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Current Opinion in Physiology

Advances in the physiology of primary visual cortex in primates

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Understanding of the physiology of primate primary visual cortex (V1) has been a gradual process. Progress over the past 70 years began with the seminal studies of single neuron physiology and led to more recent studies of the physiology of neural populations. Recent developments in techniques, such and multi-electrode recording and 2-photon imaging, combined with large-scale modeling have provided the beginnings of an approach that can integrate the multidimensional nature of the physiology in V1 circuitry to link neural activity to perceptual performance.

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Current Opinion in Physiology 2020, **16**:79–84

This review comes from a themed issue on **Vision physiology**

Edited by **Andrew J Parker** and **Kristine Krug**

For a complete overview see the Issue and the Editorial

Available online 21st July 2020

https://doi.org/10.1016/j.cophys.2020.07.005

In the past few years there have been considerable advances in our understanding of the physiology of primate primary visual cortex: how visual signals are encoded, the information that they are carrying at the single neuron and population levels and the relationships that can be made between neural activity and behavior.

In primates, V1 is the site of emergent properties including orientation selectivity; the mechanisms generating orientation selectivity are reviewed by Priebe [1] with an emphasis on feedforward mechanisms. The classical receptive field (CRF) encodes local stimulus features while the extra-classical receptive field (eCRF) plays an important role in signaling contextual influences (reviewed by [2]). V1 is a crucial area for understanding the link between physiology and behavior [3•]. This brief review of cortical physiology in primates concentrates on three currently active approaches to elucidate neurophysiological mechanisms in V1: single neuron physiology, population activity and the influence of neuromodulation.

Many studies of V1 physiology used reduced artificial stimulus sets to probe responses to single stimulus dimensions. A more general understanding of visual processing will also entail using natural image stimuli [4], which engage a combination of bottom-up and top-down processes involved in visual processing and decoding. Understanding V1 physiology is multidimensional and depends on multiple factors including: local filtering, nonlinear transformations from voltage to spiking behavior, eCRF influences from V1 [3•] and extrastriate feedback [2], the local population state and correlations in activity, neuromodulation, population dynamics, higher order feedback, gain control, and adaptation. Understanding the interplay between all these factors is essential to a comprehensive understanding of V1 physiology.

Single unit physiology and receptive field organization

V1 in cat and monkey has been key to understanding cortical function ever since the seminal studies of Hubel and Wiesel [5,6], followed by later work that introduced quantitative study of orientation, spatial frequency (SF) and disparity processing in V1. Further, how the eCRF acts to modulate the responses in the CRF and the circuitry underlying eCRF-CRF interactions [7] is still an area of active investigation.

Orientation selectivity — feedforward and feedback processing. The importance of different circuit mechanisms in generating orientation selectivity in macaque V1 is a matter of debate. One approach generalizes across species and suggests there are common mechanisms [1]. Specifically, a feedforward model with contrast-dependent response variability in the LGN input [8] is sufficient to account for observed intracellular membrane voltage responses in cat area 17 simple cells. The size of the excitatory post-synaptic potentials (EPSPs) from individual LGN neurons onto V1 simple cells in cat area 17 is relatively small [9,10], but only LGN neurons with RF centers that overlap with the ON or OFF subfield of the simple cell are connected. These observations, combined with earlier studies of extracellular connectivity, have reinforced the proposal that many LGN neurons contribute monosynaptic, feedforward, sign-specific inputs to each subregion of a simple cell CRF (Reid and Alonso, 1995; [8–10]). In the primate there is less known about the direct physiological characteristics of the inputs from LGN neurons to V1 simple cells. When anatomical constraints on the possible number of overlapping afferents for each simple cell subfield [11] and the size of the EPSPs that provide feedforward input are taken into account, realistic models of macaque layer

4Cα — the main recipient zone of magnocellular LGN input to V1 [12] — show that recurrent connectivity is essential to provide the observed tuning, spike rates and pinwheel organization in the layer 4Cα population [13,14]. The number of LGN neuron afferents estimated to be connected to each V1 neuron is larger in cat than in primate. Consequently, the extent of difference between species in the number of LGN afferents contacting each V1 neuron is likely to play an important role in determining circuit functioning and the emergence of stimulus specificity in V1 neurons.

Spatial frequency and spatial scale. How does V1 represent low spatial frequency (SF) stimuli that show relatively fine orientation discrimination in psychophysical experiments? One hypothesis is that most orientation discrimination is carried out by orientation selective V1 CRF mechanisms where the CRF's are elongated in one spatial dimension as in the classical Hubel and Wiesel [6] V1 simple cell receptive field with opposing ON-subfields and OFF-subfields. At low spatial frequencies, where human observers show relatively fine orientation discrimination, the spatial extent of the visual field spread — the point spread — in cortex is not sufficient for single neurons to exhibit receptive fields with spatially separate subunits to account for the required orientation selectivity. To account for the selectivity, another hypothesis can be invoked: one that depends on decoding the population activity in different regions of cortex, and relies on the known organization of cortical topography.

Benvenuti *et al*. [15] argued that the spatial extent of integration required to form low-SF, bandpass simple cells would not be possible in V1 given the magnification factor at parafoveal eccentricities. They showed that the required spatial scale could be achieved using signals from multiple populations of lowpass neurons responsive to the low SFs, and the selective activation of different isotropic populations based on cortical topology provided the signals for orientation discrimination at low SF.

Binocularity and disparity. In random dot stereograms where disparity is the only cue to relative 3D depth it has been thought that disparity-selective V1 neurons perform binocular correlation [16] to encode depth. However, human observers can report depth in half matched stereograms [17], in which half the dots are correlated and the other half are anticorrelated so the net correlation signal is zero. It has been a puzzle as to where in the visual pathway these half-matched stereograms were being encoded because if disparity selective neurons are performing a correlation, that signal was thought to be unavailable in V1. Based on earlier studies it was hypothesized that the signals were generated by a matching process in higher visual areas such as V4 [17]. However, recent studies in macaque V1 [18] found that disparity-selective neurons do weakly signal disparity of half-matched stereograms, and it was proposed that local fluctuations in stimulus correlation allow this to happen. Hence, signals from V1 can underlie the perception of depth in the half matched stereograms and reinforces the proposal that all signals for stereopsis originate in V1.

It has generally been assumed that layer 4C neurons receiving LGN input in V1 are exclusively monocular. However, Dougherty *et al*. [19] reported there was a clear modulation of monocular neurons from the non-dominant eye; there was facilitation early in the response modulation and a later suppression. Whether the binocular modulation in the monocular neurons is disparity selective has yet to be investigated.

Extraclassical receptive field in V1. There is a consensus that stimuli in the region of the eCRF just beyond the CRF produce response suppression (reviewed in [2]). This was confirmed by local population recordings where voltage sensitive dye imaging (VSDI) signals from neighboring Gabor patches showed subadditivity, an effect that was only mildly dependent on relative orientation [20]. The circuitry that underlies CRF-eCRF interactions is a matter of debate. To address the role of extrastriate feedback on eCRF modulation, V2 feedback to V1 was inactivated [21]. V2 feedback to V1 was optogenetically inactivated in a marmoset model. During V2 feedback inactivation proximal eCRF suppression was reduced in many V1 neurons. Additionally, the response amplitude at small stimulus patch sizes was reduced while the amplitude at intermediate sizes was increased. The authors concluded that V2 feedback is enhancing proximal eCRF suppression, and they reported that this occurred in all cortical layers even though feedback is predominantly to supra and intragranular layers. These results indicate the suppression is ubiquitous and is relayed via recurrent feedback circuits to the granular layers of cortex from supragranular and infragranular layers. In a parallel study [22] studied the timing of 'near' and 'far' eCRF modulation, reporting that there is early 'near' suppression in upper layer 4 while 'far' modulation is first evident in layer 1 and lower infragranular layers suggesting feedback contributions from extrastriate cortex.

Higher level representation of texture, natural images and sparse coding. A central question in the representation of higher order spatial form is how this is encoded in the visual cortical hierarchy. Recent studies have shown that there is selectivity of single neurons to naturalistic texture patterns in V2 but not V1 [23]. However, high-frequency power in the local field potential (LPF) and gamma band activity in V1 did show selectivity for naturalistic textures compared to spectrally matched noise images [24]. Furthermore, responses to naturalistic texture were stronger in the supragranular and infragranular layers of V1, and texture-selective responses appeared later in V1 than in V2. This led to the

interpretation that the texture selective responses in V1 likely reflected feedback signals from V2.

Adopting a different approach to investigating the representation of higher order form, Tong *et al.* [25•] used 2-photon imaging of single neurons in superficial V1. They reported that many neurons were more responsive to higher-order spatial features such as curvature, corners, and junctions than to oriented edges or lines. In a further analysis of these populations [26•] presented 2000+ natural images and reported ultra-sparse coding across the population. These experiments raise the important consideration of whether there are populations representing a much more extensive range of very specific image features than is currently assumed when the cortex is probed using a standard set of reduced images. A model of V1 was developed to account for these results [27].

Population physiology in V1

Numerous recent studies have investigated how the population's activity determines perception and how population activity is regulated by correlations, attention, gain control and adaptation.

Populations and perceptual performance: correlations, active sensing and attention. Perceptual performance in visual tasks is dependent on the signal to noise ratio in the neural signals. Relating V1's signals to performance is a core aspect of linking physiology to behavior because V1 is an important performance-limiting stage. One of the current debates concerns the source(s) of decoding inefficiency in the V1 populations. Seidemann and Geisler [3•] assert, based on earlier VSDI studies from their group [28] that much of the choice-related variability in a near threshold grating detection task was introduced in or earlier than V1. In linking neuronal signals to perceptual choice it is often assumed that the behavioral choice, when there is no signal available, is determined by the trial-by-trial noise fluctuations in the neural population decoding the stimulus. Rosenbaum *et al.* [29] found that spatial structure of noise correlations was not distributed equally across the population or between V1 layers, therefore making it imperative to understand the subpopulation distribution of correlations when assessing their importance in limiting information capacity. Noise correlations can also be task-dependent; mounting evidence suggests that for some tasks, top-down feedback to V1 is important in determining noise correlation levels, affecting neural and perceptual performance [30•]. Goris *et al.* [31] showed that choice probability (CP) in a fine orientation discrimination task could be uncorrelated or negatively correlated with neuronal firing rate in V1 and V2, furthering the suggestion that many higher level factors may influence CP.

Correlations among the firing patterns of neurons in the population can play an important role in signaling the presence of visual patterns. Measurement of spike count correlations (SCCs) in a population of V1 neurons in the awake monkey showed that their structure and specificity depended on the higher order structure in complex visual stimuli [32]. Approaches based on training deep convolutional neural networks (CNNs) on neural responses to natural image sequences have also been successful in predicting responses of the population to natural images held out from the training sequence [33]. These CNNs incorporate multiple levels of non-linearities, so it will be informative to make detailed comparisons of the non-linearities of different levels of the CNNs to those in neurons in different layers of V1.

During active visual search, ongoing saccades occur between short periods of fixation. In immediate post-saccadic periods there is signal amplification while before saccade onset there is suppression [34]; these are independent of the suppression due to the saccade itself and are hypothesized to be important components of V1 modulation during active visual search. It will be of considerable interest to establish how these periods relate to particular cortical states showing high and low spontaneous rates, which strongly influence information capacity and are hypothesized to be two unique states in the temporal evolution of natural scene viewing [35].

Attention plays an important role in perceptual sensitivity. Attention to a cued location in the visual field can increase perceptual sensitivity at the cued site and enhance V1 population responses [36,37]. Attention-related signals are thought to be evident in different frequency bands of the neural response. However, the influence of attention on the signals in the LGN and different layers of V1 in different frequency bands of the LFP — alpha, beta and gamma — is dynamic, not static, making it complicated to directly relate attention to the LFP among circuits in the geniculo-cortical pathway [38]. Additionally, cue signals themselves evoke suppression, and stimulus signals at the cued location are enhanced in the supragranular and infragranular layers but not the granular layers of V1 [39], further suggesting that both cortical layer and dynamics are important in determining attentional effects in V1. Other recent studies indicate that attention may modulate responses depending on the feature similarity between the attended stimulus attributes and neuronal selectivity for those attributes [40] as well increasing efficacy of the local connectivity between these neurons [41].

Gain control and adaptation in the population. Seidemann *et al.* [42] compared responses to orientation, contrast and location measured using wide field imaging of GCaMP6f-expressing neurons with prior results obtained using VSDI. They found the same overall organization and proposed that the VSDI signal is best considered a monitor of subthreshold voltage signals while the Ca++

imaging reflects the spiking activity; the VSDI signal passed through a non-linear thresholding like the accelerating spike function, often used in cortical models, was found to match to the observed population spiking signals.

Michel *et al.* [20] used VSDI to investigate local interactions between regions of cortex at different distances and tested whether a normalization model could account for the interactions. They showed that the VSDI signal, mainly due to layer 2/3 activity, was predicted by a population gain control (PGC) model when two spatially separated regions were stimulated by localized Gabor stimuli. The VSDI signals were subadditive (suppressive) at cortical locations within about 6 mm of the centers of activation of the two stimulus patches for most interstimulus spatial conditions. In contrast, when the population voltage signal (VSDI) was converted to spike output, the spiking activity predicted suppression when the Gabor pairs were close and aligned but considerable facilitation at longer intercortical distances (2–6 mm). The predicted facilitation was similar for collinear or orthogonal Gabor pair configurations. The authors suggest that since psychophysical studies indicate facilitation only for collinearly aligned elements, the signals underlying this performance may be downstream of V1.

Cortical neurons adapt to repeated stimulus presentations. However, the population activity can alter signal strength by multiple mechanisms. A model including both adaptation and normalization predicted synchronous activation of a neuron and its normalization pool would strengthen normalization, whereas asynchronous activation would result in reduced normalization (Westrick *et al.*, 2016). Experiments probing the timing of adaptation signals confirmed that synchronous adaptation was more effective in promoting normalization [43]. Studies of the circuits involved in the V1 component of adaptation indicate that the adaptive mechanisms are initiated the supragranular layers and propagated subsequently to the granular and infragranular layers (Westerberg *et al.*, 2019).

Neuromodulators in the physiology of V1 neurons

It is increasing clear that the neuromodulators acetylcholine (ACh), serotonin (5HT) and dopamine (DA) play important roles in cortical function and may underlie some of the effects of vigilance or attention in primate V1 ([44,45]; Jacob and Nienborg, 2018; [46,47]).

ACh can enhance responses of some neurons via nicotinic ACh receptors [48] and suppress responses via muscarinic ACh receptors (Shimegi *et al.*, 2016). At a population level, local injections of ACh in V1 resulted in a suppression of evoked activity [49]. There is general agreement that these cholinergic mechanisms are likely to underlie some of the effects of attention [46,47].

One of the principal effects of serotonin in primate V1 is response suppression. In the awake behaving macaque, iontophoretic application of 5HT resulted in reduced response gain in most neurons [50], most likely via a subtractive mechanism. There were no systematic effects on tuning width for orientation or spatial frequency or changes in variability. In an earlier study 5HT had more subtle effects, specifically within layer 4 of macaque V1 [51].

Dopamine afferents are scarce in primate visual cortex except for layer 1. Nonetheless, Zaldivar *et al.* [52] found systemic L-Dopa increased the amplitude of oscillations in the mid-frequency range in the LFP in V1 during both resting state and active viewing. The authors suggest that this increase in power might be a proxy for increased DA in the system, even if it is acting indirectly on V1 activity.

Concluding remark

In the future, the use of new techniques such as optogenetics along with advanced large scale visualization applied to primate cortex, such as 3-photon imaging [53] and recording via arrays of Neuropixels electrodes [54] will generate large data sets of simultaneously recorded and manipulated neuronal populations. In addition, large scale modeling of these new data sets via biologically realistic approaches [13,14] and more abstract CNNs [33] combined with the further development of new frameworks for understanding the physiology of communication subspaces of inter-areal connectivity — as between V1 and V2 [54] — will unify the many facets of single unit and population level function to link perceptual behavior to the underlying physiology.

Conflict of interest statement

Nothing declared.

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