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Variability and interdependence of local field potentials: Effects of gain modulation and nonstationarity

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Abstract

Cortical potentials following sensory stimulation are widely analyzed as the linear combination of an invariant evoked response component, time-locked to the stimulus, and an independent, ongoing noise component. We consider two alternative models and compare their predictions with data. In the first model, neuronal populations coupled through nonlinear sigmoid functions have their effective connectivity modulated by the evoked response. This leads to fast changes in the ongoing activity measured by ensemble variance, cross-correlation, spectral power, or coherence time functions. In the second model, trial-to-trial amplitude variability of a stereotyped evoked response leads to similar modulation in ongoing activity. Specific predictions from both models are tested against local field potentials recorded intracortically from monkeys performing a visuomotor task.

Keywords: Variability; Event-related potential; Cross-correlation; Coherence; Functional connectivity

1. Introduction

At least since the time of Dawson [3], cortical potentials following sensory stimulation have been commonly understood as the linear combination of a stimulus-evoked invariant response, which is time-locked to the stimulus onset, and independent, ongoing, broadband noise activity. The trial-to-trial variability of cortical potentials is

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thus attributed to the variability of the ongoing component. We call this the signal plus noise (SPN) model, which can be formally expressed as

$$Z^r(t) = E(t) + \eta^r(t),$$

where $Z^r(t)$ is the recorded cortical potential at time t for the rth trial, with the stimulus onset at $t = 0$; $E(t)$ is the stereotyped deterministic stimulus-evoked response, and $\eta^r(t)$ is a "noise" component reflecting ongoing activity that is independent of the evoked response $E(t)$. In practice, the average $\langle Z^r(t)\rangle$, taken over an ensemble of trials, is considered an approximate representation of $E(t)$ and is referred to as the average event-related potential (AERP). Accordingly, the ongoing activity can then be estimated by the residual time series computed by subtracting the ensemble mean from each trial: $\eta^r(t) = Z^r(t) - \langle Z^r(t)\rangle$.

The SPN model predicts that statistical quantities computed on the residuals $\eta^r(t)$ do not display temporal modulations that are event-related. Examples of such quantities are the time-varying ensemble variance $\langle(\eta^r(t))^2\rangle$, power spectral density $\langle|\eta^r(f,t)|^2\rangle$, lagged cross-correlation $\langle\eta_1^r(t)\eta_2^r(t+\tau)\rangle/(\langle[\eta_1^r(t)]^2\rangle\langle[\eta_2^r(t+\tau)]^2\rangle)^{1/2}$, and coherence, the frequency-domain analogue of the cross-correlation. However, experimental evidence from behaving animals indicates that stimulus-related modulation of these quantities on a time scale of $\sim$100 ms do in fact occur [1]. It is not clear how these temporal modulations arise or whether they relate systematically to different phases of the AERP. In this paper we explore the origins of these modulations by studying models in which the assumptions of the SPN model are no longer maintained. In models of neuronal populations with sigmoid activation functions, such modulatory effects on the ongoing activity can arise from modulations of the input-output gain (local slope of the sigmoid function) that depend on the evoked response. Predictions derived from this nonlinear model are tested on a data set of local field potentials (LFPs) recorded from intracortical electrodes implanted at distributed cortical sites in macaque monkeys performing a visual pattern discrimination task. In another model, the effect of trial-to-trial nonstationarity of the stimulus response amplitude on the referred measures is examined and tested on the same experimental data.

2. Methods

2.1. Experiments

All experiments were performed by Dr. Richard Nakamura in the Laboratory of Neuropsychology at the National Institute of Mental Health. Visual evoked responses were sampled at 200 Hz from chronically implanted surface-to-depth bipolar electrodes, in four macaque monkeys, at several (11–15) cortical sites in one hemisphere. The monkeys performed a visual pattern discrimination task. The prestimulus stage began when the monkey, while viewing a computer screen, depressed a hand lever with the preferred hand. Following a random interval from 0.5 to 1.2 s, a visual stimulus appeared for 100 ms on the screen. Two types of visual patterns were

presented: four dots arranged as a diamond or as a line. The monkey was rewarded for lifting the hand in response (GO) to one pattern type, while maintaining pressure (NO-GO) to the other pattern type. The contingency between stimulus pattern and response type was reversed on successive sessions. The present study focuses on the initial stages of the visual evoked response to presentation of one of the stimulus patterns (line). For each subject, an ensemble of trials, taken from multiple sessions, was balanced for response type (GO and NO-GO). A detailed description of the experiment and data preprocessing have been presented elsewhere [1,4].

2.2 Cross-correlation time function

The lagged cross-correlation at time t between time series from two electrodes Z_1 and Z_2, in an ensemble of N trials, was computed as

$$C_{z_1 z_2}(t,\tau) = \left(\sum_{r=1}^{N} \eta_1^r(t)\eta_2^r(t+\tau) \right) \Big/ \left(\sum_{r=1}^{N} [\eta_1^r(t)]^2 \sum_{r=1}^{N} [\eta_2^r(t+\tau)]^2 \right)^{1/2}.$$

The cross-correlation was computed on the filtered residual time series (lowpass, -3 db at 22 Hz). Zero-phase forward and reverse digital filtering was employed to prevent phase distortion (MATLAB FIR2 and FILTFILT functions with filter order of 7).

2.3. Absolute phase histograms

In Section 4 a prediction is made about the phase of the Fourier component $\eta(f,t)$ at a specific frequency f for a time segment around t during the evoked response period. To test this prediction, absolute phase histograms were computed as a function of time. Specifically, an analysis window of 80 ms (16 data points) in length, centered at time t, was shifted one data point at a time, starting from 50 ms before the stimulus onset to 350 ms after. The single-trial time series within each window was Fourier transformed (FFT) and phase was computed at the 12.5 Hz Fourier component. A phase histogram was constructed from the ensemble of trials for each window, channel and subject. The histogram's bin width was $2\pi/100$. The choice of the 12.5 Hz component was motivated by the fact that, for many of the electrodes with significant evoked response, the AERP showed a very clear characteristic oscillation with a period around 80 ms (12.5 Hz).

2.4. AMVAR spectral estimation

Power and coherence time functions were estimated by the application of adaptive multivariate autoregressive (AMVAR) analysis to the residual time series. Each single-trial residual (600 ms long) was divided in 110 consecutive (shifted by one data point) windows of 10 points (50 ms) each. A detailed description of the technique is found in [4]. AMVAR models were fitted on time series following both temporal and ensemble normalization.

Before computation of the ensemble mean (AERP) and variance, each single trial was normalized by mean subtraction and standard deviation division. For this reason, the AERP, ensemble variance, and power spectral density are dimensionless quantities.

3. Event-related gain modulation: nonlinear model perspective

Dynamical models of neuronal population activities [5,6] relate the field potentials and the pulse density (the number of spikes per unit volume) in a local neuronal population by a nonlinear function of a sigmoid type. A resulting property of networks of such populations is the dynamic modulation of gain and effective connectivity by the network's mean activity level [10]. This modulation can affect both the local population properties and the interactions among local populations. First, transient changes in the population's mean level of activity, like that produced by stimulus-evoked responses, can place the system at regions of different gain levels in their output sigmoid function, resulting in amplification or attenuation of the ongoing activity leading to transient changes in the time course of the ensemble variance and power spectral density time functions of the residuals $\eta(t)$. Second, the residual time series from different populations, through the transient modulation of their shared variances, can exhibit an event-related modulation of their statistical interdependence leading to fast transients in the time course of the cross-correlation (or coherence) time functions.

The main predictions of the nonlinear model are twofold. First, if in the ensemble of trials, the mean level of activity represented by the AERP tends to fluctuate beyond the near linear range of the sigmoid function, the ensemble variance time function $\langle(\eta^r(t))^2\rangle$ will show peaks that coincide with the extrema of the AERP. The power spectral density time function, $\langle|\eta^r(f,t)|^2\rangle$, will show peaks in its time course and should be more smoothed than the variance time function because of its computation in a sliding time window. Second, this temporal modulation effect should occur for a broad range of frequencies f, especially if the pre-stimulus activity is itself broad-band. Temporal modulation of the lagged cross-correlation, $\langle\eta^r_1(t)\eta^r_2(t+\tau)\rangle/(\langle[\eta^r_1(t)]^2\rangle\langle[\eta^r_2(t+\tau)]^2\rangle)^{1/2}$, and spectral coherence time functions for interacting cortical sites will be expected to exhibit peaks that coincide with peaks in the variance time function, and with peaks in the power time function, respectively.

To check these predictions, we performed analysis on LFP data (see Methods). Fig. 1 shows examples from four monkeys of time functions of the AERP, the ensemble standard deviation and 12 Hz power.

It is quite apparent that the peaks of the ensemble variance and power functions tend to coincide with extrema of the AERPs near 100 ms (negative for monkeys GE, LU, and PE, positive for monkey TI). The 12 Hz power was employed because of a narrow-band peak at this frequency in the power spectra for many of the recorded sites (see Fig. 3).

Peaks in the cross-correlation functions for many pairs of cortical sites also were temporally related to peaks in variance and to the first extrema of the relevant AERPs as illustrated in Fig. 2 for one monkey. Furthermore, peaks in the post-stimulus

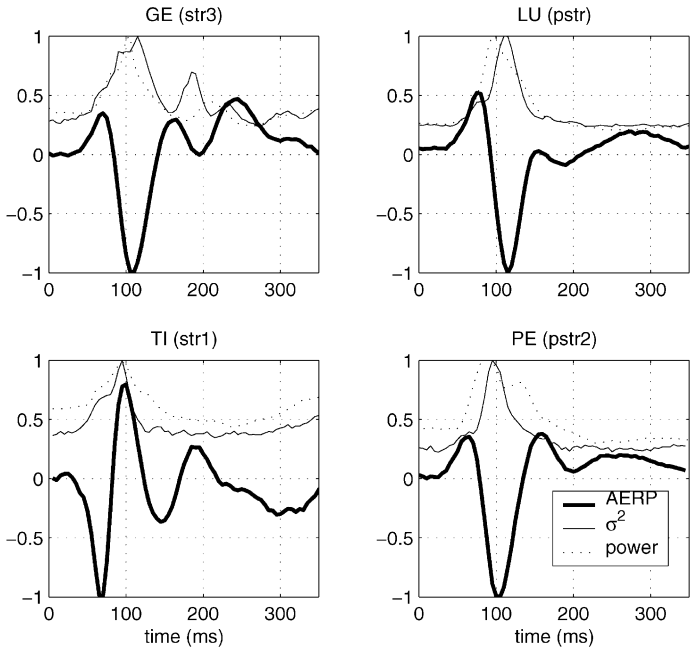

Fig. 1. Examples from four monkeys of time functions of ensemble mean (AERP), variance (σ^2) and 12 Hz power from striate (str) and pre-striate (pstr) sites. To facilitate the comparison between the shapes, all quantities were further normalized by their own maximal amplitude. Stimulus onset is at time 0 ms.

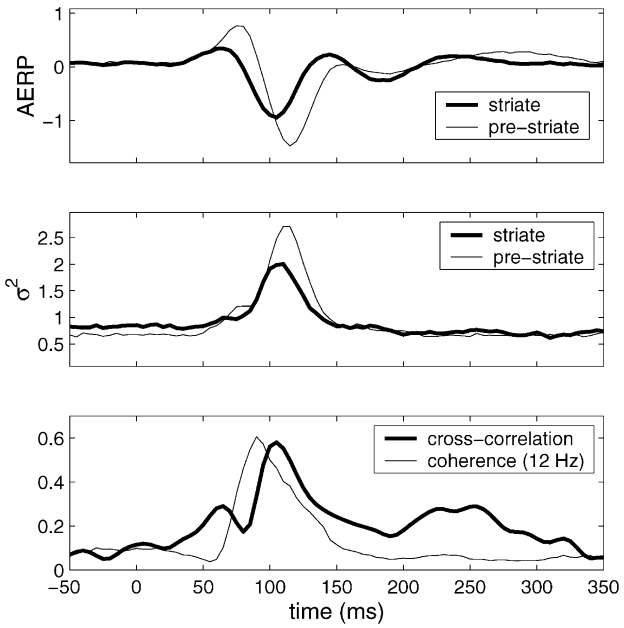

Fig. 2. Relations between AERP, variance, cross-correlation and coherence.

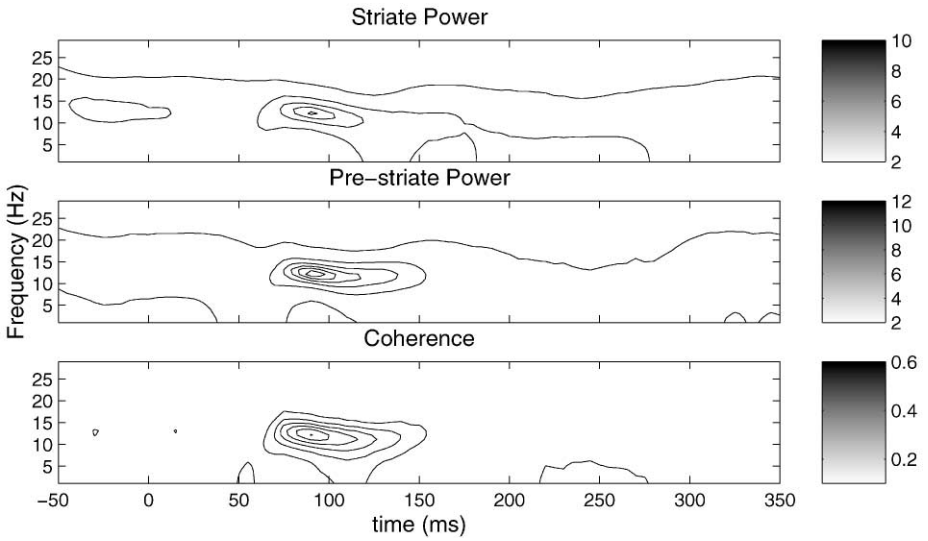

Fig. 3. Contour plots of power and coherence time functions for a striate and pre-striate site in one of the monkeys. Note the high levels of post-stimulus power in the 12 Hz range for the striate and pre-striate sites, as well as the high level of post-stimulus coherence between them in the same range.

spectral coherence time function at 12 Hz showed a strong tendency to coincide in time with the 12 Hz power peaks (Fig. 3). The time course of the 12 Hz coherence resembles a smoothed version of the cross-correlation time function.

Thus far the predictions of the nonlinear model seem to agree with the data. However, more careful examination of the frequency dependence of the power modulation reveals this model's shortcomings. Fig. 4 shows the power functions in the beta and gamma bands (lower two panels) over several of the recorded sites in addition to the power function at 12 Hz (second panel from top). Contrary to the prediction that the gain modulation effect will be similar for all frequencies, the power functions in the high frequency bands actually decrease during the evoked response period. Another example of this abrupt decrease in high frequency power, from the pre-stimulus to post-stimulus period, is the strong perturbation, followed by abolishment of a pre-stimulus narrow-band ($\sim$20 Hz) oscillation, resulting in lowered power at this frequency at a parietal site (Fig. 5). This event is also associated with decreases in coherence among several sites. Overall our results indicate that the modulation, especially in the power of beta and gamma frequencies, could be the result of gain modulation. However, this modulation seems to exhibit a more complex nature than the one presented by the current nonlinear model.

4. Nonstationarity of evoked responses: Amplitude variability

The frequency specific nature of the observed ongoing activity modulation, coupled with the fact that the modulation frequency is close to that of the AERP, led us to

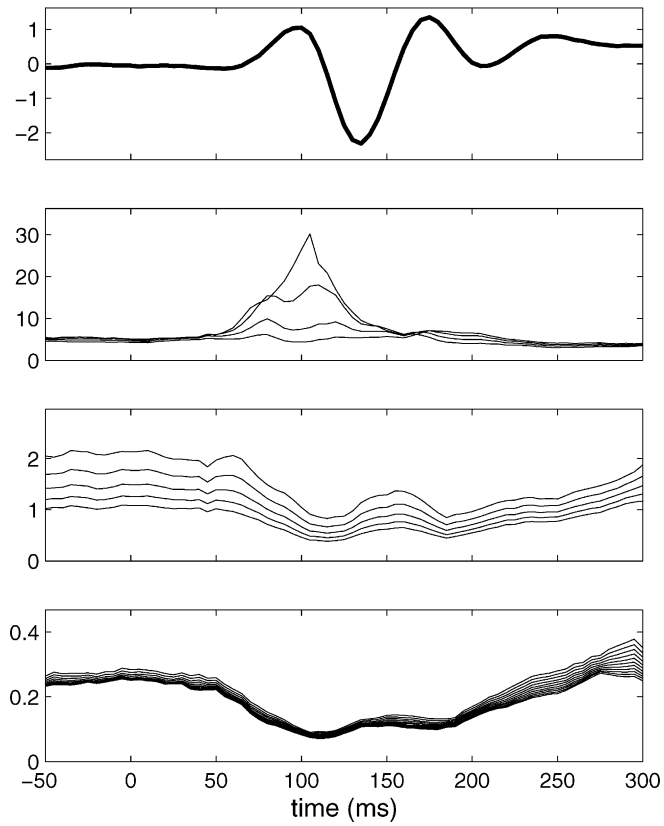

Fig. 4. Example of an AERP function and power functions from a pre-striate site. The top plot shows the AERP. In the three bottom plots, the power spectral density function is shown. Each line represents the power at a specific frequency computed from a short (50 ms) moving window (see Methods). In the second plot (from top to bottom): 9–12 Hz (peak in power at 12 Hz); third plot: 20–24 Hz; and fourth plot: 40–50 Hz. In the last two plots, power decreases with increasing frequency.

investigate an alternative explanation for the observed modulations in variance and in the $\sim$12 Hz power and coherence. This alternative abandons the assumption in the SPN model that the stimulus-evoked response is invariant over trials. It is known, for example, that the amplitude of evoked responses can vary according to states of arousal and attention [9]. Thus, spontaneous fluctuations in these factors, could lead to trial-to-trial nonstationarity of the evoked responses. If we assume that the evoked response has a stereotyped shape, this variation may occur as amplitude variability across trials, increasing the ensemble variance during the evoked response period. The alternative model incorporating this trial-to-trial amplitude variability [2,7], referred to as the Variable amplitude Signal Plus Noise (VSPN) model, can be expressed as: $Z^r(t) = \alpha^r E(t) + \xi^r(t)$, where the variable α^r represents the amplitude variability of the response and is assumed to be time independent for a given trial; and the component $\xi^r(t)$ is the ongoing activity. The terms α^r and ξ^r are assumed to be independent.

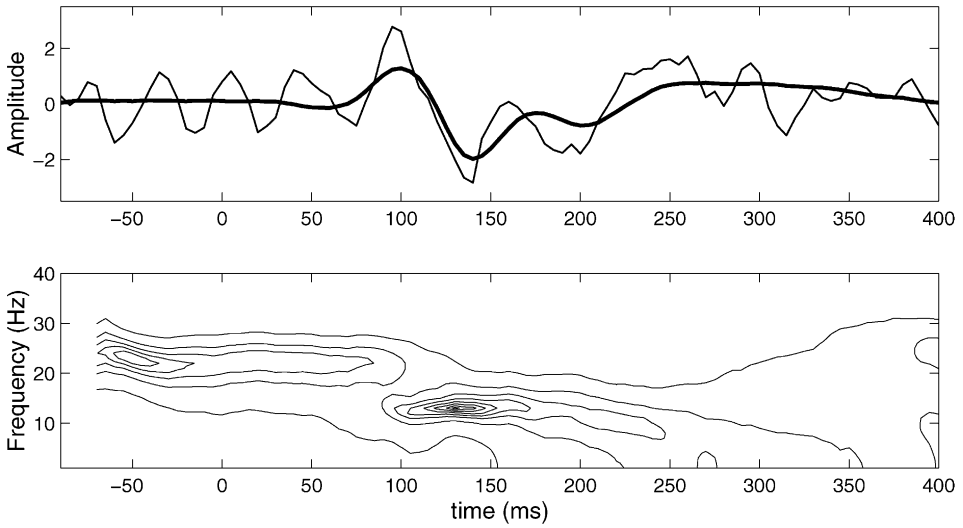

Fig. 5. Top plot shows a single-trial example of abrupt perturbation of ongoing ~20 Hz oscillation at a parietal site with the advent of the stimulus-evoked response (the AERP appears in the thicker line). The single-trial amplitude has been subtracted by its own mean and normalized by its standard deviation. The bottom panel shows the corresponding contour plot of the power spectral density time function for the whole ensemble of trials. Peaks in power are represented by the centers. Note the shift of the peak from ~22 to ~12 Hz.

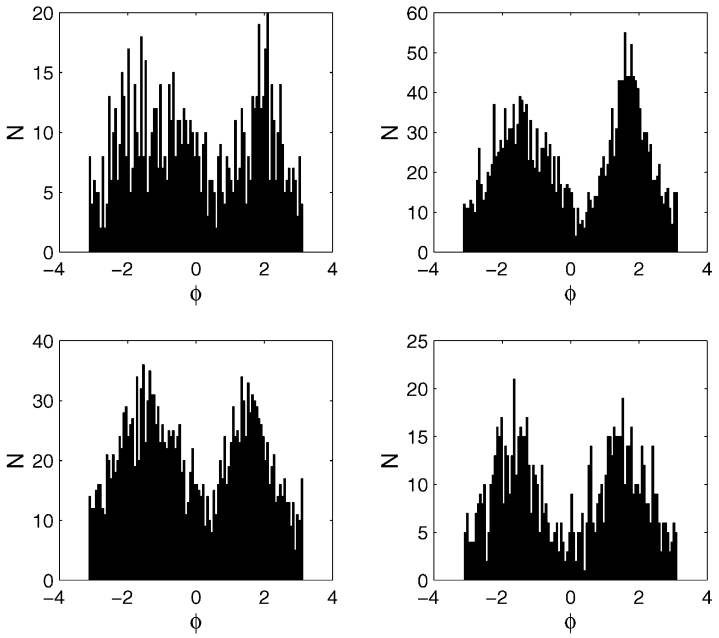

Fig. 6. Examples of absolute phase histograms from the four monkeys. Abscissa: phase in radians. Ordinate: number (N) of occurrences.

Recast the VSPN model as $Z^r(t) = \langle Z^r(t)\rangle + \eta^r(t)$ where $\langle Z^r(t)\rangle = \langle \alpha^r\rangle E(t)$. The residual term then becomes: $\eta^r(t) = \alpha^r E(t) - \langle Z^r(t)\rangle + \xi^r(t) = (\alpha^r - \langle \alpha^r\rangle)E(t) + \xi^r(t)$. It contains two components: a stimulus time locked component, $S^r(t) = (\alpha^r - \langle \alpha^r\rangle)E(t)$, and the ongoing activity $\xi^r(t)$. The ensemble variance as a function of time can be evaluated as $\langle(\eta^r(t))^2\rangle = \langle(\alpha^r - \langle \alpha^r\rangle)^2\rangle E^2(t) + \langle(\xi^r(t))^2\rangle$.

It is clear that the variance of the residual follows the shape of $E^2(t)$. In particular, the peaks of the variance function should occur at the same time as the extrema of the AERP. Moreover, since $E(t)$ often resembles a damped oscillation with a clear characteristic frequency component, the power spectrum time function, $\langle|\eta(f,t)|^2\rangle$, at this characteristic frequency will be similarly modulated, also exhibiting a significant increase during the evoked response time period, a feature that is consistent with the data.

The validity of the VSPN model can be tested by way of a prediction that can distinguish it from the SPN model. Specifically, since $(\alpha^r - \langle \alpha^r\rangle)$ fluctuates between positive and negative values in the VSPN model, it predicts that the Fourier component $\eta(f)$, computed for each single trial at the main characteristic frequency f of the AERP, will exhibit a bimodal phase distribution with the two modes separated by the value of π. In contrast, if there is no time-locked component in the residual, as in the SPN model or during the pre-stimulus period, a uniform phase distribution is expected.

In fact, the computed histograms from the LFP data set (see Methods) significantly departed from the uniform distribution during the initial stages of the evoked response, presenting strongly bimodal distributions. Typical examples are shown in Fig. 6 for four monkeys. This result is clear evidence for the presence of the amplitude variability proposed in the VSPN model. The VSPN model also predicts modulations of ensemble variance and power according to the shape of the AERP, and for interacting cortical sites, AERP-related modulations of cross-correlation and coherence. A detailed analysis of these effects is presented elsewhere [11].

5. Conclusions

Many computational theories of brain function hypothesize fast transient stimulus- or task-dependent changes in the interdependence between neuronal populations [8,12]. Usually those changes are thought to be caused by fast transient changes in connectivity strength both at short and long ranges. The common way to search for supporting evidence for these theories is to look for event-related changes in the ensemble variance, power spectral density, and interdependency measures like cross-correlation and coherence. The interpretation of the causes of event-related modulations of these statistical measures becomes then a fundamental problem in system neurosciences. In this paper we have explored a nonlinear interaction perspective where the interdependence between neuronal populations is modulated by their mean activity levels. We have shown that nonstationarities due to amplitude variability of evoked responses can also be a significant contributor to event-related modulation of statistical measures, even though they do not relate to changes in connectivity

strength. We have also presented evidence that appears to contradict a main assumption of the classical SPN model. Thus the standard interpretation of the AERP and of the residual time series may require re-evaluation.

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