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Tuning dissimilarity explains short distance decline of spontaneous spike correlation in macaque V1

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ABSTRACT

Fast spike correlation is a signature of neural ensemble activity thought to underlie perception, cognition, and action. To relate spike correlation to tuning and other factors, we focused on spontaneous activity because it is the common 'baseline' across studies that test different stimuli, and because variations in correlation strength are much larger across cell pairs than across stimuli. Is the probability of spike correlation between two neurons a graded function of lateral cortical separation, independent of functional tuning (e.g. orientation preferences)? Although previous studies found a steep decline in fast spike correlation with horizontal cortical distance, we hypothesized that, at short distances, this decline is better explained by a decline in receptive field tuning similarity. Here we measured macaque V1 tuning via parametric stimuli and spike-triggered analysis, and we developed a generalized linear model (GLM) to examine how different combinations of factors predict spontaneous spike correlation. Spike correlation was predicted by multiple factors including color, spatiotemporal receptive field, spatial frequency, phase and orientation but not ocular dominance beyond layer 4. Including these factors in the model mostly eliminated the contribution of cortical distance to fast spike correlation (up to our recording limit of 1.4 mm), in terms of both 'correlation probability' (the incidence of pairs that have significant fast spike correlation) and 'correlation strength' (each pair's likelihood of fast spike correlation). We suggest that, at short distances and non-input layers, V1 fast spike correlation is determined more by tuning similarity than by cortical distance or ocular dominance.

1. Introduction

Fast spike correlation ('synchrony' or 'coincident spiking') is thought to be a code or signature of spiking ensembles, enabling the brain to perform efficient computations relating to perception and behavior (Salinas & Sejnowski, 2001; Singer, 1999). Although the functional roles of different timescales of spike correlation is unclear, synchrony within a narrow time window, approximating the temporal integration window of downstream neurons acting as coincidence detectors, is considered separately from slower changes in correlated excitability (noise correlation, 'Rsc', (Cohen & Kohn, 2011)). To develop computational models of spiking ensembles, it is necessary to know which neurons fire coincidently (including before stimulus onset), and how much of the coincident firing is related to the neurons' tuning properties vs. due to cortical distance (Masquelier & Thorpe, 2007).

Previous studies of neural ensembles have been based on analysis of relative spike times between two neurons or based on anatomical tracing (Gilbert & Wiesel, 1983; Malach et al., 1993; Toyama, Kimura, & Tanaka, 1981; Ts'o, Gilbert, & Wiesel, 1986). In cats and monkeys, spike correlation has been tied to tuning similarity for orientation (Ferster & Miller, 2000; Kohn & Smith, 2005; Nowak et al., 1995; Ts'o, Gilbert, & Wiesel, 1986), color processing (Roe & Ts'o, 1999), and disparity (Ts'o, Roe, & Gilbert, 2001), revealing interactions between distant functionally related domains within and across cortical areas.

Although several reports have focused on the dynamic or context-dependent nature of spike correlations (Das & Gilbert, 1999; Gray et al., 1989; Hung, Ramsden, & Roe, 2007; Roelfsema et al., 1997; Stettler et al., 2002), here we focus on spike correlations during spontaneous activity because the variation in correlation strength across cell pairs is typically many times larger than the variation across stimulus conditions in the same pairs (Hung,

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Ramsden, & Roe, 2011; Luczak, Bartho, & Harris, 2009), suggesting that the mechanism is mostly intrinsic (i.e. tied to the functional architecture) rather than stimulus-dependent (Ringach, 2009).

Although visual stimulation typically reduces neural variability (Churchland et al., 2010), correlations presented in both evoked and spontaneous activity are thought to share similar mechanisms (Jermakowicz et al., 2009). Understanding variability of spike correlations during spontaneous activity (i.e. whether this variability is random or systematic) is thus a necessary component to understanding signal processing in basic cortical circuits. Also, identifying the factors underlying spontaneous correlations may provide a fairer and more consistent baseline for comparing across studies that examine different stimuli and different mixtures of cells. Although new methods combining slice physiology, in vivo calcium imaging, and/or electron microscopy have been developed that have enabled precise alignment between tuning, morphology, and circuitry in rodents and small animals (Bock et al., 2011; Ko et al., 2011; Lefort et al., 2009; Shepherd et al., 2005), such methods are extremely difficult to implement, especially in larger animals such as macaque monkeys which are more similar to humans. Analyses of spontaneous extracellular spiking may thus offer an enormous advantage in studying coordinated assembly activity.

Although many studies have suggested that coincident spiking declines with cortical distance, it is unclear whether this distance dependency is simply due to examining too few factors. It is well known that different tuning factors are related, and that the interaction of these factors may lead to a residual effect of cortical distance when only single factors are examined (e.g. a study may find that spike correlation depends on both orientation and distance, but the distance dependency may be due to an unexamined factor that is co-linear with distance). However, no study has sampled sufficient tuning properties (typically no more than 2 or 3, analyzed separately) and cell pairs to disentangle the effect of cortical distance from the effect of the overall decline in tuning similarity across combinations of tuning properties. Also, rather than sampling one site per penetration, it would be better to sample multiple sites per penetration (multiple pairs of neurons with equal horizontal separation and the same topography) to disentangle this relationship.

Here, we asked what are the relative contributions of different tuning properties to spike correlation, and whether horizontal cortical distance has a separate contribution, beyond that already predicted by tuning dissimilarity. The standard hypothesis is that spike correlation depends on horizontal cortical distance (Das & Gilbert, 1999; Gray et al., 1989; Hata et al., 1991; Hung, Ramsden, & Roe, 2007; Maldonado, Friedman-Hill, & Gray, 2000; Smith & Kohn, 2008; Toyama, Kimura, & Tanaka, 1981), in addition to tuning similarity (e.g. for orientation, ocular dominance, chromatic preference, and spatiotemporal receptive field similarity (Das & Gilbert, 1999; DeAngelis et al., 1999; Engel et al., 1990; Hata et al., 1991; Nowak et al., 1995; Schwarz & Bolz, 1991; Ts'o & Gilbert, 1988; Ts'o, Gilbert, & Wiesel, 1986)). However, whether if and to what extent spike correlations actually depend on cortical distance is unclear, because not all factors were significant (Chiu & Weliky, 2002), including horizontal cortical distance (Samonds et al., 2006; Schwarz & Bolz, 1991), and horizontal interactions can be found at up to 4–7 mm (Engel et al., 1990; Smith & Kohn, 2008), and even across hemispheres (Bosking et al., 2000; Engel et al., 1991; Nowak et al., 1999). We suggest an alternative hypothesis, that the decline of fast spike correlation with cortical distance, at least for short distances (<1.4 mm, about 1–2 hypercolumns), can be explained by the decline in tuning similarity with distance (this possibility was also mentioned in (Ts'o, Gilbert, & Wiesel, 1986)). If so, it should be possible to use GLM to precisely quantify weights (beta coefficients) for both spike correlation probability and correlation strength, and to determine whether cortical distance is a significant predictor beyond that already predicted by tuning similarity.

2. Materials and methods

2.1. Animal preparation and surgery

We recorded from two 4–5 kg Formosan macaque monkeys (*Macaca cyclopis*). *M. cyclopis* is a member of the group *M. mulatta* along with *M. fuscata*, and is paraphyletic to *M. nemestrina* and *M. fascicularis* based on mitochondrial DNA sequences (Li & Zhang, 2005). All experimental procedures were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of National Yang-Ming University.

Anesthesia was induced with ketamine (10 mg/kg IM). Monkeys were artificially respired and continuously monitored for EEG, EKG, body temperature, expired CO_2, and pO_2. Light anesthesia was maintained with sodium thiopental (Pentothal 2 mg/kg/h IV) and the muscle relaxant rocuronium bromide (Esmeron 1.2 mg/kg/h IV), and anesthetic depth was maintained via custom software that continuously measured delta vs. gamma EEG power. Pupils were dilated with atropine sulfate. The center of gaze was estimated via reverse ophthalmoscopy of the optic discs, and the eyes were focused via contact lenses and converged upon the monitor at 57 cm distance.

At the start of each session, the eyes were converged via rotating wedge prisms (Thorlabs RSP1). Based on the alignment of small ~0.2 deg receptive fields from the two eyes (three neurons per monkey), we estimate the precision of alignment to be less than 0.1 deg. Except for ocular dominance (OD) measurements, all other blocks were presented monocularly to avoid the possibility of phase mis-alignment of receptive fields from the two eyes (phase mis-alignment alone could elevate OD as a factor). The longest block, spatiotemporal receptive field (STRF) mapping, took 25 min and yielded RFs as small as 0.44° wide with 0.22° wide subfields, indicating that the eyes were stable throughout the recording. The "orientation/SF/phase" recording block took 15 min and also yielded reliable phase preference even at 2 cyc/deg (Fig. 2E and F).

2.2. Electrophysiology

We inserted 64-site multi-electrode arrays (A8 × 8–5 mm200–200–413, 8 penetrations ('shanks'), 8 sites per penetration, spanning 1.4 × 1.4 mm horizontally and in depth, 200 μm spacing, Neuronexus Technologies, Inc.) normal to the cortical surface, 14 mm anterior of the occipital ridge and 10 mm lateral of midline (approximately 3–4 deg eccentricity). The width of the array was thus sufficient to span two complete cycles of ocular dominance hypercolumns (as measured in a third monkey by aligning the array across OD columns). Cortical depth was assessed by DiI and cytochrome oxidase staining (Fig. S1A and B), current source density analysis (Fig. S1C) and by the temporal frequency limit outside layer 4 (Fig. S1D–H). Spikes (400–5000 Hz) and local field potentials (LFPs, 1–300 Hz) were filtered (48 dB/octave) and continuously digitized at 24.4 kHz (RZ2, Tucker-Davis Technologies, Inc.). Single units were isolated offline via super-paramagnetic clustering (Quiroga, Nadasdy, & Ben-Shaul, 2004). To avoid possible errors from the unsupervised spike sorting algorithm, we rejected and manually resorted all spike clusters ('units') if over 5% of interspike intervals were <2.5 ms. Manual sorting was done by adjusting the temperature of the annealing in the super-paramagnetic clustering algorithm. At low temperature, all spikes are assigned to the same cluster, whereas at high temperature, each spike forms a single cluster. We chose an 'optimal' temperature by gradually increasing the temperature until less than 5% of interspike intervals were <2.5 ms. This criterion is considered 'good' in extracellular