.2. Types

**2.2.1. Sensory.** Sensory ERPs may be evoked by an external stimulus in one of the sensory modalities. They can be recorded by electrodes placed in sensory brain structures, on the surface of sensory cortices, or on the overlying scalp. The early poststimulus components in the average ERP are directly related to stimulus-evoked sensory processing, and because their characteristics depend on the physical properties of the stimulus, they are called *exogenous*. In the auditory and somatosensory modalities, early components generated by sensory relay nuclei in the brain stem are revealed in extracranial recordings by the ensemble averaging of large numbers of trials. Since these early components are considered obligatory, they have clinical value as a test of the integrity of the subcortical sensory pathways. In the visual modality, the brain stem nuclei apparently generate closed potential fields, and thus the earliest components observable from the scalp are generated within the cortex (8). In animal studies, sensory nerve stimulation produces a positive-negative wave complex at the cortical surface. The positive deflection may arise from a dipole field with a superficial source generated by depolarization of layer 4 neurons in primary cortex, and the negative deflection from a superficial-sink dipole generated by depolarization in the superficial layers (9). The latencies of early sensory cortical components are of great interest to researchers who study cortical information processing (10).

In addition to the transient responses that occur in the brief period following a sensory stimulus, sensory ERPs may also take the form of a continuous periodic response when sensory stimuli are presented rapidly and repetitively. These steady-state evoked potentials show the same repetition frequency as the stimulus, within limits, and preferred frequencies at which the steady-state response is maximal have been suggested to represent the natural resonant frequencies of oscillating neuronal populations in the sensory cortices (11). Steady-state visual evoked potentials have proven useful in the assessment of cognitive function (12).

**2.2.2. Motor.** Motor ERPs are extracted from noise by ensemble averaging with respect to a movement-related event rather than a sensory stimulus. Since the characteristics of motor ERP components do not depend on external stimulus properties, but rather on a subject's internal state, they are called *endogenous*. The most well-known motor component is the Readiness Potential (RP), a



slow, ramplike negative potential shift that begins as early as 1.5 sec before the production of voluntary limb movements. The RP magnitude grows larger in recordings over the sensorimotor cortex contralateral to the movement, as compared to the ipsilateral side, as the time of the movement approaches. Together with the observation that the RP has a somatotopic organization in the contralateral sensorimotor cortex, this finding indicates that the RP component is related to preparation for limb movement. The RP (also designated N1) is terminated by a positive-negative (P1-N2) complex prior to muscle contraction, which is then followed by a late positive (P2) component. The P1 deflection is often absent unless the movements are brisk and forceful.

**2.2.3. Cognitive.** Cognitive ERP components are related to cognitive, rather than sensory or motor, processes in the brain. By definition, cognitive components are considered to be endogenous. The aforementioned CNV is an endogenous cognitive ERP component that occurs in the interval between two stimuli (S1 and S2), presented in any sensory modality, for which a contingency has been established by their prior pairing. Most often, the subject is required to execute a motor response to the S2. The CNV arises as a ramplike, negative-going wave that peaks shortly after S2. It appears maximally in the EEG over frontal and central regions and can be as large as 20 microvolts. When the S1-to-S2 duration is sufficiently long, the CNV resolves into early and late subcomponents, the early one related to the sensory processing of S1, and the late one associated with anticipation of S2 and motor preparation. The late subcomponent is thought to be generated by the prefrontal cortex (13) in relation to that structure's role in mediating cross-temporal contingencies (14).

Whereas the late CNV occurs prior to a stimulus, reflecting anticipation and preparation, other cognitive effects appear following a stimulus in relation to selective attention to particular stimulus attributes. In the auditory modality, when sequences of brief tones at different frequencies are presented to the two ears, attention to the sequence in either ear is associated with a greater negativity between 100 and 200 ms poststimulus. Subtraction of the average ERP of unattended trials from that of attended trials yields a difference wave, but the question of whether this wave represents an attentional modulation of the N1 component, or a separate attentional component, has not yet been resolved. Attentional effects also occur in the visual modality, where spatial attention effects are different from, and usually occur earlier than, the effects of attention to nonspatial stimulus attributes (15).

The P3 component appears as a positive deflection between 300 and 900 ms poststimulus that is related to the cognitive context of the stimulus. Context is usually established by presenting a subject with a series of events of one class interspersed with rarer events of a second class to which the subject must respond. An earlier, frontal P3a component can be distinguished from a later, parietal P3b component. The P3a is elicited by unexpected novel stimuli. The amplitude of the P3b depends on the relative

event probability, and the latency reflects the degree of difficulty in categorizing the stimulus.

The N400 component is a negative wave that occurs around 400 ms after a word stimulus, when that stimulus is incongruent with the prevailing semantic context established by previous stimuli. The amplitude of the N400 is directly related to the degree of semantic deviance of the word from its sentence context and is attenuated by prior priming with semantically related words.

### 2.3. Violations of the Standard Model

The sensory, motor, and cognitive ERP components heretofore described are generally considered as signals to be extracted from noise by ensemble averaging. Theoretical justification for this analytic procedure is provided by the standard signal-plus-noise model (7), which entails three important assumptions. First, although the amplitude and latency of a component may be affected by a host of different conditions, as described above, once the conditions are fixed the component itself is considered to be an entirely reproducible signal whose waveform does not vary from one trial to the next. Second, the component is considered to be unitary in form, meaning that it is not composed of more basic waveforms. Third, the signal is considered to be completely independent of any ongoing neural processes, which if they exist are simply treated as noise.

Despite the fact that the standard model has proven to be remarkably robust, substantial evidence suggests that each of these three assumptions may require modification. First to be considered are findings of variability in both component amplitude and latency across trials, even under controlled conditions. Trial-to-trial variability of component amplitude does not seriously affect signal detection by ensemble averaging as long as the polarity remains constant: the averaged component retains the latency and shape of the single-trial signal despite variations in amplitude. Ensemble averaging is also robust to latency variability, providing that the signal waveform does not contain polarity reversals: the averaged component degrades smoothly as the degree of latency variability increases.

Changes in component polarity over trials, or latency variability of a component containing polarity reversals, may result in destructive cancellation of the signal during the ensemble averaging process. This possibility is particularly relevant in the case of high-frequency oscillatory field potential responses of the brain to sensory stimulation (16). These oscillatory components are said to be *induced* rather than *evoked* because the oscillatory waves within the component have variable latency (or phase), although the onset times of the component itself may be relatively constant with respect to the stimulus event. The high-frequency oscillatory waveform of these induced signals guarantees that polarity reversals will destructively cancel with even a small degree of trial-to-trial latency variability. Therefore, the standard model cannot be assumed to hold in the case of induced high-frequency oscillations, and methods other than ensemble averaging are required for signal detection.

Other studies have brought into question the second assumption from the standard model that ERPs represent fundamental, indecomposable waveforms. Some investigators have argued that evoked oscillations are fundamental to brain function, and that ERPs arise from the summation of evoked oscillations of different frequencies (17). Others have suggested instead that evoked Gaussian potentials are fundamental basis functions that combine to form ERP components (18).

Both the second and third assumptions of the standard model are violated by evidence indicating that ongoing activity at the time of a stimulus may contribute to the poststimulus ERP (19). It is generally agreed that the EEG and MEG contain ongoing oscillatory activity at specific frequencies and that the phases of ongoing oscillations at the time of the stimulus are random from trial to trial. If the stimulus acted to reset the phase of these oscillations to the same value on each trial, summation of poststimulus phase-aligned waves would result when the trials were averaged. To distinguish phase resetting models from the standard model requires techniques that allow comparison of prestimulus and poststimulus activity on a single-trial basis.

In summary, a wealth of knowledge about ERPs has been obtained from the ensemble averaging of single-trial time series, under assumptions of the standard model of ERP generation. Nonetheless, substantial evidence indicates that this model is not completely adequate, and that exclusive reliance on ensemble averaging may obscure important issues relating to the genesis and functional relevance of ERPs. To provide a more detailed understanding of ERP component structure than is available by ensemble averaging, additional methods are required that derive information from the entire ensemble of single-trial time series. Frequency domain analysis is a class of methods that quantifies oscillatory activity in the trial ensemble in terms of its frequency, amplitude, and phase. It may be advantageous for addressing issues such as the occurrence of induced oscillations and the phase reorganization of ongoing oscillations. These considerations emphasize the need for the more sophisticated forms of ERP analysis reviewed in the next section.

### 3. ANALYTIC TECHNIQUES

#### 3.1. Time Domain Analysis

The most common form of ERP analysis is performed in the time domain by measurement of the amplitudes and latencies of components identified in the ensemble-averaged waveform. This approach necessarily involves a loss of information about the distributional properties of the ensemble of single-trial time series. Various alternative time domain techniques have been devised for analysis of the entire ensemble of single-trial time series rather than the single ensemble average.

One general class of time domain technique operates by application of a weighting function, or *filter*, directly to the single-trial time samples. The filter is applied either to the entire time series of each trial, or to segments of it. One such weighting function, called the minimum mean

square error filter (or “Wiener” filter), is designed to selectively enhance the ERP signal while suppressing the noise (20). Of course, to implement such a filter requires knowledge of the signal, which may be problematic. A related technique is matched filtering, in which the average ERP is used as a template that is “matched” by correlation with the single-trial time series. Matched filtering has been used to improve the average ERP by recreating it from “latency-corrected” trials (21), as well as to correlate the distributions of single-trial latency and amplitude values with behavioral or other parameters (22). Another weighting function is the band-pass filter, which is used to extract ERP components on the basis of their frequency characteristics. This approach is related to frequency domain analysis, which is described below. Similar to band-pass filtering are single-trial filtering techniques based on wavelet transforms (23). Time domain filtering techniques have been used in a variety of applications to investigate ERP function and composition.

Statistical feature extraction represents another approach to understanding the ERP from the analysis of ensembles of single-trial time series data. Principal component analysis (PCA) is one such method that has been used to extract overlapping (principal) ERP components based on the inherent variability structure of the data set (24). This variability occurs over time in the trial, over the ensemble of trials, over simultaneously sampled locations, and over different experimental conditions. The method involves computing the eigenvalues and eigenvectors of the covariance matrix of the original time series data, with the principal components being derived from the eigenvectors that are located along the directions of maximal data variance. Thus, the principal components reflect the intrinsic morphology of the single-trial waveforms, rather than a predetermined set of basis functions as in most filtering techniques. However, due to the orthogonality of the components that comes from the eigenvector decomposition, a potential problem with the PCA procedure is the misallocation of variance between the components (25). Various proposals have been made for overcoming this and other problems with the application of PCA to ERPs (26). A related approach that avoids the imposed component orthogonality constraint of PCA is independent component analysis (ICA) (27).

#### 3.2. Frequency Domain Analysis

A second general class of techniques operates in the frequency domain by converting a voltage time series into a frequency function through application of the Fourier transform. Frequency domain (or spectral) analysis offers the promise of providing greater insight into the organization and function of ERPs than is available from time domain techniques alone. Issues relating to the role of oscillatory components in ERP generation are particularly amenable to spectral analysis. However, in its traditional form, spectral analysis is unsuitable for ERP analysis because it is only defined with respect to stationary time series. Since the voltage time series containing ERPs are typically nonstationary, it is necessary in most cases to perform spectral analysis in a short, moving

window in which stationarity is approximated (28). Short-window spectral analysis seeks to provide an adequate time-frequency representation of the ERP within the bounds set by the uncertainty principle. A number of time frequency analysis methods have been advanced, including multitaper (28), wavelet or Hilbert transform (29), and parametric modeling techniques (30–32).

### 3.3. Spatial Analysis

The neural processes underlying ERP generation are extended in space within the brain. Spatial analysis is therefore an important tool for understanding the relations between ERPs recorded at different spatial locations within or outside the brain (33). When simultaneous recordings are obtained with a sufficiently dense grid of electrodes on the brain or at the scalp, a basic form of spatial analysis, called topographic mapping, may be performed. The topographic distribution is an important feature of ERP components that complements other features such as latency, amplitude, polarity, and frequency content. Components that may otherwise be difficult to disambiguate, may be easily distinguished in some cases by their topographic distributions. In fact, topographic patterning of the ERP may be fundamentally related to brain state at spatial scales from microscopic to macroscopic (34). Beyond simple topographic mapping, spatial analysis of the ERP takes the form of spatial spectral analysis (35), spatiotemporal PCA analysis (36), and inverse transformation to obtain estimates of cortical sources (37).

### 3.4. Interdependency Analysis

The ERP may be defined not only by its timing, frequency content, and spatial distribution, but also by higher-order features. Interdependency measures attempt to characterize the similarity structure of the waveform morphology of ERPs recorded at different spatial locations. Interdependency analysis is performed in either the temporal or frequency domain. In either case, stationarity considerations dictate that when applied to ERPs the analysis be performed in short, moving windows. A relatively simple tool for interdependency analysis in the time domain is the cross-correlation function, which measures linear relations between different time series. Nonlinear relations are characterized by measures based on the concept of mutual information (38).

Another form of interdependency analysis is derived from the concept of causal influence. Wiener (39) proposed that, for two simultaneously measured time series, one series may be considered causal to the other if knowledge of the first allows better prediction of the second. This concept was later adopted and formalized by Granger (40) in the context of linear regression models of stochastic processes. Specifically, if the variance of the prediction error for the second process at a given time is reduced by including past measurements from the first in the second's linear regression model, then the first process is considered to have a Granger causal influence on the second process. The possibility that the measured Granger causality from one process to a second is actually the result of

common driving from a third process cannot be excluded when that third process is not recorded. However, when a third process is recorded, the technique of conditional Granger causality analysis can be used to unequivocally determine whether that third process is responsible for Granger causality between the first two.

Interdependency analysis may be accomplished in the frequency domain by parametric spectral estimation techniques such as Adaptive MultiVariate AutoRegressive (AMVAR) modeling (32). Parametric spectral estimation allows spectral interdependency quantities such as multiple coherence and ordinary coherence to be computed from the model parameters. When applied to simultaneously recorded ERPs from a distributed set of recording sites in the brain, this analysis is useful for investigating oscillatory network interdependencies. The multiple coherence is a group measure that provides a concise assessment of the interdependency of each recording site with the group of all the other sites. When the multiple coherence of a site is high at a particular frequency, it indicates that the site is coordinated at that frequency with a set of other sites. By comparing all the sites for the times and frequencies at which significant episodes of multiple coherence appear, one can directly obtain a depiction of the spatial configuration of coordinated sites. Then, the specific interdependencies of particular pairs of sites may be investigated using the ordinary coherence. This measure gauges the degree of interdependency between two sites as a function of frequency. When the ordinary coherence between two sites is high at a particular frequency, it means that there is a high degree of consistency in the relative phase at that frequency across the ensemble of trials. The mean relative phase value need not be zero: the precise value is provided by the relative phase spectrum.

Causal influences may also be characterized in the frequency domain using a spectral decomposition for Granger causality derived by Geweke (41). As one example of its application, the Geweke spectral measure has revealed important aspects of event-related oscillatory network dynamics in the sensorimotor cortex (42).

## 4. CONCLUSIONS

The ERP and ERF are important neural signals that provide a window onto the dynamics of sensory, motor, and cognitive processing in the brain. Their usefulness in this regard can be heightened by careful applications of the analytic techniques described here. At present, ERP recording represents a critical complement to unit recording for measuring the dynamics of brain function in animals. In humans, ERP and ERF recordings provide a temporal resolution that can detect changes in brain activity on the order of milliseconds, whereas the hemodynamic response measured by neuroimaging techniques such as functional magnetic resonance imaging can only resolve changes on the order of seconds. Other recording methodologies with temporal resolution comparable to the ERP, such as voltage-sensitive optical imaging and direct magnetic resonance imaging of neuronal magnetic fields, are currently under development. However, even if these



other modes of recording should eventually supplant the ERP and ERF, the same types of functional consideration and analytic technique discussed in this article will nevertheless apply to them as well.

### Acknowledgments

This work was supported by NIMH grants MH64204, MH071620, and MH070498.

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