

# Phase synchronization between LFP and spiking activity in motor cortex during movement preparation

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## Abstract

A common approach to measure and assess cortical dynamics focuses on the analysis of mass signals, such as the local field potential (LFP), as an indicator for the underlying network activity. To improve our understanding of how such field potentials and cortical spiking dynamics are related, we analyzed the phase and amplitude relationships between extracellular recordings from motor cortex of monkey in a delayed pointing task. We applied methods from phase synchronization analysis to extract the instantaneous phase of the LFP time series and to characterize the degree of phase coupling between the spike train and oscillation cycles in a frequency-independent manner. In particular, we investigated the dependence of observed phase preferences on the different periods of a behavioral trial. Furthermore, we present evidence to support the hypothesis that increased LFP oscillation amplitudes are related to a stronger degree of synchronization between the LFP and spike signals. However, neurons tend to keep a fixed phase relationship to the LFP independent of the amplitude or the choice of the electrode used to record the LFP.

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## 1. Introduction

Cortical spiking activity is often recorded in parallel with the local field potential (LFP) obtained by low-pass filtering of the electrode signal. The LFP typically exhibits prominent oscillatory features and has been shown to display modulations that contain information about relevant behavior [11,18]. To date, the detailed mechanisms that relate LFP oscillations and network dynamics are not well understood. A current hypothesis describes the magnitude of LFP oscillations as an indicator for the presence of synchronous synaptic activity of many neurons

in a large volume around the electrode (e.g., [3,4,12]). Such cooperate network activity has been reported as a possible mechanism in the processing of information in motor cortex [2,15]. Assuming that increases in the magnitude of LFP oscillations indicate that a larger part of the neural population contributes to such coordinated activity, a neuron receiving this input would respond with increased temporal precision. This relation suggests a connection between the magnitude of LFP amplitudes and a preference for spike occurrences in a distinguished phase of the oscillation cycle. Previous studies have demonstrated the possibility to exploit such relationships between instantaneous LFP phase and spike time to extract information carried by the networks (see, e.g., [5]).

In this study we analyzed recordings from primary motor cortex of a behaving monkey in a time discrimination task

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[17]. Preceding the actual execution of the movement, the experimental design involved two periods in which different amounts of prior information about the upcoming movement were available. Previous work provides evidence that the dynamics observed in motor cortex are closely related not only to the movement itself, but also to movement preparation [14,18].

Here, we employed newly developed methods (Denker et al., in prep.) that directly utilize the instantaneous phase of the LFP time series to measure the degree of phase coupling between spike trains and oscillation cycles. This approach provided an amplitude-independent measure of the current position on the oscillation cycle irrespective of the instantaneous frequency. We show that the observed locking periods of single LFP-neuron pairs exhibited a variety of different properties in terms of duration, strength and phase preference. In particular, we investigated the dependence of the precision of phase coupling on the different periods of a behavioral trial. Furthermore, we tested if periods of increased LFP amplitudes are related to a stronger degree of synchronization between the spike train and LFP time series. In addition, the observed phase preferences were compared between LFPs recorded at local or distant electrodes.

## 2. Methods

### 2.1. Behavioral task and recording

A rhesus monkey was trained to perform arm movements from a center position to one of the two possible peripheral targets left and right of the center, depending on the prior information provided by the preparatory signal (PS) and a time discrimination performed by the monkey [17]. The peripheral targets were presented simultaneously at PS, one in red, the other in green, the side of the color was chosen at random. An auditory response signal (RS) was then presented after either a short delay (600 ms) or a long delay (1200 ms). The monkey learned to associate to each color a delay and responded accordingly to the respective target. Each type of experimental configuration was presented with equal probability. As a result, during the first preparatory period (PP1) of 600 ms length the probability for the monkey to move at the end of this delay was 0.5, whereas when RS did not occur at that time (i.e., in long trials), the probability turned to 1 during the second preparatory period (PP2) after the expected signal (ES) at 600 ms. For analysis, all trials were aligned to PS occurrence.

LFPs and spikes of single neurons, detected by an online sorting algorithm (MSD, Alpha Omega, Nazareth, Israel), were obtained simultaneously from multi-electrode recordings of two to four electrodes in primary motor cortex. The inter-electrode distance was  $\lesssim 400 \mu\text{m}$ . LFPs were sampled at a resolution of 250–500 kHz and hardware filtered from 1 to 100 Hz. In total, we analyzed nine recording sessions,

which yielded 22 single neurons in approximately 40 trials per experimental condition.

### 2.2. Data analysis

We analyzed the spike trains and their relationship to the LFP by using methods that originate from phase synchronization analysis (see, e.g., [8,16,20]) and adapted them to the treatment of signals described by discrete points in time, such as spikes [6,7,19]. In a first step, we prefiltered the LFP signals to a frequency band that contained the dominant oscillatory component (phase-preserving implementation, MATLAB). In our case, we used a 10–22 Hz band, a prominent frequency band observed during an instructed delay in motor cortex (see [9] for a review). This frequency band was primarily observed during the preparatory periods between PS and RS (cf. Fig. 1a).

In a second step, we extracted the instantaneous phases of the remaining oscillatory LFP component. The phase  $\phi(t)$  is a function with values in the range  $[0; 2\pi]$  and serves as an indicator of the current position in the oscillation cycle, independent of the instantaneous cycle frequency (cf. Fig. 1b). For harmonic signals the phase is simply given by the argument, e.g.,  $\sin(\phi(t))$ . Several methods have been proposed to obtain the instantaneous phase for oscillatory time series (see, e.g., [13]). Here we calculated the phase  $\phi(t)$  as the angle of the complex-valued analytic signal  $\tilde{L}(t) = A(t) \exp[i\phi(t)]$  corresponding to the LFP signal. The analytic signal was obtained as  $\tilde{L}(t) = L(t) + i\mathcal{H}[L(t)]$ , where  $L(t)$  is the original real-valued LFP time series and  $\mathcal{H}[\cdot]$  denotes the Hilbert transform. In addition, the amplitude  $A(t)$  of the analytic signal provides a measure for the magnitude of the LFP, i.e., its envelope.

We collected the instantaneous phase  $\phi(t_i)$  of the LFP at the individual spike times  $t_i$  across trials in six different time windows related to the experiment: the complete range from PS to RS (Total), and 400 ms windows around PS, around ES (long trials only), during PP1, during PP2 (long trials only) and after RS (Mvt). Spikes that occurred at extremely low LFP amplitudes were omitted when the phase signal was not monotonous and smooth. We analyzed phase distributions in these time windows using methods from circular statistics (cf. [10]). This allowed us to quantify the degree of non-uniformity in the phase distribution, and to test if a measured phase preference is statistically significant compared to a uniform distribution. The underlying assumption for a uniform phase distribution is that  $2NR^2$  is  $\chi^2$ -distributed with two degrees of freedom, where  $N$  is the number of spikes and  $R = N^{-1} \sum_{i=1}^N \exp[i\phi(t_i)]$  is the vector strength.

In a further step, we categorized individual spikes according to the envelope, or amplitude,  $A(t_i)$  of the LFP signal at spike occurrence. Note that this is not equivalent to the amplitude  $L(t)$  of the LFP itself, but rather measures the instantaneous oscillation amplitude, given by  $\tilde{L}(t)$ . We subdivided each spike train into two exclusive groups, where one group contained the spikes that occurred at high

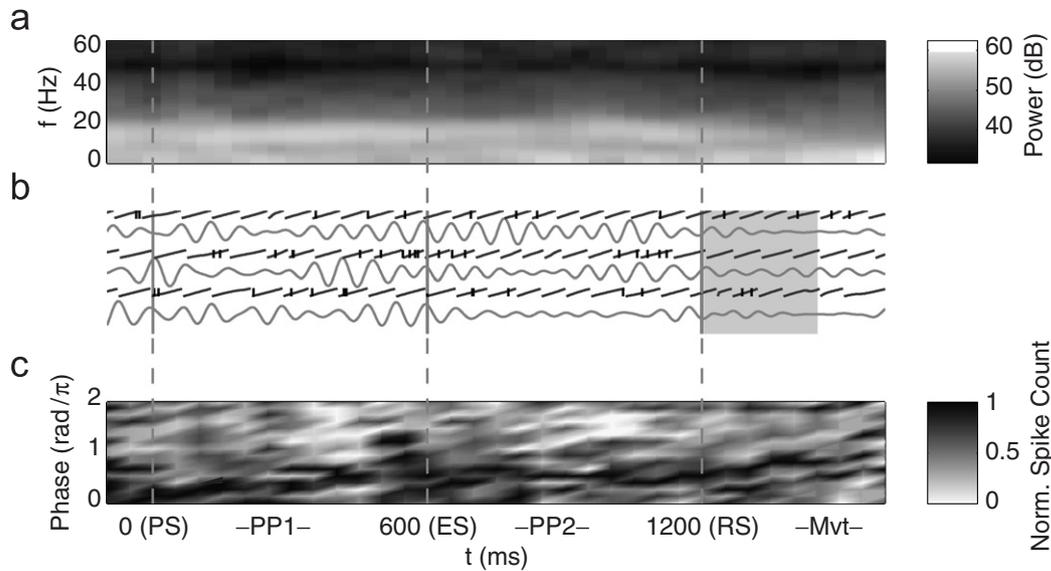


Fig. 1. Detecting instantaneous phase relationships between LFP and spikes. (a) Trial-averaged power spectrum of one LFP recording in one possible experimental condition (long delay) calculated in sliding windows of 200ms. During the preparatory periods (PP1 and PP2) a prominent oscillatory component around 16 Hz is visible. (b) Filtered LFP signal (gray) of three example trials. The extracted phase signal  $\phi(t)$  (black) from 0 to  $2\pi$  is sketched above each LFP (troughs correspond to  $\phi(t) = \pi$ ). Ticks indicate the location of spikes of a neuron recorded from the same electrode. The shaded region marks the time interval where movement started. (c) Time-resolved histogram of the phase distribution  $\phi(t_i)$  for the LFP-neuron pair shown in (b), but across all trials (sliding windows  $\Delta t = 100$  ms (50 ms overlap), 16 phase bins). For each time window, the distribution was normalized with respect to its maximum. The neuron shows a sustained preference for spiking during the falling flank ( $0 \leq \phi \leq \pi$ ) of the LFP.

amplitudes (“Hi”), and the second group contained spikes that occurred at low amplitudes (“Lo”). The threshold  $\theta$  for the separation of spikes into these groups is expressed as the ratio of number of spikes in the Lo group compared to the original number of spikes. Consequently,  $1 - \theta$  denotes the relative number of spikes assigned to the Hi group. Subsequent phase analysis was then performed separately and independently on each of these two groups in the manner described above.

Robustness of our results was tested by a bootstrap procedure. The mean and standard deviation of the bootstrap measurements served as an estimate of the variability across the data set.

### 3. Results and conclusions

Single neurons showed a variety of locking behavior with respect to the LFP. In Fig. 1c the phase relationship of one neuron and the LFP recorded simultaneously from the same electrode is shown in a time-resolved manner. This particular neuron exhibited a constant tendency towards spiking on the falling flank ( $0 - \pi$ ) of LFP cycles. However, few neurons displayed such a clearly pronounced, sustained phase preference.

To investigate the dependence between spike timing and LFP phase in relation to behavior, we calculated phase distributions during the six time windows described above related to specific periods in the experiment. In Fig. 2a we visualized the relative number of LFP-neuron pairs that showed a significant phase preference in these time

windows for any one of the experimental configurations (black bars). Note that due to the pooling of experimental configurations individual LFP-neuron pairs may enter the distribution more than once. We observe that about one fourth of the pairs shows a phase preference when considering the complete trial (Total). The fact that the other time windows showed fewer pairs is an indication of our earlier observation that sustained phase preferences across the experiment are rare. During movement, only few neurons showed a pronounced phase preference, as might be expected from the diminished LFP magnitude in the investigated frequency band during movement onset, where the LFP is dominated by a strong, slow triphasic component (movement related potential, [18]).

In particular, looking at the mean phase of LFP-neuron pairs with a significant phase preference confirmed that if a phase preference is detected, it occurred in roughly 60–70% of the cases on the falling flank of the LFP as opposed to the rising flank (not shown). Furthermore, we did not detect a dependence of the preferred phase on the experimental conditions of the task.

The envelopes of the LFP oscillation were typically modulated in time on a time scale much longer than individual oscillation cycles (cf. e.g., Fig. 1b). This modulation shows no correlation or fixed locking to trial onset or the behavioral task. The instantaneous phase typically remained well defined even for low amplitudes. To investigate the dependence of phase preferences on the amplitude, we separated individual spike trains into Hi and Lo groups of equal numbers of spikes ( $\theta = 0.5$ ). Analysis of

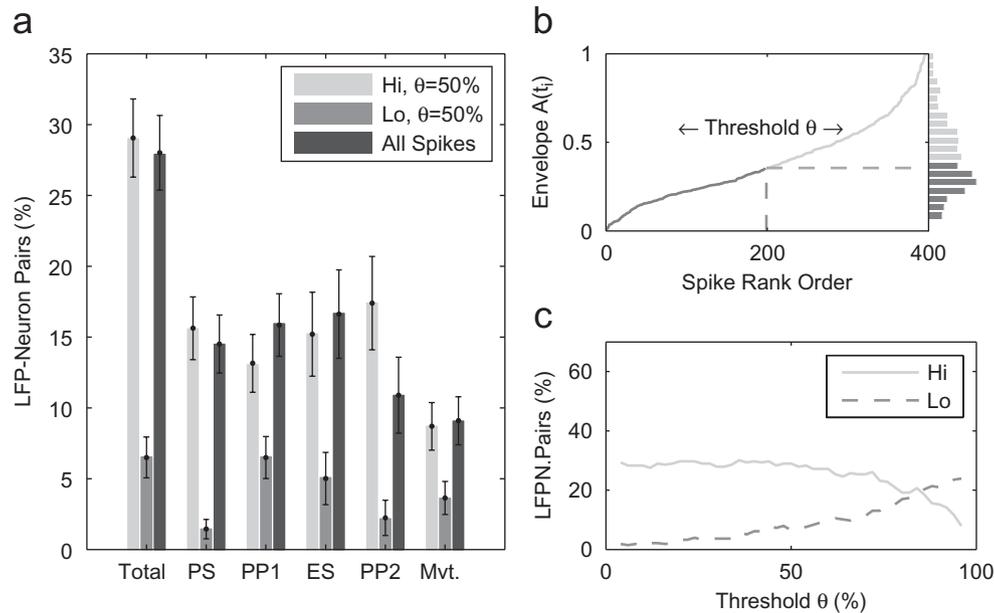


Fig. 2. Relation of phase locking to the magnitude of LFP oscillations. (a) Relative number of LFP-neuron pairs (all possible combinations) that exhibit a non-uniform phase distribution ( $p = 0.01$ ) during the six defined time periods (Total, PS, PP1, ES, PP2 and Mvt) and across experimental configurations. Statistics was performed on the original spike train of each trial (black bars), as well as diluted spike trains which contain only those spikes that occur during the highest (Hi, light gray bars) and lowest (Lo, dark gray bars) LFP envelopes ( $\theta = 0.5$ , i.e., groups Hi and Lo have equal number of spikes). Error bars were obtained by 100 bootstraps that each comprised of 70% of the data. (b) Values of the envelope  $A(t_i)$  at spike occurrences (normalized to maximum) of one typical LFP-neuron pair, sorted in ascending order. Dashed line shows the threshold of  $\theta = 0.5$  separating the Hi and Lo groups containing equal number of spikes (shading as in panel (a)). Right: corresponding distribution of envelopes  $A(t_i)$ . (c) Effect of changing the threshold  $\theta$  on the relative number of LFP-neuron pairs with non-uniform phase distributions in the Hi (light gray, solid) and Lo (dark gray, dashed) groups during PS–RS (Total). Low values of  $\theta$  correspond to most spikes attributed to the Hi group and only few to the Lo group and vice versa. A large number of LFP-neuron pairs that displayed a phase preference for the spikes of the Hi group persisted even for high values of  $\theta$ .

these groups revealed that primarily spikes occurring at high LFP envelopes (group Hi) lead to the phase preferences of a given LFP-neuron pair (Fig. 2a). In fact, uniformity in the phase distributions of spikes in the Lo group led to a smaller number of significant LFP-neuron pairs in the original spike train as compared to the Hi group (see, e.g., time period PP2). The corresponding amplitude distributions (see Fig. 2b for an example) were unimodal, but skewed towards low amplitudes.

In Fig. 2c we investigated the dependence of phase preferences in the complete preparatory period (Total) as a function of the threshold  $\theta$ . Only at a threshold of  $\theta = 0.8$  (i.e., the top 20% of spikes associated with the highest LFP envelopes are in the Hi group, while the remaining spikes are categorized as Lo) we find an equal number of LFP-neuron pairs that display a phase preference in both groups. This finding suggests not only that spikes at high LFP magnitudes exhibit a stronger tendency for locking to the LFP cycle, but moreover that observed phase preferences are due to spikes occurring at the highest amplitudes.

We investigated the distribution of the mean phase of all LFP-neuron pairs that showed a significant phase preference pooled across experimental configurations. The analysis was done independently for the two groups Hi and Lo (at  $\theta = 0.5$ ). In addition, we grouped according to

whether spikes and LFP were recorded from the same or different electrodes. Fig. 3 shows the results for the Hi group. In both possible configurations (same/different electrode) the mean of the histograms was centered on the falling flank of the LFP (cf. also [1]). In particular, this peak was more pronounced for recordings on the same electrode as compared to different electrodes. Due to the low number of LFP-neuron pairs that showed a significant phase preference, the distribution for the Lo group lead to weak statistics. Nevertheless, the distribution of phase preferences for both electrode combinations showed a similar tendency as for the Hi group. We conclude that individual LFP-neuron pairs that exhibit a phase preference tend to have a fixed preferred phase independent of the LFP amplitude. This preference is more pronounced when spikes and LFP are taken from the same electrode. Although simultaneously recorded LFPs are typically highly correlated, our finding may be understood under the assumption that the LFP is a reflection of synaptic input activity preceding a spike. Therefore, when LFP and spikes are taken from the same electrode the LFP would be more closely related to this local input and therefore expected to exhibit a more precise temporal relationship to the spike times.

In summary, our analysis demonstrates that spikes of neurons in motor cortex have a tendency for a phase

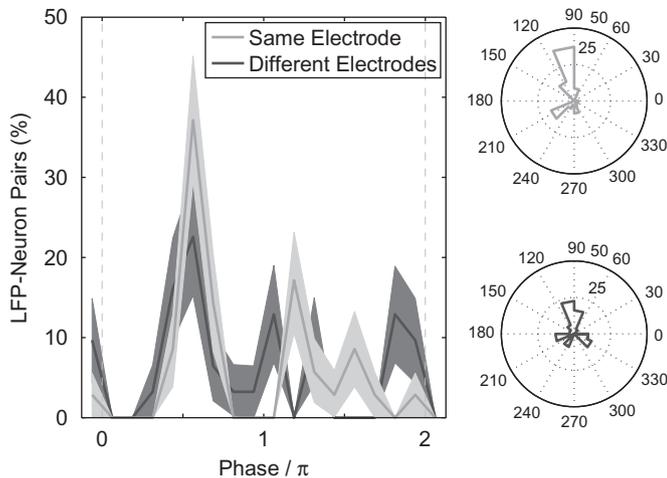


Fig. 3. Distribution of mean phases of LFP-neuron pairs that showed a non-uniform phase distribution ( $p = 0.01$ ) for the spikes of the Hi group ( $\theta = 0.5$ ) during PS-RS (Total) across experimental configurations. Data from pairs recorded from the same electrode are shown in light gray, whereas pairs taken from different electrodes are shown in dark gray (equal number of pairs as for same electrode). Error margins were obtained by boot-strapping as performed in Fig. 2. To aid the visualization of the distributions, polar plots on the right show the same distributions as on the left.

preference. The preferred phase relationship is specific for the individual LFP-neuron pair. Nonetheless, across pairs this phase preference showed a tendency to be located on the falling flank of the LFP oscillation. Furthermore, our analysis revealed that periods of higher LFP amplitudes tend to show an increase in the precision of locking between spikes and LFP. We hypothesize that this effect is a result of neurons becoming entrained to take part in a cooperative network activity that is manifested in an increased oscillatory activity.

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