Role of Neuronal Synchrony in the Generation of Evoked EEG/MEG Responses

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INTRODUCTION

Evoked responses (ERs) in EEG/MEG are the primary objective real-time measures of cognitive, perceptual, and motor activity in the human brain. They are usually seen as phase-locked upward or downward deflections in electric/magnetic fields best visible after averaging of many epochs.

Although ERs are used frequently in basic and cognitive neuroscience, their neurophysiological generator mechanisms are still debated. ER parameters, such as amplitude, latency, and the anatomical locus of generation, are commonly compared between different experimental conditions/tasks, and conclusions are drawn without referring to the exact mechanisms by which ERs are generated. However, such an approach allows only for a correlative appreciation of underlying neuronal activity without insight into how information is actually processed in the brain and what possible differences in ERs might indicate.

Three basic generic models of ER generation have been proposed thus far. 1) In the added-energy model, stimuli produce ERs that are superimposed on the ongoing neuronal activity; the latter is considered to be noise and typically is averaged out (Dawson 1950; Mäkinen et al. 2005; Mazaheri et al. 2006; Shah et al. 2004). The model implies that a phase-locked neuronal activation, such as postsynaptic potentials, is triggered by the stimulus. 2) In the phase-reset model, there is no added component, but stimuli reset the phase of ongoing oscillations to a specific value such that, after averaging, phase-locked evoked responses become discernible (Fell et al. 2004; Hanslmayr et al. 2006; Makeig et al. 2002; Sayers et al. 1974). 3) In the baseline-shift model, ERs are produced through the amplitude modulation of ongoing oscillations, which do not have zero mean (Nikulin et al. 2007).

This study primarily focuses on the first two models, i.e., added-energy and phase-reset. For the last 30 yr, these two mechanisms have been scrutinized for explaining the generation of visual (Becker et al. 2008; Hanslmayr et al. 2006; Makeig et al. 2002; Mazaheri and Jensen 2006), auditory (Klimesch et al. 2006; Mäkinen et al. 2005; Sayers et al. 1974), or somatosensory ERs (Valencia et al. 2006) and, a number of criteria have been advanced to distinguish between these two scenarios.

In parallel, the concept of phase reset was studied at the level of single neurons to describe their responses to injection of brief current pulses (Guttmann et al. 1980; Reyes and Fetz 1993). Although the main phenomenon is the same—the stimulation modifies the phases of ongoing oscillations without affecting their amplitude—there is a significant difference in the spatial scales at which the phase reset occurs. In the EEG/MEG literature, the phase reset model concerns the observed phase of ensemble activity (macroscopic phase reset), whereas in cellular neurophysiology, it relates either to spike timing of a single cell or the phase of its membrane potential (microscopic phase reset).

The main objective of this study is to clarify some common misconceptions originating in the ER research because of varying definitions of the spatial scale at which the phase reset occurs. We first show theoretically that an ER generation through either the microscopic added-energy or phase-reset mechanisms cannot be, in principle, differentiated on the basis of macroscopic EEG/MEG recordings alone. Next, we consider specific criteria regularly used for proving one or another mechanism and show that they provide only ambiguous results regarding microscopic processes because they are based on a specific manifestation of neuronal interactions (specifically, coupling strength in an ensemble of responsive cellular units), which are not accessible readily to noninvasive EEG/MEG techniques. Finally, we study how synchrony between neuronal elements, which is mediated, for example, by mutual interactions, affects the macroscopic properties of evoked responses.

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and subsequently show that both phase-reset and added-energy ER models can be unified within one framework.

Based on these results, we conclude that, without the knowledge of the extent/width of synchronization between microscopic neuronal oscillators, the added-energy and phase-reset mechanisms of evoked response generation cannot be reliably distinguished. Because the spatial synchronization is a microscopic ensemble property that cannot be assessed with state-of-the-art EEG/MEG, these techniques might not aid to disentangle the mechanisms of ER generation. This does not imply that the added-energy and phase-reset mechanisms cannot be distinguished in principle. Other techniques, particularly those based on single-cell recordings, can be informative for deciding between the two alternatives.

METHODS

Model of microscopic neural sources

Microscopic neural elements are modeled by a population of \( N \) simplified phase oscillators with the following phase dynamics (Tass 2005)

\[
\frac{d\phi_j}{dt} = \omega - \frac{K}{N} \sum_{k=1}^{N} \sin(\phi_k - \phi_j) + X(t) \sin(\phi_j) + \gamma_{\text{dep}} F_j(t) + \gamma_{\text{comm}} G(t) \tag{1}
\]

where \( j \) is the index of an oscillator. The phase of each oscillator advances linearly with the angular eigenfrequency \( \omega \). The individual oscillators are pairwise coupled; the interaction is described by the coupling coefficient \( K \) multiplied by a phase-resetting curve (PRC) (Pavlidis 1974). The PRC is a periodic function of phase; thus it can be represented in terms of Fourier series. Here, we choose the first nonconstant term of the series, which is already sufficient to synchronize the population of oscillators (Kuramoto 1984; Strogatz 2000; Tass 2005). Other shapes of PRC and their effects on these results are addressed in Discussion.

The external stimulus \( X(t) \) applied by the experimenter is modeled by a pulse of intensity \( I \) that is switched on at a time \( t_{\text{on}} \), and after a stimulation period \( T \) is switched off again, so that

\[
X(t) = \begin{cases} 
1 & \text{if } t_{\text{on}} \leq t \leq t_{\text{on}} + T \\
0 & \text{otherwise} 
\end{cases} \tag{2}
\]

Each oscillator’s phase can be advanced or delayed because of the external stimulation, depending on its value at the time of stimulus’ arrival. The stimulus-induced phase shift is assumed to be produced by synaptic elements with dynamics similar to those involved in mutual coupling and therefore is described by the same PRC curve as defined above, i.e., it is proportional to the sine of the phase at stimulation onset (Tass 2007) (Fig. 1).

In addition, the oscillators are driven by white noise sources \( F_j(t) \) and \( G(t) \) with SD \( \gamma_{\text{dep}} \) and \( \gamma_{\text{comm}} \), respectively. Intrinsic noise sources \( F_j(t) \) are independent between oscillators, whereas \( G(t) \) represents random inputs common for whole population.

Model of macroscopic activity

At the microscopic level, the model describes only the evolution of phases, and the oscillations are assumed to have unit amplitude. This is consistent with theoretical findings where microscopic systems with periodic dynamics, such as an ensemble of periodically firing neurons with weak interactions, can be uniquely described by their phases (Brown et al. 2004; Gutkin et al. 2005; Kuramoto 1984). However, an electric or magnetic field measured far from such ensemble represents a superposition of fields generated by many individual elements/oscillators (Malmivuo and Plonsey 1995; Nunez and Srinivasan 2005). We calculate the macroscopic activity of the whole population as a circular sum (Winfree 1980)

\[
Z(t) = \sum_{k=1}^{N} \left[ \cos(\phi_k(t)) + i \sin(\phi_k(t)) \right] + \gamma_{\text{meas}} \eta(t) = \sum_{k=1}^{N} \exp[i\phi_k(t)] + \gamma_{\text{meas}} \eta(t) \tag{3}
\]

where \( i = \sqrt{-1} \) is the imaginary unit, \( \eta(t) \) is a Gaussian white noise modeling additive measurement errors caused by environment and amplifier noise, and \( \gamma_{\text{meas}} \) is the SD of the measurement noise.

In the whole ensemble, the contributions of individual oscillators can sum constructively or destructively depending on their relative phases. The cancellation of incoherent oscillations or, respectively, the enhancement of coherent ones will result in an amplitude modulation of the net activity. The macroscopic amplitude dynamics is described by the ensemble amplitude \( R(t) = |Z(t)| \), whereas ensemble phase \( \phi(t) = \arg[Z(t)] \) corresponds to the ensemble phase dynamics.

Quantitative measures of evoked responses

We simulate \( M \) trials by calculating numerical solutions to Eq. 1 with the same stimulus \( X(t) \) but each time reinitializing the phases with random numbers drawn from a uniform distribution in the interval \([0, \pi]\). In each run of the simulation, the complex amplitude \( Z^{(k)} \) is calculated from Eq. 3, where index \( k = 1, 2, \ldots, M \) enumerates the trials. From these simulation results, we calculate the average evoked response (ER\(_{\text{avg}}\))

\[
\text{ER}_{\text{avg}}(t) = \frac{1}{M} \sum_{l=1}^{M} \Re[Z^{(l)}(t)] \tag{4}
\]

its envelope (ER\(_{\text{env}}\))

\[
\text{ER}_{\text{env}}(t) = \frac{1}{M} \sum_{l=1}^{M} |Z^{(l)}(t)| \tag{5}
\]

the phase-locking index (PLI) (Tallon-Baudry et al. 1996)

\[
\text{PLI}(l) = \frac{1}{M} \sum_{l=1}^{M} \exp[i\phi^{(l)}(t)] \tag{6}
\]

and the average of single-trial amplitude envelopes.

![Fig. 1. The effect of an external stimulus on the phase of a single neuronal oscillator. The phase of the oscillator after stimulation (\( \phi_{\text{on}} \)) is dependent on its phase before stimulus onset (\( \phi_{\text{on}} \)). The mapping between initial and final phases of the forced oscillator (stimulus intensity \( I = 1.5 \), solid line) compared with a freely advancing oscillator (stimulus intensity \( I = 0 \), diagonal dashed line) shows periods of phase advance and delay. The crossing point between both lines lying between \( \pi/2 \) and \( \pi \) corresponds to an attractor, which draws all of the phases in the course of the stimulation. Inset: a sample evolution of a population of \( n = 20 \) oscillators whose phases are initially uniformly distributed (thin lines): after the stimulation, the phases are concentrated around the fixed point, which results in an increased ensemble amplitude. Model parameters: \( \gamma_{\text{dep}} = 0 \), \( \gamma_{\text{comm}} = 0 \), \( T = 1 \), \( \omega = 1 \), \( K = 0 \). (2005). We calculate the macroscopic activity of the whole population as a circular sum (Winfree 1980).](http://jn.physiology.org/DownloadedFrom/bnj1000561716/image/3558_b.telec.jpg)
where $\phi^0(t) = \arg[Z^0(t)]$ and $R^0(t) = |Z^0(t)|$ are the ensemble phase and amplitude in the simulation trial $t$.

**Comparison to baseline**

To estimate the change in the ER$_{avg}$, ER$_{env}$, PLI, and ST$_{env}$ induced by the stimulation, we compare the measures to the corresponding values derived from a stimulus-free baseline. The baseline is calculated by running the simulation with the same initial conditions and model parameters but without the stimulus $X(t)$ set to 0 for all $t$. As a result, the simulation is run twice: with stimulation (target) and without stimulation (baseline); in both runs, the initial conditions and the random number generator are reset. In the following, we calculate the above-defined measures for the baseline and target trials separately. Finally, the results obtained from the baseline simulation are subtracted from the target measures, and the difference is averaged within the window defined by the stimulus duration ($t_{onset} \leq t \leq t_{onset} + T$).

**RESULTS**

**Phase reorganization at microscopic level may mimic both phase-reset and added-energy mechanisms of macroscopic ER generation: an overview**

Before a detailed quantitative analysis, we introduce the key findings of the study with a simplified illustration. It is generally accepted that the amplitude of ongoing ensemble activity depends both on the synchrony among the microscopic elements and the number of elements being active (Nunez and Srinivasan 2005). Thus any increase of the ensemble activity may be caused by a stronger coherence and/or by the recruitment of additional synchronous units. To scrutinize this point, we consider the case of a group of simplified neural sources. If the sources are not interacting, their activities will be incoherent (Fig. 2, Ia and IIa). Because neuronal tissue acts as a volume conductor, the fields generated by individual neural sources sum up linearly, resulting in cancellation of the incoherent activity and enhancement of the coherent one. Therefore uncoupled sources (coupling coefficient $K = 0$) while being active would not produce observable macroscopic potentials/fields measured with EEG/MEG (Fig. 2, Ib and IIb).

Incoming stimuli may increase the amplitude of the macroscopic potentials/fields by modifying the synchrony or number of active elements. According to the added-energy model of ER generation, the response is produced by additional neural activity induced by the stimulus. Mechanistically, this corresponds to a recruitment of previously inactive set of neurons without interference with the spontaneously active population. In this scenario, schematically represented in Fig. 2I, the measured macroscopic EEG/MEG response reflects activity of the neurons that are recruited with a fixed phase to the stimulus processing (Fig. 2, Ic and Id). The stimulus-driven activity of the otherwise quiescent neurons results in an increase of the signal power, which is considered a hallmark of ERs generated by the added-energy model.

Critically, however, a similar increase in power can also be produced by the reorganization of the incoherent ongoing activity present before the stimulation—a scenario essentially different from the recruitment model considered above. In this case, the external stimulus drives oscillation phases toward a specific value (it “resets” the phases), thus rendering them more coherent. Because at the microscopic level multiple oscillators are simultaneously active, the phase of each of them is modified accordingly. As a result of this mechanism, called microscopic phase reset, the microscopic oscillations become more coherent, and they sum up constructively generating visible macroscopic (e.g., EEG/MEG) oscillations (Fig. 2, IIc and IIId). In both mechanisms, i.e., in the recruitment of inactive neurons and for the microscopic phase reset of ongoing activity, the macroscopic responses to a single presentation of the stimulus are identical: there are no oscillations in the prestimulus period (Fig. 2, Ib and IIb, black line), but there are stimulus-locked oscillations in the poststimulus period (Fig. 2, Ic and IIc, black line).

Let us now consider a situation in which the microscopic sources are coupled and thus spontaneously synchronized before the stimulus (Fig. 2, IIIa and IIIb). In this case, the external stimulation cannot increase the synchrony further, and consequently, the microscopic phase reset will not affect the amplitude of macroscopic oscillations (Fig. 2, IIIb and IIIc). Although the amplitude is not affected, the phases of macroscopic and consequently macroscopic oscillations are aligned to the stimulus onset (Fig. 2, IIIc and IIId). The resulting poststimulus activity is identical to the one observed in the previous two scenarios, but the prestimulus period contains large ongoing oscillations absent in the other scenarios. Such a response is consistent with the microscopic phase-reset model as discussed in the EEG/MEG literature.

In the following, we construct an ER model based on the microscopic phase-reset phenomenon and provide detailed quantitative analysis of the obtained responses.

**Standard macroscopic ER measures might confuse microscopic phase reset with recruitment model**

To study the effect of microscopic phase-reset on macroscopic ER quantitatively, we simulated an ensemble of uncoupled noisy phase oscillators (coupling coefficient $K = 0$, see Methods), each of which represents a local neural unit. The initial phases are uniformly distributed so that at the beginning of the stimulation the oscillations are asynchronous. However, the application of an external stimulus common to all oscillators changes the phase distribution in a specific manner. The effect of such stimulation on any single oscillator is phase dependent: a stimulus arriving at the end of the oscillation period delays the oscillations, whereas a stimulus arriving at the beginning of the period advances them. In effect, after the stimulation the distribution of phases over the ensemble tends to be concentrated around a preferred mean phase (Fig. 1). The situation is similar to the scenario presented in Fig. 2II, where the hard “reset” of the phase was replaced by a more realistic phase shift.

We repeated the simulation procedure ($M = 100$; each run with different initial phases) to obtain a set of independent trials/epochs. Based on these simulation trials, we calculated four indices routinely used to differentiate between mechanisms of evoked response generation: the average evoked response (ER$_{avg}$), its amplitude envelope (ER$_{env}$), the phase locking index (PLI), and the averaged single-trial amplitude envelope (ST$_{env}$; see Methods) (Jansen et al. 2003; Makeig et al. 2002; Sayers et al. 1974; Tallon-Baudry et al. 1996; Valencia et al. 2006).
Stimulus-locked averaging of the macroscopic simulation trials (Fig. 3A) exhibits a significant increase of activity (Fig. 3B) analogous to ERs recorded with EEG/MEG. To elucidate the mechanism of ER generation, we compared the oscillatory power of single-trial macroscopic signals after the stimulus to the baseline condition without stimulation (see METHODS). Estimating an instantaneous power modulation in experimental data involves applying rectification/squaring of band-pass filtered recordings (based on Hilbert or wavelet transform) before trial-averaging, which avoids cancellation of phases variable...
over trials (Le Van Quyen et al. 2001). Accordingly, in this study, the simulated macroscopic responses were first rectified using an analytical calculation of the amplitude envelope (see METHODS) and subsequently trial-averaged. The resulting average single-trial envelope $S_{\text{env}}$ showed a prominent increase after stimulus onset (Fig. 3C). Similarly, the prominent trial-averaged ER ($E_{\text{avg}}$; Fig. 3B) has an amplitude envelope ($E_{\text{env}}$; Fig. 3E), which closely followed the single-trial power modulation. This presence of single-trial power increase accountable for trial-averaged ER is in agreement with the predictions of the added-energy mechanism of ER generation. Crucially, however, the microscopic mechanism underlying the simulated data is a pure phase reset where neither amplitude nor the number of active oscillators has been changed. The same ambiguity is inherent also to other often-used measures, such as PLI (see METHODS). When applied to the simulated data, PLI showed strong and significant coherence between the simulation trials shortly after the stimulus onset (Fig. 3D). Naturally, high coherence is expected in all mechanisms of ER generation, because only those components that are locked to the stimulus onset will survive trial averaging and thus contribute to the ER (Mäkinen et al. 2005).

It is important to emphasize that the energy increase measured in macroscopic EEG/MEG signals owing to microscopic phase reset is not specific to model details. On the contrary, it can be shown theoretically that macroscopic signals can be represented equivalently in terms of microscopic processes involving either phase or amplitude dynamics (see Supplementary Information). This ambiguity cannot be resolved unless the microscopic phase and amplitude distributions are known or can be experimentally measured.

Degree of synchrony across the microscopic sources can bias inferences about the mechanism of macroscopic ERs

To study how different levels of neuronal synchrony affect a poststimulus amplitude increase, we simulated an ensemble of coupled phase oscillators. The single oscillators resemble those described above, but here all oscillators are globally coupled between each other (coupling coefficient $K = 1.5$, see METHODS). This coupling enables them to synchronize their activity spontaneously, thereby making the phases more clustered. In contrast to the uncoupled ensemble studied above, the prestimulus activity in the coupled model does not cancel out on summing over the whole ensemble, and consequently, it produces ongoing (prestimulus) macroscopic oscillations (Fig. 4A). The external stimulation has no or little effect on the synchrony within the coupled ensemble, and consequently, the amplitude of the single-trial macroscopic oscillations remains unchanged at a level higher than in the uncoupled case ($S_{\text{env}}$, cf. Figs. 3C, uncoupled, vs. 4C, coupled).

Interestingly, although there is no single-trial power increase induced by the stimulation, a prominent ER locked to the stimulus is observed after averaging (Fig. 4B). The reason is that the instantaneous intraensemble synchrony does not imply cross-trial coherence in ongoing (prestimulus) oscillations. On the contrary, the ongoing activity, which is not locked to the stimulus, will largely cancel out after trial averaging. However, the external stimulation, while not affecting the (already strong) ensemble synchrony, aligns the ensemble oscillations in each trial, so that macroscopically ER peaks become visible after trial averaging. This phenomenon is reflected in the time course of PLI (Fig. 4D): being low initially, it increases strongly after stimulation onset. These poststimulus oscillations being locked to stimulus onset survive averaging and produce a visible ER (Fig. 4E) whose amplitude envelope is
similar to the uncoupled case (Fig. 3E). After the end of the stimulation, the stimulus locking will decay as a result of random inputs common to all oscillators, but the ensemble synchrony will not change because of the strong endogenous mutual coupling.

The models discussed thus far represent two opposite ends of a “synchrony” spectrum: in the uncoupled ensemble, the phases of all microscopic oscillators are independent, whereas in the strongly coupled ensemble, they are close to identical. What happens in the intermediate range of coupling strengths? To answer this question, we simulated the model with varying coupling coefficients (K, see METHODS) and calculated the stimulus-induced increase of single-trial amplitudes (STenv) and the amplitudes of evoked responses (ERenv) in relation to their respective baselines (see METHODS). We found that, whereas the amplitude of ERs does not change much, there is a smooth transition from a significant amplitude increase in the low-coupling case to no single-trial increase in the high-coupling case (Fig. 5). These findings indicate that the standard ER generation mechanisms (phase-reset and added-energy) described in the literature (Arieli et al. 1996; Sayers et al. 1974) represent the outermost instances of a continuous spectrum of “mixed” models.

The macroscopic measures obtained by simulation of microscopic phase reset mechanisms under different coupling strengths are compared with predictions of macroscopic phase reset and added-energy oscillators in Fig. 6. Summarizing the results presented above, Fig. 6 shows that three different microscopic scenarios are qualitatively consistent with the predictions of macroscopic added-energy model (Fig. 6A, gray background): neuronal recruitment scenario at low and high neuronal coupling, and microscopic phase reset scenario at low coupling (Fig. 6B, gray background). Conversely, the remaining scenario of microscopic phase-reset in a highly coupled ensemble (Fig. 6B, white background) produces responses in agreement with macroscopic phase reset (Fig. 6A, white background).

**Discussion**

This study showed that one generic microscopic mechanism for ERs, i.e., the one which is produced by phase reset of ongoing oscillations in an ensemble of neuronal single units, can be consistent with either the macroscopic phase-reset or added-energy models of ER generation depending on the strength of spatial synchronization between the neurons. Consequently, use of EMG/EEG recordings without exact knowledge of intraensemble coupling strength makes it difficult to decide which microscopic mechanisms are responsible for the generation of evoked responses.

**Phase reset versus added-energy mechanism**

The most fundamental criterion, which is frequently used for differentiating between phase-reset and added-energy mechanisms of ER generation, is the presence/absence of a single-trial energy increase in the poststimulus interval. If present,
achieved easily by a (microscopic) phase reset in an ensemble of oscillating cells with a very low level of spatial synchronization. Thus at the macroscopic level of EEG/MEG, an observed amplitude increase is consistent with both recruitment of additional cellular oscillators and microscopic phase-reset mechanisms. Consequently, this most frequently used criterion, which captures the differential essence of the two ER mechanisms, cannot be used as a reliable criterion for deciding on the genuine neuronal processes underlying the observed macroscopic ER.

Another frequently used prerequisite (Sauseng et al. 2007) or criterion (Becker et al. 2008; Shah et al. 2004) associated with phase reset is the presence of ongoing neuronal oscillations. Although it is true that a phase reset is possible only in the presence of oscillations (otherwise there is nothing to reset), these results showed that oscillations at the microscopic level might not be easily observed in macroscopic EEG/MEG recordings in case of a low level of spatial synchronization in a given ensemble of oscillating neurons. Such macroscopically “masked” oscillations could lead to the conclusion that ERs are produced without the presence of ongoing oscillations (a result favoring the added-energy mechanism), which would be a premature statement if there is no information available about the strength of the spatial synchronization.

Another ambiguity for both phase-reset and added-energy mechanisms is the so-called phase concentration in the post-stimulus interval (measured, for example, by PLI). It is present for both mechanisms and, although it is important for obtaining phase-locked responses, it does not allow to differentiate between the two models.

Although further secondary criteria were proposed for distinguishing between the phase-reset and added-energy mechanisms, such as a similar spatial location for the generation of oscillations and evoked responses (Barry 2009) or sensitivity to the phase/amplitude of ongoing oscillations (Becker et al. 2008; Sauseng et al. 2007), they also cannot be resolved unambiguously in favor of one or another model at the level of EEG/MEG (Sauseng et al. 2007).

The possible mechanistic connection linking a microscopic phase reset to an macroscopically apparent added-energy measured with EEG/MEG is the main topic of this study. Although it is a direct consequence of established electrophysiological facts concerning the generation of EEG, it has not yet been rigorously studied. Although Sauseng et al. (2007) mentioned that phase resetting of a large population of neurons may result in EEG power increase, they did not provide a quantitative analysis and, specifically, did not address the question under what conditions such a power increase may occur, what parameters are influencing its magnitude, and how the notion of a variable spatial synchronization can aid to reconcile within one framework the apparently contradictory findings favoring phase-reset versus added-energy mechanisms. Here, we developed a stringent argumentation conceptually sharpening the issue and report on detailed simulations and theoretical analysis supporting the multifaceted insights.

**Role of spatial synchronization**

The key parameter manipulated in this study is the coupling between the neuronal sources, which affects the amount of spatial synchronization before the stimulus. In the low cou-
pling regime, a stimulus-triggered simultaneous phase reset of multiple oscillators produces a poststimulus increase in macroscopic single-trial energy. However, when the intraensemble coupling is increased, many of the individual sources become spontaneously synchronized and can behave almost as a single macroscopic oscillator, producing spontaneous on-going EEG/MEG oscillations. The response of this oscillator to the presentation of a stimulus is consistent with the notion of phase reset as regularly used in the ER literature: the prestimulus macroscopic oscillations become aligned to the stimulus onset, thereby increasing the poststimulus cross-trial coherency. Only in this scenario, in which tightly coupled neuronal oscillators are phase-reset by the stimulus, could one conclude correctly about microscopic mechanisms from their macroscopic manifestation. Notably, in practice, this situation may be difficult to discern from added-energy mechanism because an added component may be masked by noise or by ongoing oscillations, and consequently, the response may be incorrectly interpreted as a phase reset (Becker et al. 2008; G. Waterstraat, B. Teleanzczuk, M. Burghoff, H. J. Scheer, G. Curio, unpublished data).

Experimental estimates of coupling strength come from the measurements of the synchronization of alpha oscillations (which are most often implicated in the generation of evoked responses through a phase reset) recorded from very closely spaced electrodes. These measurements show that the spatial synchronization can be attenuated by 50% within just a few millimeters (Bullock et al. 1995). In another study in cats, it was also found that the neuronal synchronization between neurons attenuated rapidly within just a few millimeters (Destschke et al. 1999). Both results suggest that the coupling between neuronal sources is low. Clearly, in such situations, the amplitude of macroscopic EEG/MEG oscillations depends strongly on the amount of synchronization between the neurons (Naruse et al. 2010).

Baseline-shift model of ER

The third model for ER generation states that the amplitude modulation of ongoing oscillations with nonzero mean can lead to ERs (Mazaheri and Jensen 2008; Nikulin et al. 2007, 2010) even when these oscillations are not visible at the macroscopic MEG/EEG level. This is because a low spatial synchronization between neurons can abolish macroscopic oscillations, but it would have no effect on the corresponding changes of the baseline shifts arising from the modulation of nonzero mean oscillations (Nikulin et al. 2010). In such situations, one would tend to believe that ERs are generated through an added-energy mechanism; yet, again, without knowledge of the spatial synchronization, such a conclusion would be premature. In general, the formal inclusion of this third ER model would further increase the uncertainty about the mechanisms, thus strengthening the main point of this study.

Details of the phase oscillator model

The phase oscillator model used in this study is a widely used approach for simulation of coupled oscillators (Hansel et al. 1993; Pikovsky et al. 2002; Schuster and Wagner 1990; Seliger et al. 2002; Sompolinsky et al. 1990). The dynamical properties of such models and their dependence on the parameters were studied in depth both analytically and using computer simulations (Acebron et al. 2005). In particular, the conditions under which the individual oscillators synchronize their activities are well understood (Kuramoto 1984; Strogatz 2000). Building on these fundamental findings, we chose here a specific model that is general enough to reproduce different regimes of neuronal dynamics affecting ER generation and that avoids the plethora of details of more complex models that could obscure this main point.

The parameters for the model were chosen to reflect either experimental findings or theoretical work on the neuronal dynamics. Specifically, the PRC, which quantifies the coupling between different neurons and between neurons and stimulus (Fig. 1) can be measured experimentally and calculated analytically. The biphasic PRC used here is qualitatively similar to the PRC obtained, for example, by an analytical reduction of a realistic axon model (Brown et al. 2004) or recorded experimentally from in vivo neurons (Tateno and Robinson 2007). However, monophasic PRCs are found in some in vivo and in silico neurons (Gutkin et al. 2005; Reyes and Fitz 1993). Oscillators interacting via such monophasic PRCs, in contrast to these simulations based on a biphasic PRC, desynchronize their activities (Hansel et al. 1995) unless a noninstantaneous response of the synapse is additionally taken into account (Van Vreeswijk et al. 1994). Nevertheless, even in the asynchronous population, an external stimulus in the ensemble can still lead to a concentration of their phases by driving simultaneously all oscillators and induce an accompanying increase of macroscopic energy, in analogy with the uncoupled model presented above.

Because PRCs are periodic functions of phase, they can be expanded in the form of a Fourier series. Without loss of generality, we held only the first nonconstant term of the expansion. Fourier modes of higher order can enrich the dynamics, for example, introducing clustering (Sakaguchi et al. 1987). This intriguing phenomenon is independent of the effects described in this study and imposes further complications on the interpretation of macroscopic EEG/MEG signals (Tass 2007).

To make this model more realistic, we also introduced two types of phase noise to the model (see METHODS): individual noise independent for each oscillator \( F[t] \) and shared noise common for all oscillators \( G[t] \). The former reflects the intrinsic noise sources within each neuron (Faisal et al. 2008; White et al. 2000), whereas the latter models unspecific “background” inputs arriving simultaneously at all oscillators (Fontanini and Katz 2008; Shadlen and Newsome 1998). The effect of the noise is the desynchronization of the oscillators after the stimulus is switched off, which results in the decay of the evoked response. In additional numerical simulations (data not shown), we found that the amplitude of the individual noise affects mainly the decay time of ERs generated in the uncoupled population, whereas the amplitude of the shared noise shapes the decay of ERs in the coupled population. It is important to note that these are only quantitative differences without an influence on the accuracy of the main conclusions, which would still hold even if one or both of the noise terms is dropped.

In our model, we assume identical eigenfrequencies for all oscillators. This assumption could be easily generalized for the case where the frequencies are distributed over some range. It was shown that even in this case the phase
oscillators can spontaneously synchronize their activities, provided that the coupling is strong enough to overcome the variability of eigenfrequencies. In this case, the oscillators will become spontaneously entrained to an ensemble oscillation with a net frequency (Kuramoto 1984; Strogatz 2000). Therefore such a modification of our model, after the proper adjustment of the coupling coefficient, would not affect qualitatively our results.

**Generality of the conclusions**

In the discussed model, the key neuronal population property affected by the stimulus is the amount of synchronization between the neurons. This, in turn, relates to the strength of the measured electric/magnetic field, which was shown to be proportional to the number of synchronously firing neurons (Nunez and Srinivasan 2005). In a given network, the strength of spatial synchronization varies, which consequently leads to the fluctuations in the amplitude of ongoing oscillations.

For the purposes of this study, it is not important how exactly the synchronization between neurons is achieved. It can be based on direct excitatory connections between neurons or on the involvement of inhibitory neurons (Bibbig et al. 2002; Naruse et al. 2010). For the generation of EEG/MEG signals, it is only important that a large number of neurons become synchronous and thus macroscopically measurable signals can be produced.

More detailed models that incorporate anatomical and electrophysiological data about a given system may help to elucidate what are the contributions of population synchrony and number of active oscillators to ERs generated in this specific system. For example, a detailed mathematical modeling of the alpha rhythm in primary visual cortex indicated that visually evoked ERs might be caused predominantly by stimulus-induced changes in coherence (phase-locking) between multiple trials (Naruse et al. 2010) in agreement with a macroscopic phase reset model. In this study, we abstract from such details to expose the general problem of ambiguity between microscopic and macroscopic phase reset and its far-reaching consequences for ERs.

To reinforce our conclusions, we complement the study with a theoretical analysis (Supplementary Information), which is not bound to any specific mechanism of synchronization. In line with the simulation results, it shows that arbitrary ERs can be described equivalently in terms of amplitude or phase dynamics of oscillators involved in the generation of macroscopic EEG/MEG signals.

**Reliable demonstration of microscopic phase reset in the CNS**

An unambiguous demonstration of microscopic phase-reset has been provided in the work of Reyes and Fetz (1993), who studied phase-dependent effects of brief current pulses on the length of interspike intervals, whereas Kazantsev et al. (2004) showed that oscillations of the membrane potential can be reset by a current input. Similar phenomena have been observed across a variety of different neural system including visual cortex (Stiefel et al. 2008), early somatosensory cortex (Tateno and Robinson 2007), and hippocampus (Lengyel et al. 2005).

Although such level of description might not be viable in human neurophysiology, recording techniques, which are based on a very closely spaced set of recording electrodes, might be very useful when assessing the amount of spatial synchronization and thus more reliably drawing conclusions about the mechanisms of evoked responses (Ritter and Becker 2009).

**On the importance of differentiation between added-energy and phase-reset models**

Evoked responses are among the most frequently used objective measures of human brain activity and are used for a description of different perceptual, motor, and cognitive processes. Changes in evoked responses do show that neuronal processing is different between the conditions. However, if one is interested in knowing what these changes reflect, the knowledge of how evoked responses are generated is of prime importance.

In the case of a phase-reset mechanism, changes in evoked responses might indicate adaptive fine-tuning of neuronal oscillations for current processing demands (Bonte et al. 2009; Hanslmayr et al. 2006). On the other hand, ER changes consistent with added-energy mechanism would reflect either the number of neurons being recruited for the current processing demands or their mean activity (Jones et al. 2007).

Because the macroscopic signals reflect summed activity of microscopic sources, the macroscopic phase dynamics is necessarily only a reflection of phase reorganization processes occurring in the underlying neuronal population. Therefore macroscopic phase reset is a secondary phenomenon, and thus it is mechanistically realized mainly through phase reset of microscopic oscillations. Pragmatically, one can refrain from the question of mechanisms and rather limit oneself to the analysis of correlations between macroscopic oscillations’ phase or amplitude and some cognitive process or behavior (Dustman and Beck 1965; Sauseng et al. 2005). Nevertheless, in any phenomenological approach, the study of phase reset and added energy models cannot elucidate specific mechanisms behind the registered EEG responses. Were such mechanisms pursued, one should focus on how other properties with a clear microscopic interpretation, such as synchrony, cortical geometry, neuronal morphology (Lindén et al. 2010), and trans-membrane currents (Jones et al. 2009; Murakami et al. 2003), shape ERs. The theoretical analysis and computer modeling as presented here, provide a well-controlled framework for such studies.

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