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Rhythmic neuronal synchronization in visual cortex entails spatial phase relation diversity that is modulated by stimulation and attention

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ABSTRACT

Groups of neurons tend to synchronize in distinct frequency bands. Within a given frequency band, synchronization is defined as the consistency of phase relations between site pairs, over time. This synchronization has been investigated in numerous studies and has been found to be modulated by sensory stimulation or cognitive conditions. Here, we investigate local field potentials (LFPs) and multi-unit activity (MUA) recorded from area V4 of two monkeys performing a selective visual attention task. We show that phase relations, that are consistent over time, are typically diverse across site pairs. That is, across site pairs, mean phase relations differ substantially and this across-site-pair phase-relation diversity (SPHARED, for Spatial PHAse RElation Diversity) is highly reliable. Furthermore, we show that visual stimulation and selective attention can shift the pattern of phase relations across site pairs. These shifts are again diverse and this across-site-pair phase-relation-shift diversity (SPHARESD) is again highly reliable. We find SPHARED for LFP–LFP, LFP–MUA and MUA–MUA pairs, stimulus-induced SPHARESD for LFP–LFP and LFP–MUA pairs, and attention-induced SPHARESD for LFP–LFP pairs. SPHARESD is a highly interesting signal from the perspective of impact on downstream neuronal activity. We provide several pieces of evidence for such a role.

Introduction

Neuronal synchronization occurs in distinct frequency bands, as is clear from the oscillations that are often observed in local field potentials (LFPs). The amplitude of these oscillations is related to external stimuli as well as to cognitive functions such as selective attention (Womelsdorf and Fries, 2007), working memory (Pesaran et al., 2002), and sensory-motor coordination (Murthy and Fetz, 1992). Oscillatory amplitude measures the degree of local synchronization of neuronal activity, which is an important parameter of the putative mechanisms that underlie cognitive functions (Buzsaki and Draguhn, 2004; Engel et al., 2001; Fries, 2005; Schroeder and Lakatos, 2009).

Although synchronization is likely to be relevant for the function of neuronal networks, extended synchronization across neuronal space prohibits flexibility and differentiation in information processing. Therefore, functional synchronization likely involves oscillations that are coherent, but rather than being zero-phase-synchronous across space, they might have systematic phase differences or phase relations. From the perspective of cognitive functions, phase relation is a highly interesting neuronal variable because it can vary on a much faster timescale than the comparatively slow amplitude fluctuations. Therefore, phase relations could reflect fast neuronal mechanisms that underlie cognitive functions.

We investigated phase relations across multiple sites in awake macaque area V4 while the animals were engaged in a perceptual task involving attentional selection. We found diversity in these phase relations in three discrete frequency bands: theta, alpha and gamma. We also found that the presentation of a visual stimulus produced substantial and reliable shifts in these phase relations, in exactly the same three frequency bands.

Materials and methods

Experimental procedure

Experiments were performed in two hemispheres of two male rhesus monkeys (*Macaca mulatta*), and followed guidelines of the National Institutes of Health with approval by the National Institute of Mental Health Intramural Animal Care and Use Committee. Experimental procedures for data collection have been described in detail elsewhere (Fries et al., 2001, 2008) and are summarized below. We localized the prelunate gyrus using MRI scans. Recording chambers

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were then implanted over the prelunate gyrus under surgical anesthesia. Small trepanations of the skull were performed within the recording chamber. Through the trepanation, four tungsten microelectrodes (impedances of 1–2 MΩ) were advanced separately at a very slow rate (1.5 μm/s) to minimize deformation of the cortical surface by the electrode ("dimpling"). Electrode tips were separated by 650 or 900 μm. Data amplification, filtering and acquisition were done with a multichannel acquisition processor (Plexon Inc.). The signal from each electrode was passed through a headstage with unit gain and then split to separately extract the spike and the LFP components. For spike recordings, the signals were filtered with a passband of 100–8000 Hz, further amplified and digitized at 40 kHz. A threshold was set interactively and spike waveforms were stored for a time window from 150 μs before to 700 μs after threshold crossing. The threshold clearly separated spikes from noise, but was chosen to include multi-unit activity. Offline, we performed a principal component analysis of the waveforms and plotted the first against the second principal component. Those waveforms that corresponded to artifacts were excluded. For multi-unit analyses, all other waveforms were accepted and the times of threshold crossing were kept and down-sampled to 1 kHz. For LFP recordings, the signals were filtered with a passband of 0.7–170 Hz, further amplified and digitized at 1 kHz.

The analyses in this study crucially depend on the phase relations between LFP and MUA channels. For this reason it is important that our phase relation estimates can be trusted and do not depend on confounding factors such as electrode impedance. For our headstage model, electrode type and impedance, the absolute phase shift is less than two degrees, and the resulting non-physiological between-electrode phase relations would be much smaller than that (Chris Heydrick, Plexon Inc., personal communication, May 22, 2012).

At the start of the recordings, each electrode was lowered separately until it recorded visually driven activity. Once this had been achieved for all electrodes, we fine tuned the electrode positions to optimize the signal-to-noise ratio of the multiple spike recordings and to obtain as many isolated single units as possible. Since the penetration was halted as soon as clear visually driven activity was obtained, most of the recordings were presumably done from the superficial layers of the cortex. To confirm the recording position without sacrificing the animal, we obtained a structural magnetic resonance image (MRI) with one electrode in place, confirming the placement in the appropriate portion of the prelunate gyrus. Receptive field (RF) position and neuronal stimulus selectivity were as expected for the target part of area V4.

Visual stimulation and experimental paradigm

Stimuli were presented on a 17 in. CRT monitor 0.57 m from the monkey's eyes that had a resolution of $800*600$ pixel and a screen refresh rate of 120 Hz non-interlaced. Stimulus generation and behavioral control were accomplished with the CORTEX software package (www.cortex.salk.edu).

A trial started when the monkey touched a bar and directed its gaze within 0.7° of the fixation spot on the computer screen. When we used trial-by-trial cueing of selective attention, first the cue appeared, followed after 1500–2000 ms by a pair of stimuli of which one was cued (see below for more details on the different cueing regimes used). Both stimuli were patches of drifting square wave luminance gratings with a frequency between 0.8333 and 1.8750 Hz (one out of five possible frequencies), differing across sessions. One of the two patches was presented inside the RF of the recorded neuronal population, and the other was presented outside this RF. Procedures for the initial mapping of visual RFs and orientation tuning have been described elsewhere (Fries et al., 2008). For the present study, it is important to know that the RFs of the multiple recording sites typically overlapped substantially. For the recordings, we selected a stimulus orientation that had resulted in a strong co-activation of the simultaneously recorded units. Note that the selected grating could therefore not activate all sites to the same extent, but necessarily ended up being suboptimal or (rarely) even suppressive for some sites. The second patch of drifting grating that was placed outside the RF was identical to the inside-RF patch with regard to eccentricity, size, contrast, spatial and temporal frequency, but its orientation was rotated by 90°. This was done in order to avoid pre-attentive perceptual binding of the two patches of grating. Two patches of grating moving in orthogonal direction can nevertheless be perceived as part of one pattern moving behind two apertures, if the movement directions are consistent with this interpretation. To preclude this, the movement direction of the patch outside the RFs was chosen to be inconsistent with this interpretation. For most recording sessions, the orientation of the outside-RF patch was 90° away (counterclockwise) from the inside-RF patch at that eccentricity. For a subset of recordings, it was moved to be as close as possible to the RF without evoking a stimulus driven response.

The general task of the monkey was to release the bar between 150 and 650 ms after a change in color of the cued stimulus. The color change occurred at an unpredictable moment in time between 500 and 5000 ms after stimulus onset, with change times drawn from a normal probability distribution. Successful trial completion was rewarded with four drops of diluted apple juice. If the monkey released the bar too early or if it moved its gaze out of the fixation window, the trial was immediately aborted and followed by a timeout.

Both stimuli could change color with equal likelihood, and their change time distributions were equal. The monkey's task was to respond to color changes in the stimulus that was cued (using one of three cueing paradigms; see below) as target and ignore changes in the other stimulus, the distracter. The color changes were close to the monkey's detection threshold, ensuring that the task could only be performed when attention was actually allocated to the target. On the 50% of the trials in which the distracter changed color before the target, the target changed color later on in the trial. Those target changes were distributed uniformly in the remaining time between distracter changes and 5000 ms after stimulus onset. Signals recorded after the target or distracter change were not analyzed (see Trial selection and preprocessing section). However, the monkey's behavioral responses on trials in which the distracter changed first inform us about their attentional engagement: correct responses (bar release within 0.15–0.65 s after target change) were made in 85% of these trials.

We used three different cueing paradigms for directing selective visual attention and all of them gave essentially identical results. Two of the paradigms used trial-by-trial cueing. The cue stayed on during the trial and was either a short line next to the fixation spot, pointing to the location of the target, or alternatively, the fixation spot color, red cueing the upper, and green cueing the lower stimulus. In the rest of the recording sessions, we used a blocked trial design. Blocks consisted of 20 trials. The first two trials in a block were instruction trials in which only one of the two stimuli was shown and the monkey performed the task on that stimulus. The location of that stimulus was the target location for that block. For the remainder of the block, both stimuli were shown together without any further cue. Thus, in the block design, the different attention conditions were physically identical. We recorded 100 to 300 correctly performed trials per attention condition.

Trial selection and preprocessing

We calculated power and coherence spectra (see below for details of spectral estimation) separately for the pre-stimulus period (the 1500–2000 ms before stimulus onset) and for the sustained epoch. We defined the sustained epoch as the epoch from 300 ms after stimulus onset until the first change in one of the two stimuli. Because we wanted to compare the pre-stimulus and the sustained epochs, we