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SELECTIVE STIMULATION OF NEURONS IN VISUAL CORTEX ENABLES SEGREGATION OF SLOW AND FAST CONNECTIONS

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Abstract—Organization of the central visual pathway is generally studied from a perspective of feedforward processes. However, there are horizontal connections and also strong feedback from extra striate to visual cortex. Here, we use visual stimuli designed to maximize relative differential involvements of these three main types of connections. The approach relies on differences between stimulation within the classical receptive field (CRF) and that of the surround region. Although previous studies have used similar approaches, they were limited primarily to spatial segregation of neural connections. Our experimental design provides clear segregation of fast and slow components of surround modulation. We assume these are mediated by feedback and horizontal connections, respectively, but other factors may be involved. Our results imply that both horizontal and feedback connections contribute to integration of visual information outside the CRF and provide suppressive or facilitative modulation. For a given cell, modulation may change in strength and sign from suppression to facilitation or the reverse depending on surround parameters. Sub-threshold input from the CRF surround increases local field potential (LFP) power in distinct frequency ranges which differ for suppression and facilitation. Horizontal connections have delayed CRF-surround modulation and are sensitive to position changes in the surround. Therefore, surround information beyond the CRF is initially processed by fast connections which we consider to be feedback, whereas spatially tuned mechanisms are relatively slow and presumably mediated by horizontal connections. Overall, results suggest that convergent fast (feedforward) inputs determine size and structure of the CRFs of recipient cells in visual cortex. And fast connections from extra striate regions (feedback) plus slow-tuned connections (horizontal) within visual cortex contribute to spatial influences of CRF surround activation.

Key words: visual cortex, feedforward, feedback, horizontal connections, classical receptive field, extra-classical receptive field.

INTRODUCTION

The classical receptive field (CRF) of the visual system refers to spatial territory within which, appropriate stimulation can generate spike activity from a single neuron. Stimulation outside the CRF cannot independently activate the neuron, but it can influence output from the cell. CRF organization changes from early to central visual pathways. Most neurophysiological studies assume a hierarchical processing model such that information is encoded sequentially along the pathway (Hubel and Wiesel, 1962).

However, along with serial processing, parallel information flow occurs within a feedforward mechanism (Livingstone and Hubel, 1988; Nassi and Callaway, 2009). Anatomical studies demonstrate two additional major types of intercellular connections. One is feedback from extra striate regions (Peters et al., 1994; Sherman and Guillery, 1996; Budd, 1998; Galuske et al., 2002). The other is a horizontal pathway between adjacent cells in visual cortex (Rockland and Lund, 1983; Hirsch and Gilbert, 1991; McGuire et al., 1991; Bosking et al., 1997; Kisvárday et al., 1997). Feedback and horizontal connections share some similar characteristics. They do not exhibit retinotopic alignment as in the feedforward system (Alonso, 2002; Angelucci and Bullier, 2003). They represent large visual areas. They have many synaptic connections which are relatively weak as shown by inactivation of feedback which has minimal effects on spiking activity of cortical cells (Hupé et al., 1998; Bullier et al., 2001). Feedback and horizontal input do not appear to affect spike generation unless there is simultaneous feedforward activation (Toth et al., 1996; Bringuier et al., 1999).

Considered together, the three main neural connection types appear to have different functions. Feedforward processing consists of clear input to retinotopically aligned target cells. Non-feedforward connections may integrate visual information from outside the CRF which may be used to modulate CRF activity (Walker et al., 1999; Cavanaugh et al., 2002a, 2002b; Angelucci and Bullier, 2003; Seriès et al., 2003). The relative roles of feedback and horizontal connections are not clear but conduction velocities may provide clues. Onset times of surround suppression in V1 have been reported to be nearly

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Abbreviations: CRF, classical receptive field; LFP, local field potential; RF, receptive field; *RR*, relative ratio.

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constant over wide areas outside the CRF (Bair et al., 2003). However, the method used to reach this conclusion did not provide isolation of temporal parameters of horizontal transmission. Our current protocol is designed specifically to incorporate this important feature (see Experimental procedures and Results sections).

We use visual stimulation patterns intended to separate functional activity of the three major visual connection types. Two sets of stimuli are designed to differentially activate CRF and non-CRF regions in order to provide activity that emphasizes feedforward, feedback, or horizontal connections. Although we cannot confirm that we have exclusively isolated these three types of connections, our findings are consistent with their selective activation. Results show that activation outside the CRF can result in suppression or facilitation which can change depending on surround (non-CRF) parameters. The amount of response modulation of the CRF region varies with surround position. We find that excitatory and inhibitory inputs from surround areas are associated with different local field potential (LFP) frequency ranges. There are also temporal response modulation changes dependent on stimulus configurations. Overall, our results identify and imply some important functional differences in visual processing of feedforward, feedback, and horizontal connections.

EXPERIMENTAL PROCEDURES

Experiments were conducted using anesthetized and paralyzed cats (2.4–3.5 kg, 12 female). All procedures followed the guidelines by NIH and by the Animal Care and Use Committee at the University of California, Berkeley.

Surgical preparation

Initial anesthesia was induced with isoflurane (3%). After venous catheters were inserted, anesthesia was continued with intravenous infusion of propofol (20 mg/kg h) combined with fentanyl (10 μg/kg h). A tracheotomy was performed, a tracheal cannula was inserted and the animal was artificially ventilated (25% O_2 and 75% N_2O). A craniotomy was then made in both hemispheres at 4 mm posterior and 2 mm lateral to Horsley–Clarke zero. The dura was incised carefully and reflected, then the cortical surface was covered with agar and wax. After the surgery, propofol and fentanyl infusion rates were reduced to an appropriate level for stabilized anesthesia (propofol: ~6–8 mg/kg h, fentanyl: 4 μg/kg h) which was determined individually for each animal. After stabilization, a continuous intravenous infusion of pancuronium (0.2 mg/kg h) was initiated to block eye movements.

Recording procedures

Neural activity was recorded with two-channel tungsten microelectrodes. Signals from each electrode were amplified, bifurcated and then differentially filtered to extract single-unit activity (500 Hz–8 MHz, digitized at 25 kHz) and LFPs (0.7–170 Hz, digitized at 500 Hz). Electrode penetrations were made down the medial bank of the posterolateral gyrus to a depth of 5–6 mm. Cells were encountered in multiple layers at receptive field (RF) eccentricities within the central 15° of the visual field (DeAngelis et al., 1993). RF eccentricity information for individual neurons was not recorded for this study. Once a unit was identified by spike waveform, optimal RF parameters were measured using drifting sinusoidal grating stimuli in the following sequence: orientation → spatial frequency → temporal frequency → binocular phase (for binocular cell) → size. RF dimension was determined as the peak of a size tuning curve for which response of a neuron ceases to increase. For cells that did not show clear peaks in size tuning curves, we used the smallest inner diameter at which a cell stopped responding to an annulus grating stimulus as in a previous study (Cavanaugh et al., 2002a).

Design of visual stimuli

A crucial part of these experiments is the use of carefully selected visual stimuli that permit maximized separation of the three types of neural connections noted above. Anatomical findings show that feedforward connections cover a small visual space that is limited to the projection of the CRF region (Alonso et al., 2001; Angelucci and Bressloff, 2006). Therefore, the role of non-feedforward connections can be investigated by comparisons of visual responses to CRF activation versus those for which stimulation includes both CRF and adjacent non-CRF regions.

Since non-feedforward includes both feedback and horizontal connections, we require stimuli to separate them. For this, we note different characteristics for these two types of connections in spatial and temporal domains. Anatomical studies with use of retrograde tracers show that feedback connections can convey information to V1 from a much larger visual space than that for horizontal connections (Salin et al., 1989, 1992; Angelucci et al., 2002; Angelucci and Bressloff, 2006). In this case, the spatial extent of horizontal connections is approximately matched to the size of a low-contrast summation field. This implies that beyond the low-contrast summation field, feedback connections may dominate in surround suppression. In previous studies, surround suppression for spatial locations close to and far from the CRF was used to investigate horizontal connections (Hashemi-Nezhad and Lyon, 2012; Shushruth et al., 2013). However, the distribution of labeled neurons in V1 only covers monosynaptic connections, so the complete spatial extent of a horizontal pathway is not clear. Surround input is probably also transmitted via polysynaptic horizontal connections which will cause an enlargement of the spatial extent.

Besides a difference in spatial extent, another variation between horizontal and feedback connections is conduction velocity. Axons of horizontal connections are thin and unmyelinated with slow conduction velocities (Grinvald et al., 1994; Salami et al., 2003). Feedback and feedforward connections between macaque V1 and V2 have similar conduction velocities, which are about ten times faster than those of a horizontal type within V1 (Girard et al., 2001). Hence, if visual information