

# Brain Function, Nonlinear Coupling, and Neuronal Transients

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The brain can be regarded as an ensemble of connected dynamical systems and as such conforms to some simple principles relating the inputs and outputs of its constituent parts. The ensuing implications, for the way we think about, and measure, neuronal interactions, can be quite profound. These range from 1) Implications for which aspects of neuronal activity are important to measure and how to characterize coupling among neuronal populations; 2) Implication for understanding the emergence of dynamic receptive fields and functionally specialized brain architectures; and 3) teleological implications pertaining the genesis of dynamic instability and complexity, which is necessary for adaptive self-organization. This review focuses on the first set of implications by looking at neuronal interactions, coupling, and implicit neuronal codes from a dynamical perspective. By considering the brain in this light, one can show that a sufficient description of neuronal activity must compose activity at the current time *and its recent history*. This history constitutes a neuronal transient. Such transients represent an essential metric of neuronal interactions and, implicitly, a code employed in the functional integration of brain systems. The nature of transients, expressed conjointly in different neuronal populations, reflects the underlying coupling among brain systems. A complete description of this coupling, or *effective connectivity*, can be expressed in terms of generalized convolution kernels (Volterra kernels) that embody high-order or nonlinear interactions. This coupling may be *synchronous*, and possibly oscillatory, or *asynchronous*. A critical distinction between synchronous and asynchronous coupling is that the former is essentially linear and the latter is nonlinear. The nonlinear nature of asynchronous coupling enables the rich, context-sensitive interactions that characterize real brain dynamics, suggesting that it plays an important role in functional integration. NEUROSCIENTIST 7(5):406–418, 2001

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This article is about the dynamical aspects of brain function. Brain states are inherently labile, with a complexity and transience that renders their invariant characteristics elusive. The position adopted in this review is that the best approach is to embrace these dynamical aspects. Its aim is to introduce the notion of neuronal transients and the underlying framework. In this framework, issues such as neuronal coupling, neuronal codes, functional integration, self-organization, and the special complexity of brain dynamics can be addressed. A full discussion of these issues will be found in Friston (2000a, 2000b, 2000c).

The central tenet is that the dynamics of neuronal systems can be viewed as a succession of transient spatiotemporal patterns of activity that mediate perceptual synthesis and adaptive sensorimotor integration. This integration is shaped by the brain's anatomical infrastructure, principally connections, that have been selected to ensure the adaptive nature of the dynamics that ensue.

Although rather obvious, this formulation embodies one fundamental point; namely, that any description of brain dynamics should have an explicit temporal dimension. In other words, measures of brain activity are only meaningful when specified over periods of time. Appreciating this fact leads to some compelling insights that place extant concepts in a more general context. This is particularly important in relation to fast dynamic interactions among neuronal populations that are characterized by synchrony. Synchronization has become popular in the past years (e.g., Engel and others 1991; Gray and Singer 1989; Eckhorn and others 1988) and yet represents only one of many possible sorts of interactions.

This article is divided into four sections. In the first, we review the conceptual basis of neuronal transients. This section uses a fundamental equivalence, between two mathematical formulations of nonlinear systems, to show that descriptions of brain dynamics, in terms of 1) neuronal transients and 2) the coupling among interacting brain systems, is complete and sufficient. The second section uses this equivalence to motivate a taxonomy of neuronal codes and establish the relationship among neuronal transients, asynchronous coupling,

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*dynamic correlations*, and nonlinear interactions. In the third section, we illustrate nonlinear coupling using magnetoencephalography (MEG) data. The final section discusses some neurobiological mechanisms that might mediate asynchronous transients.

## Neuronal Transients

The assertion that meaningful measures of brain dynamics have a temporal domain is neither new nor contentious (e.g., von der Malsburg 1985; Optican and Richmond 1987; Engel and others 1991; Aertsen and others 1994; Freeman and Barrie 1994; Abeles and others 1995; deCharms and Merzenich 1996). A straightforward analysis demonstrates its veracity: Suppose that one wanted to posit some variables  $x$  that represented a complete and self-consistent description of brain activity. In other words, everything needed to determine the evolution of the brain's state, at a particular place and time, was embodied in these measurements. Consider a component of the brain (e.g., a neuron or neuronal population). If such a set of variables existed for this component system, they would satisfy some immensely complicated nonlinear equations

$$\frac{\partial x}{\partial t} = f(x(t), u(t)), \quad 1$$

where  $x$  is a huge vector of state variables that range from depolarization at every point in the dendritic tree to the phosphorylation status of every relevant enzyme, from the biochemical status of every glial cell compartment to every aspect of gene expression.  $u(t)$  represents a set of inputs conveyed by afferent from other regions. Equation (1) simply says that the changes in the state variables are nonlinear functions of the variables themselves and some inputs. The vast majority of these variables are hidden and not measurable directly. However, there are a small number of derived measurements  $y$  that can be made,

$$y(t) = \lambda(x(t)), \quad 2$$

such as activities of whole cells or populations. These activities could be measured in many ways, for example firing at the initial segment of an axon or local field potentials. The problem is that a complete and sufficient description appears unattainable, given that the underlying state variables cannot be observed directly. This is not the case. The resolution of this apparent impasse rests upon two things: 1) a fundamental mathematical equivalence relating the inputs and outputs of a dynamical system and 2) the fact that these measurable outputs constitute the inputs to other cells or populations.

### A Fundamental Equivalence

Assume that every neuron in the brain is modeled by a nonlinear dynamical system of the sort described by

Equation (1). Under this assumption, it can be shown that the output is a function of the recent history of its inputs.

$$y(t) = h(u(t - \sigma)), \quad 3$$

where represents the inputs in the recent past. Furthermore, this relationship can be expressed as a Volterra series of the inputs (see Box 1). The critical thing here is that we never need to know the underlying and "hidden" variables that describe the details of each cell's electrochemical and biochemical status. We only need to know the history of its inputs, which, of course, are the outputs of other cells. Because the inputs and outputs are homologous, we can rewrite Equation (3) so that all connected brain systems are considered together.

$$y(t) = h(y(t - \sigma)). \quad 4$$

Equation (4) is, in principle, a sufficient description of brain dynamics and involves the variables that represent activity at all times preceding the moment in question. These are simply neuronal transients. The degree of transience depends on how far back in time it is necessary to go to fully capture the brain's dynamics. The sensible nature of Equation (4) can be readily seen. For example, if we wanted to determine the behavior of a cell in V1 (primary visual cortex), then we would need to know the activity of all connected cells in the immediate vicinity over the last millisecond or so to account for propagation delays down afferent axons. We would also need to know the activity in distant sources, like the lateral geniculate nucleus and higher cortical areas, some 10 or more milliseconds ago. In short, we need the recent history of all inputs.

Transients can be expressed in terms of firing rates (e.g., chaotic oscillations; Freeman and Barrie 1994) or individual spikes (e.g., syn-fire chains, Abeles and others 1994, 1995). The analysis above is not just a mathematical abstraction, it has real implications at a number of levels: For example, the emergence of fast oscillatory interactions among simulated neuronal populations depends on the time delays implicit in axonal transmission and the time constants of postsynaptic responses. Another slightly more subtle aspect of this formulation is that changes in synaptic efficacy, such as short-term potentiation or depression, take some time to be mediated by intracellular mechanisms. This means that the interaction between and  $y(t)$ , that models these activity-dependent effects in Equation (4), again depends on the relevant history of activity.

### Levels of Description

The above arguments lead to a conceptual model of the brain that comprises a collection of dynamical systems (e.g., cells or populations of cells), each representing as an input-state-output model, where the state remains, for us, forever hidden. However, the inputs and outputs are accessible and are causally related where, in this special case of the brain, the output of one system constitutes the input to another. A complete description therefore

## Box 1: Dynamical Systems and Volterra Kernels

### Input-State-Output Systems and Volterra Series

Neuronal systems are inherently nonlinear and lend themselves to modeling with nonlinear dynamical systems. However, owing to the complexity of biological systems, it is difficult to find analytic equations that describe them adequately. Even if these equations were known, the state variables are often not observable. An alternative approach to identification is to adopt a very general model (Wray and Green 1994) and focus on the inputs and outputs. Consider the single input–single output (SISO) system:

$$\begin{aligned}\dot{x}(t) &= f(x(t), u(t)) \\ y(t) &= \lambda(x(t)).\end{aligned}\tag{B.1}$$

The Fliess fundamental formula (Fliess and others 1983) describes the causal relationship between the outputs and the recent history of the inputs. This relationship can be expressed as a Volterra series, which expresses the output  $y(t)$  as a nonlinear convolution of the inputs  $u(t)$ , critically without reference to the state variables  $x(t)$ . This series is simply a functional Taylor expansion of  $y(t)$  in Equation (3) (main text).

$$\begin{aligned}y(t) &= h(u(t - \sigma)) = \\ &\kappa_0 + \sum_{i=1}^{\infty} \int_0^t \cdots \int_0^t \kappa_i(\sigma_1, \dots, \sigma_i) u(t - \sigma_1) \\ &\cdots u(t - \sigma_i) d\sigma_1 \cdots d\sigma_i \kappa_i(\sigma_1, \dots, \sigma_i) = \\ &\frac{\partial^i y(t)}{\partial u(t - \sigma_1) \cdots \partial u(t - \sigma_i)},\end{aligned}\tag{B.2}$$

comprises the nature of these relationships (the Volterra series corresponding to the function  $h$ ) and the neuronal transients. This constitutes a *mesoscopic* level of description that permits a degree of “black-boxness” but with no loss of information.

The equivalence, in terms of specifying the behavior of a neuronal system, between microscopic and mesoscopic levels of description, is critical. In short, the equivalence means that all the information inherent in the unobservable microscopic variables that determine the response of a neuronal system is embodied in the history of its observable inputs and outputs. Although the microscopic level of description may be more mechanistically informative, from the point of view of response prediction, neuronal transients are an entirely equivalent representation.<sup>1</sup>

were is the  $i$ th order kernel. Volterra series have been described as a “power series with memory” and are generally thought of as a high-order or “nonlinear convolution” of the inputs to provide an output. See Bendat (1990) for a fuller discussion.

### Volterra Kernels and Effective Connectivity

Volterra kernels are essential in characterizing the effective connectivity or influences that one neuronal system exerts over another because they represent the causal input-output characteristics of the system in question. Neurobiologically, they have a simple and

$$\begin{aligned}\kappa_1(\sigma_1) &= \frac{\partial y(t)}{\partial u(t - \sigma_1)}, \\ \kappa_2(\sigma_1, \sigma_2) &= \frac{\partial^2 y(t)}{\partial u(t - \sigma_1) \partial u(t - \sigma_2)}, \dots\end{aligned}$$

compelling interpretation—they are synonymous with effective connectivity: From B.2,

It is evident that the first-order kernel embodies the response evoked by a change in input at  $t - \sigma_1$ . In other words, it is a time-dependant measure of *driving* efficacy. Similarly, the second-order kernel reflects the *modulatory* influence of the input at  $t - \sigma_2$  on the response evoked by input at  $t - \sigma_1$ . And so on for higher orders.

### Effective Connectivity and Volterra Kernels

The first conclusion so far is that neuronal transients are necessary to specify brain dynamics. The second conclusion is that a complete model of the influence one neuronal population exerts over another should take the form of a Volterra series. This implies that a complete characterization of these influences (i.e., effective connectivity) comprises the Volterra kernels that are applied to the inputs to yield the outputs.

Functional integration is usually inferred using correlations among measurements of neuronal activity in different brain systems. However, correlations can arise in a variety of ways. For example, in multiunit electrode recordings, they can result from stimulus-locked transients evoked by a common input or reflect stimulus-

1. We have focused on the distinction between microscopic and mesoscopic levels of description. The *macroscopic* level is reserved for approaches, exemplified by synergistics (Haken 1983), that characterize the spatiotemporal evolution of brain dynamics in terms of a small number of macroscopic order parameters (see Kelso [1995] for an engaging exposition). Order parameters are created and determined by the cooperation of microscopic quantities and yet, at the same time, govern the behavior of the whole system. See Jirsa and others (1995) for a nice example.

induced oscillations mediated by synaptic connections (Gerstein and Perkel 1969). Integration within a distributed system is better understood in terms of “effective connectivity.” Effective connectivity refers explicitly to “the influence that one neural system exerts over another, either at a synaptic (i.e., synaptic efficacy) or population level” (Friston 1995a). It has been proposed (Aertsen and Preißl 1991) that “the notion of effective connectivity should be understood as the experiment- and time-dependent, simplest possible circuit diagram that would replicate the observed timing relationships between the recorded neurons.”

If effective connectivity is the influence that one neural system exerts over another, it should be possible, given the effective connectivity and the afferent activity, to predict the response of a recipient population. This is precisely what Volterra kernels do. Any model of effective connectivity can be expressed as a Volterra series, and any measure of effective connectivity can be reduced to a set of Volterra kernels (see Box 1). An important aspect of effective connectivity is its context sensitivity. Effective connectivity is simply the “effect” that an input has on the output of a target system. This effect will be sensitive to other inputs, its own history, and of course the microscopic state and causal architecture intrinsic to the target population. This intrinsic dynamical structure is embodied in the Volterra kernels. In short, Volterra kernels are synonymous with effective connectivity because they characterize the measurable effect that an input has on its target. An example of using Volterra kernels, to characterize context-sensitive changes in effective connectivity, is shown in Box 2. This example uses hemodynamic responses to changes in neuronal activity as measured with functional magnetic resonance imaging (fMRI).

## Neuronal Codes

### *Different Sorts of Code*

Functional integration refers to the concerted interactions among neuronal populations that mediate perceptual binding, sensorimotor integration, and cognition. It pertains to the mechanisms of, and constraints under which, the dynamics of one population influences those of another. It has been suggested by many that functional integration, among neuronal populations, uses transient dynamics that represent a temporal “code.” A compelling proposal is that population responses, encoding a percept, become organized in time, through reciprocal interactions, to discharge in synchrony (von der Malsburg 1985; Singer 1994). The use of the term *encoding* here speaks directly to the notion of codes. Here a neuronal code is taken to be a metric that reveals interactions among neuronal systems by enabling some prediction of the response in one population given that

metric in another.<sup>2</sup> Clearly, from the previous section, neuronal transients represent the most generic form of code because, given the Volterra kernels, the output can be predicted exactly. Neuronal transients have a number of attributes (e.g., interspike interval, duration, mean level of firing, predominant frequency, etc.), and any of these could be contenders for a more parsimonious code. The problem of identifying possible codes can be reduced to identifying the form of the Volterra kernels in Box 1. If we know their form, then we can say which aspects of the input will cause a response. Conversely, it follows that the different forms that the kernels can take should specify the various codes that might be encountered. This is quite an important point and leads to a clear formulation of what can and cannot constitute a code. We will review different codes in terms of the different sorts of kernels that could mediate them.

### *Instantaneous versus Temporal Codes*

The first kernel characteristic that engenders a coding taxonomy is kernel depth. The limiting case here is when the kernels shrink to a point in time. This means that the only relevant history is the immediate activity of inputs (all earlier activities are “ignored” by the kernel). In this case, the activity in any unit is simply a nonlinear function of current activities elsewhere. An example of this is instantaneous rate coding.

Rate coding considers spike trains as *stochastic processes* whose first-order moments (i.e., mean activity) describe neuronal interactions. These moments may be in terms of spikes themselves or other compound events (e.g., the average rate of bursting; Bair and others 1994). Interactions based on rate coding are usually assessed in terms of cross-correlations. From the dynamical perspective, instantaneous rate codes are considered insufficient. This is because they predict nothing about a cell, or population, response unless one knows the microscopic state of that cell or population.

The distinction between rate and temporal coding (see Shadlen and Newsome 1995; de Ruyter van Steveninck and others 1997) centers on whether the precise timing of individual spikes is sufficient to facilitate meaningful neuronal interactions. In temporal coding, the exact time at which an individual spike occurs is the important measure and the spike train is considered as a *point process*. There are clear examples of temporal codes that have predictive validity, for example, the primary cortical representation of sounds by the coordination of action potential timing (deCharms and Merzenich 1996). These codes depend on the relative timing of action potentials and, implicitly, an extended temporal frame of reference. They therefore fall into the class of transient codes, where selective responses to particular interspike intervals are modeled by temporally extended second-order kernels. A nice example is provided by de Ruyter van Steveninck and others (1997)

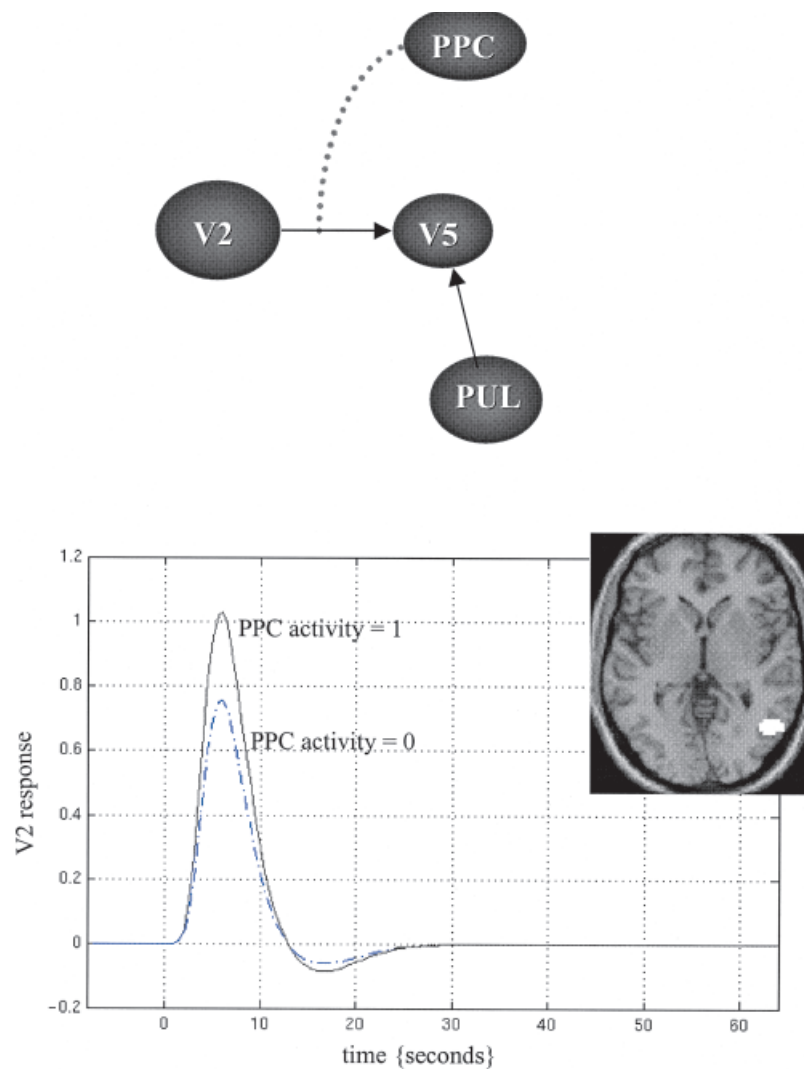
2. Although the term *code* is not being used to denote anything that “codes” for something in the environment, it could be used to define some aspect of an evoked transient that expresses a high mutual information with a stimulus parameter (e.g., Optican and Richmond 1987; Tovee and others 1993).

## Box 2: Volterra Kernels and Effective Connectivity

### Nonlinear Coupling among Brain Areas

Linear models of effective connectivity assume that the multiple inputs to a brain region are linearly separable. This assumption precludes activity-dependent connections that are expressed in one context and not in another. The resolution of this problem lies in adopting nonlinear models that include interactions among inputs. These interactions can be construed as a context- or activity-dependent modulation of the influence that one region exerts over another. These nonlinearities can be introduced into structural equation modeling using so-called moderator variables that represent the interaction between two regions when causing activity in a third (Büchel and Friston 1997). From a dynamical point of view, modulatory effects can be modeled with a Volterra series formulation that includes second-order kernels. Within these models, the influence of one region on another has two components: 1) the direct or *driving* influence of input from

the first (e.g., hierarchically lower) region, irrespective of the activities elsewhere, and 2) an activity-dependent, *modulatory* component that represents an interaction with inputs from the remaining (e.g., hierarchically higher) regions. These are mediated by the first- and second-order kernels, respectively. The example provided in the figure addresses the modulation of visual cortical responses by attentional mechanisms (e.g., Treue and Maunsell 1996) and the mediating role of activity-dependent changes in effective connectivity. The graph shows a characterization of this modulatory effect in terms of the increase in V5 responses, to a simulated V2 input, when posterior parietal activity is zero (broken line) and when it is high (solid lines). This sort of result suggests that backward parietal inputs may be a sufficient explanation for the attentional modulation of visually evoked extrastriate responses. The estimation of the Volterra kernels and statistical inference is described in Friston and Büchel (2000).



**Fig. 1.** *Top.* Brain regions and connections composing the model. *Bottom.* Characterization of the effects of V2 inputs on V5 and their modulation by posterior parietal cortex (PPC). The broken lines represent estimates of V5 responses when PPC activity is zero, according to a second-order Volterra model of effective connectivity with inputs to V5 from V2, PPC and the pulvinar (PUL). The solid curves represent the same response when PPC activity is 1 standard deviation of its between-condition variation. It is evident that V2 has an activating effect on V5 and that PPC increases the responsiveness of V5 to these inputs. The insert shows all the voxels in V5 that evidenced a modulatory effect ( $P < 0.05$  uncorrected). These voxels were identified by thresholding a statistical parametric map of the  $F$  statistic testing for the contribution of second-order kernels involving V2 and PPC (treating all other terms as nuisance variables). The data were obtained with fMRI under identical stimulus conditions (visual motion subtended by radially moving dots) while manipulating the attentional component of the task (detection of velocity changes).

who show that the temporal patterning of spike trains, elicited in fly motion-sensitive neurons by natural stimuli, can carry twice the amount of information than an equivalent (Poisson) rate code.

### *Transient Codes: Synchronous versus Asynchronous*

The second distinction, assuming the kernels have a non-trivial depth, is whether they comprise high-order terms. Expansions that encompass just first-order terms are only capable of mediating linear or synchronous interactions. Higher-order kernels confer nonlinearity on the influence of an input that leads to asynchronous interactions. Mathematically, if there are only first-order terms, then the Fourier transform of the Volterra kernel completely specifies the relationship (the transfer function) between the spectral density of input and output in a way that precludes interactions among frequencies, or indeed inputs. In other words, the expression of any frequency in a recipient cell is predicted exactly by the expression of the same frequency in the source (after some scaling by the transfer function).

#### *Synchronous Codes*

The proposal most pertinent to these forms of coding is that population responses, participating in the encoding of a percept, become organized in time through reciprocal interactions so that they come to discharge in synchrony (von der Malsburg 1985; Singer 1994) with regular periodic bursting. It should be noted that synchronization does not necessarily imply oscillations. However, synchronized activity is usually inferred operationally by oscillations implied by the periodic modulation of cross-correlograms of separable spike trains (e.g., Gray and Singer 1989; Eckhorn and others 1988) or measures of coherence in multichannel electrical and neuromagnetic time-series (e.g., Llinas and others 1994). The underlying mechanism of these frequency-specific interactions is usually attributed to phase-locking among neuronal populations (e.g., Aertsen and Preißl 1991; Sporns and others 1989). The key aspect of these measures is that they refer to the extended temporal structure of synchronized firing patterns, either in terms of spiking (e.g., syn-fire chains; Abeles and others 1995; Lumer and others 1997) or oscillations in the ensuing population dynamics (e.g., Singer 1994).

Many aspects of functional integration and feature linking in the brain are thought to be mediated by synchronized dynamics among neuronal populations (Singer 1994). Synchronization reflects the direct, reciprocal exchange of signals between two populations, whereby the activity in one population influences the second, such that the dynamics become entrained and mutually reinforcing. In this way, the binding of different features of an object may be accomplished in the temporal domain, through the transient synchronization of oscillatory responses. This “dynamical linking” defines their short-lived functional association. Physiological evidence is compatible with this theory

(e.g., Engel and others 1991; Fries and others 1997). Synchronization of oscillatory responses occurs within as well as among visual areas, for example, between homologous areas of the left and right hemispheres and between areas at different levels of the visuomotor pathway (Engel and others 1991; Roelfsema and others 1997). Synchronization in the visual cortex appears to depend on stimulus properties, such as continuity, orientation, and motion coherence.

The problem with synchronization is that there is nothing essentially dynamic about synchronous interactions per se. As argued by Erb and Aertsen (1992), “the question might not be so much how the brain functions by virtue of oscillations, as most researchers working on cortical oscillations seem to assume, but rather how it manages to do so in spite of them.” To establish dynamic cell assemblies, it is necessary to create and destroy synchronized couplings. It is precisely these dynamic aspects that speak to changes in synchrony (e.g., Desmedt and Tomberg 1994) and the asynchronous transitions between synchronous states as the more pertinent phenomenon. In other words, it is the successive reformulation of dynamic cell assemblies, through nonlinear or asynchronous interactions, that is at the heart of “dynamical linking” (Singer 1994).

#### *Asynchronous Codes*

An alternative perspective on neuronal codes is provided by *dynamic correlations* (Aertsen and others 1994) as exemplified in Vaadia and others (1995). A fundamental phenomenon observed by Vaadia and others (1995) is that, following behaviorally salient events, the degree of coherent firing between two neurons can change profoundly and systematically over the ensuing second or so. One implication is that a complete model of neuronal interactions has to accommodate dynamic changes in correlations, modulated on time scales of 100 to 1000 ms. Neuronal transients provide a simple explanation for this temporally modulated coherence or dynamic correlation. Imagine that two neurons respond to an event with a similar transient. For example, if two neurons respond to an event with decreased firing for 400 ms, and this decrease was correlated over epochs, then positive correlations between the two firing rates would be seen for the first 400 of the epoch, and then fade away, emulating a dynamic modulation of coherence. In other words, a transient modulation of covariance can be equivalently formulated as a covariance in the expression of transients. The generality of this equivalence can be established using singular value decomposition (SVD) of the joint-peristimulus time histogram (J-PSTH) as described in Friston (1995b). This is simply a mathematical device to show that dynamic changes in coherence are equivalent to the coherent expression of neural transients. In itself it is not important, in the sense that dynamic correlations are just as valid a characterization as neuronal transients are and indeed may provide more intuitive insights into how this phenomenon is mediated (e.g., Riehle and others 1997). What is important is that J-PSTHs can be asymmetric about the lead-

ing diagonal. This suggests that coupled transients in two units can have a different patterning of activity. This can only be explained by asynchronous or nonlinear coupling.

In summary, the critical distinction between synchronous and asynchronous coupling is the difference between linear and nonlinear interactions among units or populations.<sup>3</sup> If the transient model is correct, then important transactions among cortical areas will be overlooked by techniques that are predicated on rate coding (e.g., correlations, covariance patterns, spatial modes, etc.) or synchronization models (e.g., coherence analysis and cross-correlograms). Clearly the critical issue here is whether there is direct evidence for nonlinear or asynchronous coupling that would render the transient level of the taxonomy a useful one.

### The Evidence for Neuronal Transients and Nonlinear Coupling

Why is asynchronous coupling so important? The reason is that asynchronous interactions embody all the nonlinear interactions implicit in functional integration and it is these that mediate the diversity and context-sensitive nature of neuronal interactions. The nonlinear nature of interactions between cortical brain areas renders the effective connectivity among them inherently dynamic and contextual. Compelling examples of context-sensitive interactions include the attentional modulation of evoked responses in functionally specialized sensory areas (e.g., Treue and Maunsell 1996) and other contextually dependent dynamics (see Phillips and Singer [1997] for an intriguing discussion). Whole classes of empirical phenomena such as extra-classical receptive field effects rely on nonlinear or asynchronous interactions.

#### Nonlinear Coupling and Asynchronous Interactions

If the temporal structures of coupled transients can be distinct in two parts of the brain, then the prevalence of certain frequencies in one cortical area should predict the expression of *different* frequencies in another. In contrast, synchronization models posit a coupled expression of the *same* frequencies. Correlations among different frequencies therefore provide a basis for discriminating between synchronous and asynchronous coupling.

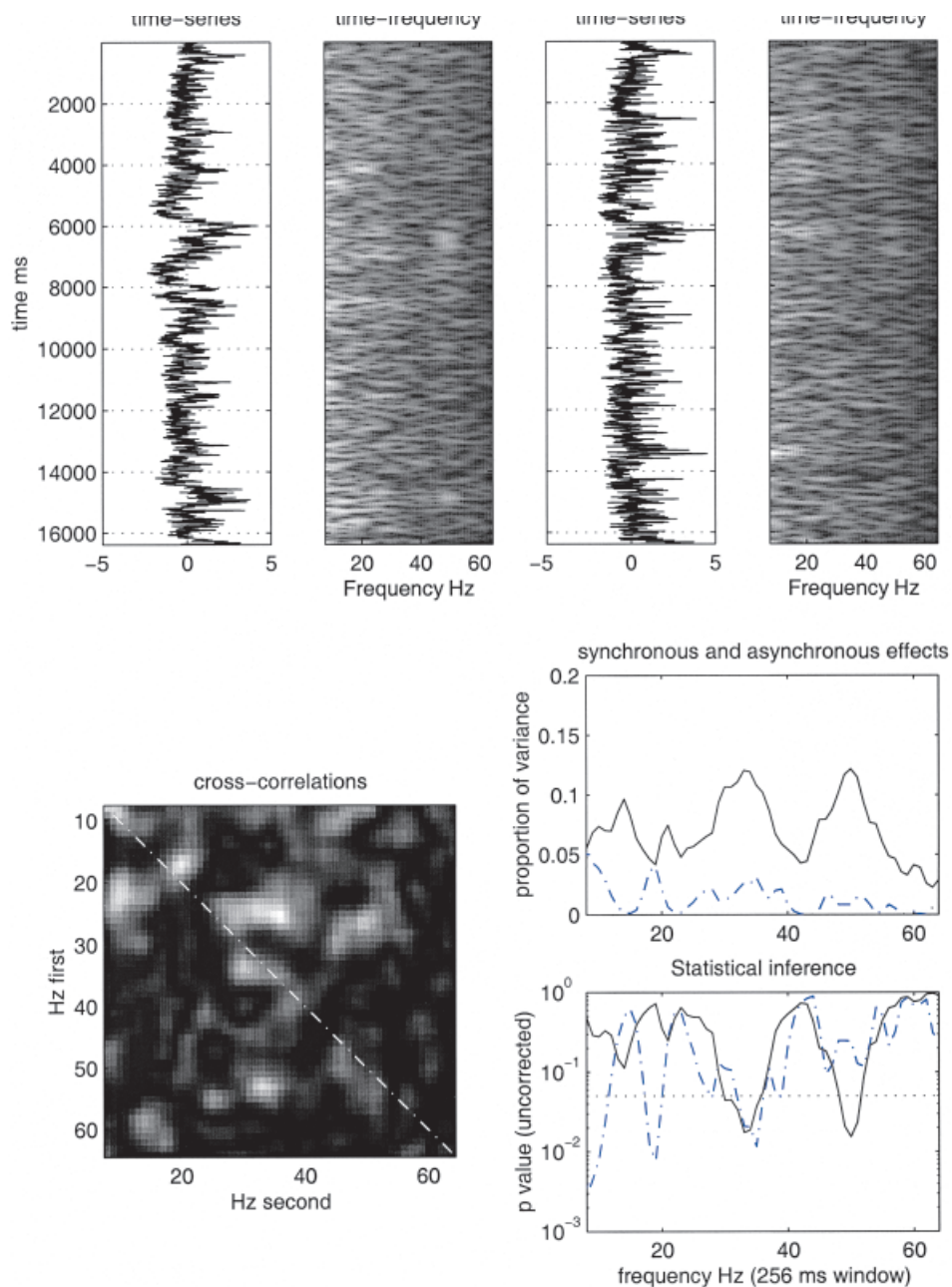
Consider time series from two neuronal populations or cortical areas. Synchrony requires that the expression of a particular frequency (e.g., 40 Hz) in one time series will be coupled with the expression of the same frequency in the other. In other words, the modulation of this frequency in one area can be explained or predicted by its modulation in the second. Conversely, asynchronous coupling suggests that the power at a reference frequency, say 40 Hz, can be predicted by the spectral density in the second time series at some frequencies other

than 40 Hz. These predictions can be tested empirically using standard time-frequency and regression analyses as described in Friston (2000a). Figure 2 shows an example of this sort of analysis, revealing the dynamic changes in spectral density between 8 and 64 Hz over 16 seconds. The cross-correlation matrix of the time-dependent expression of different frequencies in the parietal and prefrontal regions is shown in the *lower left* panel. There is anecdotal evidence here for both synchronous and asynchronous coupling. Synchronous coupling, based on the co-modulation of the same frequencies, is manifest as hotspots along, or near, the leading diagonal of the cross-correlation matrix (e.g., around 20 Hz). More interesting are correlations between high frequencies in one time series and low frequencies in another. In particular, note that the frequency modulation at about 34 Hz in the parietal region (second time series) could be explained by several frequencies in the prefrontal region. The most profound correlations are with lower frequencies in the first time series (26 Hz). Using a simple multilinear regression framework, statistical inferences can be made about the coupling within and between different frequencies (see Friston 2000a for details). A regression analysis shows that coupling at 34 Hz has significant synchronous and asynchronous components, whereas the coupling at 48 Hz is purely asynchronous (*middle* and *right* peaks in the graphs), that is, a coupling between beta dynamics in the premotor region and gamma dynamics in the parietal region.

### The Neural Basis of Asynchronous Interactions

In Friston (1997), it was suggested that, from a neurobiological perspective, the distinction between asynchronous and synchronous interactions could be viewed in the following way. Synchronization emerges from the reciprocal exchange of signals between two populations, where each *drives* the other, such that the dynamics become entrained and mutually reinforcing. In asynchronous coding, the afferents from one population exert a *modulatory* influence, not on the activity of the second but on the interactions within it (e.g., a modulation of effective connectivity or synaptic efficacies within the target population), leading to changes in the dynamics intrinsic to the second population. In this model, there is no necessary synchrony between the intrinsic dynamics that ensue and the temporal pattern of modulatory input. To test this hypothesis, one would need to demonstrate that asynchronous coupling emerges when extrinsic connections are changed from driving connections to modulatory connections. Clearly this cannot be done in the real brain. However, we can use computational techniques to create a biologically realistic model of interacting populations and test this hypothesis directly.

3. The term *generalized synchrony* has been introduced to include nonlinear interdependencies (see Schiff and others 1996). Generalized synchrony subsumes synchronous and asynchronous coupling. An elegant method for making inferences about generalized synchrony is described in Schiff and others (1996). This approach is particularly interesting from our point of view because it calls upon the recent history of the dynamics through the use of temporal embedding to reconstruct the attractors analyzed.



**Fig. 2.** Time-frequency and regression analysis of MEG time series designed to characterize the relative contribution of synchronous and asynchronous coupling. Neuromagnetic data were acquired from a normal subject using a KENIKRON 37 channel MEG system at 1-ms intervals for periods of up to 2 min. During this time, the subject made volitional joystick movements to the left, every 2 sec or so. Paired epochs were taken from a left prefrontal and left parietal region. *Top panels:* The two time series (plots) and their corresponding time-frequency profiles (images). The first time series comes from the left prefrontal region. The second comes from the left superior parietal region. *Lower left panel:* This is a simple characterization of the coupling among frequencies in the two regions and represents the [squared] cross-correlations of the time-varying expression of different frequencies from the *upper panels*. *Lower right panels:* These are the results of a linear regression analysis that partitions the variance in the second (parietal) time series into components that can be attributed to synchronous (broken lines) and asynchronous (solid lines) contributions from the first (prefrontal) time series. The *upper graph* shows the relative contribution in terms of the proportion of variance explained and (*lower graph*) in terms of the significance using a semilog plot of the corresponding *P* values. The dotted line in the latter corresponds to  $P = 0.05$ . This example was chosen because it illustrates three sorts of coupling (synchronous, asynchronous, and mixed). From inspection of the cross-correlation matrix, it is evident that synchrony in the second time series is correlated with similar frequency modulation in the first, albeit at a slightly lower frequency. The resulting correlations appear just off the leading diagonal (broken line) on the *upper left*. The proportion of variance explained by synchronous and asynchronous coupling is roughly the same and, in terms of significance, synchrony supervenes (see *upper graph*). In contrast, the high correlations, between 48 Hz in the second time series and 26 Hz in the first, are well away from the leading diagonal, with little evidence of correlations within either of these frequencies. The regression analysis confirms that, at this frequency, asynchronous coupling prevails. The variation at about 34 Hz in the parietal region could be explained by several frequencies in the prefrontal region. A formal analysis shows that both synchronous and asynchronous coupling coexist at this frequency (i.e., the middle peak in the graphs).



### Interactions between Simulated Populations

Two populations were simulated using the model described in Friston (2000a). This model simulates entire neuronal populations in a deterministic fashion based on known neurophysiological mechanisms. In particular, we modeled three sorts of synapses, fast inhibitory (GABA), fast excitatory (AMPA), and slower voltage-dependent synapses (NMDA). Connections intrinsic to each population used only GABA and AMPA-like synapses. Simulated glutaminergic extrinsic connections between the two populations used either driving AMPA-like synapses or modulatory NMDA-like synapses. Transmission delays for extrinsic connections were fixed at 8 ms. By using realistic time constants, the characteristic oscillatory dynamics of each population were expressed in the gamma range.

The results of coupling two populations with unidirectional AMPA-like connections are shown in the top of Figure 3 in terms of the simulated local field potentials (LFP). Occasional transients in the driving population were evoked by injecting a depolarizing current, of the same magnitude, at random intervals (dotted lines). The tight synchronized coupling that ensues is evident. This example highlights the point that near linear coupling can arise even in the context of loosely coupled, highly nonlinear neuronal oscillators of the sort modeled here. Contrast these entrained dynamics under driving connections with those that emerge when the connection is modulatory or NMDA-like (*lower* panel in Fig. 3). Here there is no synchrony and, as predicted, fast transients of an oscillatory nature are facilitated by the low-frequency input from the first population that has a lower frequency (cf. the MEG analyses above). This is a nice example of asynchronous coupling that is underpinned by nonlinear modulatory interactions between neuronal populations. The nature of the coupling can be characterized using the time-frequency analysis (identical in every detail) applied to the neuromagnetic data of the previous section. The results for the NMDA simulation are presented in Figure 4. The cross-correlation matrix resembles that obtained with the MEG data in Figure 2. Both in terms of the variance and inference, asynchronous coupling supervenes at most frequencies but, as in the real data, mixed coupling is also evident. These results can be taken as a heuristic conformation of the notion that modulatory, in this case voltage-dependent, interactions are sufficiently nonlinear to account for the emergence of asynchronous coupling.

### Modulatory Interactions and Nonlinear Coupling

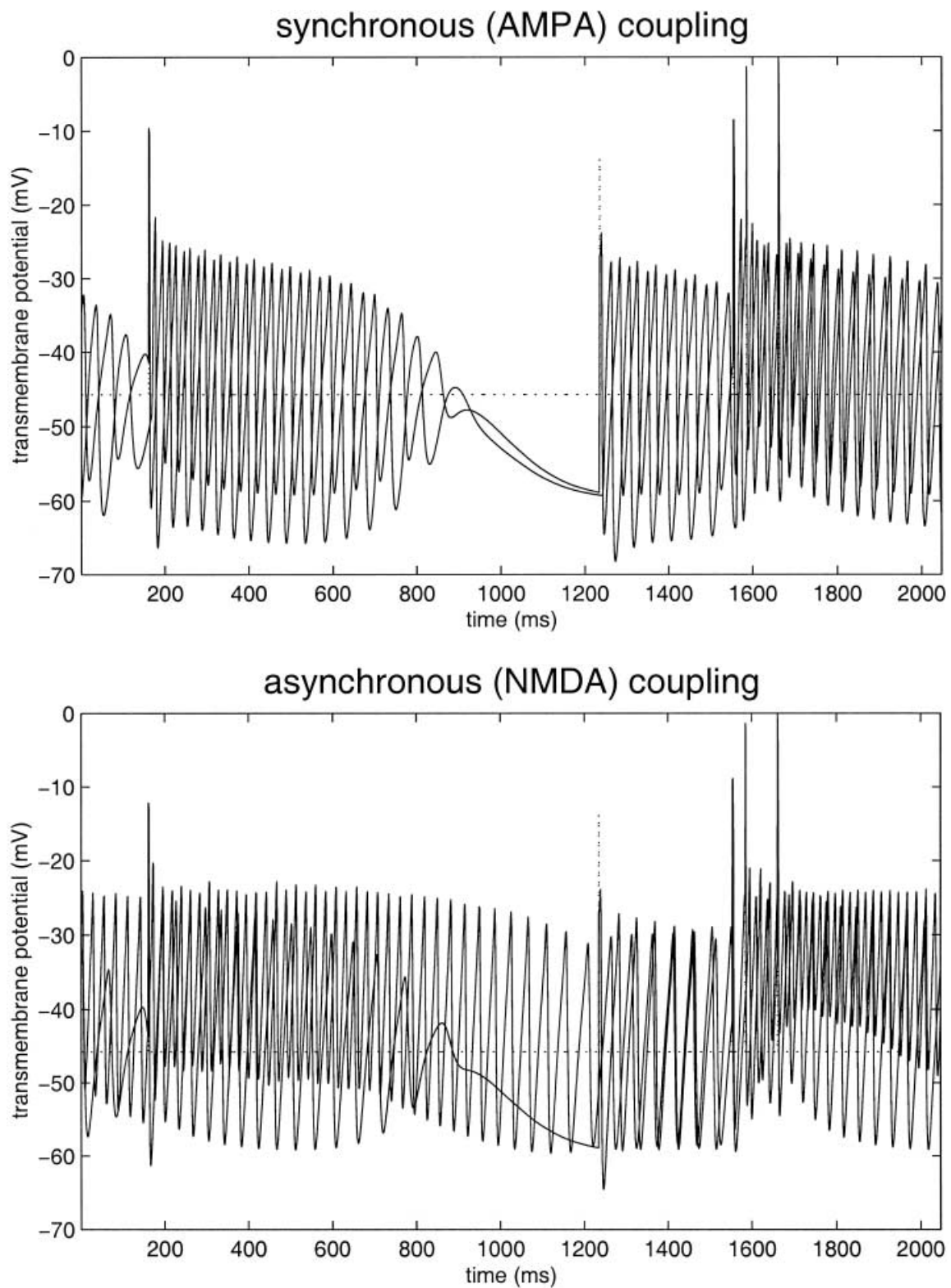
In summary, asynchronous coupling is synonymous with nonlinear coupling. Nonlinear coupling can be framed in terms of the modulation of intrinsic interactions, within a cortical area or neuronal population, by extrinsic input offered by afferents from other parts of the brain. This mechanism predicts that the modulation of fast (e.g., gamma) activity in one cortical area can be predicted by much slower changes in other areas. This form of cou-

pling is very different from coherence or other measures of synchronous coupling and concerns the relationship between the first-order dynamics in one area and the second-order dynamics (spectral density) expressed in another. In terms of the above NMDA simulation, transient depolarization in the modulating population causes a short-lived increased input to the second. These afferents impinge on voltage-sensitive NMDA-like synapses with time constants (in the model) of about 100 ms. These synapses open and slowly close again, remaining open long after an afferent volley. Because of their voltage-sensitive nature, this input will have no effect on the dynamics intrinsic to the second population unless there is already a substantial degree of depolarization. If there is, then, through self-excitation and inhibition, the concomitant opening of fast excitatory and inhibitory channels will generally increase membrane conductance, decrease the effective membrane time constants, and lead to fast oscillatory transients. This is what we observe in the *lower* panel of Figure 3. In relation to the MEG analyses, the implied modulatory mechanisms, that may underpin this effect, are entirely consistent with the anatomy, laminar specificity, and functional role attributed to prefrontal efferents (Rockland and Pandya 1979; Selemon and Goldman-Rakic 1988).

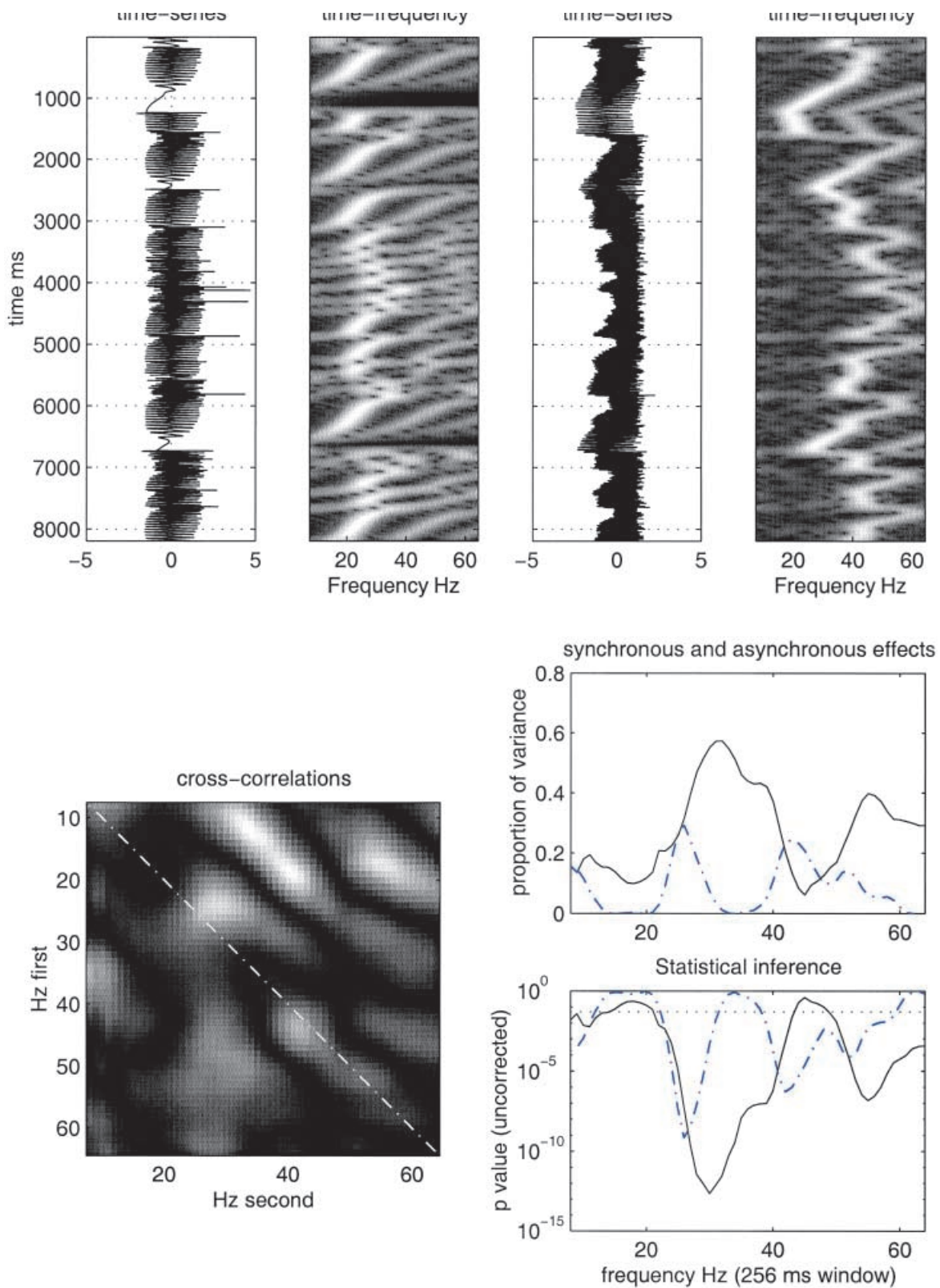
### Conclusion

In this review, we have dealt with some important and interrelated aspects of brain function. The key steps can be summarized as follows:

- Starting with the premise that the brain can be represented as an ensemble of connected input-state-output systems (e.g., cellular compartments, cells, or populations of cells), there exists an equivalent input-output formulation in terms of a Volterra series expansion of each system's inputs that produces its outputs (where the outputs to one system constitute the inputs to another).
- The existence of this formulation suggests that the history of inputs, or neuronal transients, and the Volterra kernels are a complete and sufficient specification of brain dynamics. This is the primary motivation for framing dynamics in terms of neuronal transients and using a Volterra formulation to model effective connectivity.
- The Volterra formulation provides constraints on the form that neuronal interactions and implicit codes must conform to. There are two limiting cases: 1) when the neuronal transient has a very short history and 2) when high-order terms disappear. The first case corresponds to instantaneous codes (e.g., rate codes), and the second to synchronous interactions (e.g., synchrony codes).
- High-order terms in the Volterra model of effective connectivity speak explicitly to nonlinear interactions and implicitly to asynchronous coupling. Asynchronous coupling implies coupling among the expression of different frequencies.
- Coupling among the expression of different frequencies is easy to demonstrate using neuromagnetic measurements of real brain dynamics. This implies that nonlin-



**Fig. 3.** Simulated local field potentials (LFP) of two coupled populations using two different sorts of postsynaptic responses (AMPA and NMDA-like) to connections from the first to the target population. The dotted line shows the depolarization effected by sporadic injections of current into the first population. The key thing to note is that under AMPA-like or driving connections, the second population is synchronously entrained by the first. When the connections are modulatory or voltage-dependent (NMDA), the effects are much more subtle and resemble a frequency modulation. These data were simulated using a biologically plausible model of excitatory and inhibitory subpopulations. The model was deterministic with variables pertaining to the collective, probabilistic behavior of the subpopulations (cf. a mean field treatment). See Friston (2000a) for details.



**Fig 4.** As for Figure 2, but here using the simulated data employing voltage-dependent NMDA-like connections. The coupling here includes some profoundly asynchronous (nonlinear) components involving frequencies in the gamma range implicated in the analyses of real (MEG) data shown in Figure 2. In particular, note the asymmetrical cross-correlation matrix and the presence of asynchronous and mixed coupling implicit in the *P* value plots on the lower right.

ear, asynchronous coupling is a prevalent component of functional integration.

- High-order terms in the Volterra model of effective connectivity correspond to modulatory interactions that can be construed as a nonlinear effect of inputs that interact with the dynamics intrinsic to the recipient system. This implies that driving connections may be linear and engender synchronous interactions, whereas modulatory connections, being nonlinear, may cause, and be revealed by, asynchronous coupling.
- Nonlinear coupling among brain systems is essential for neuronal computation that embodies contextual information. Context can be used to instantiate prior expectations through backward and lateral modulatory connections leading to a plausible (generative model or Bayesian) understanding of perceptual synthesis at a functional level or, empirically, things like extra-classical receptive field effects and dynamic correlations.

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