Altered functional interactions between neurons in primary visual cortex of macaque monkeys with experimental amblyopia

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Abstract

Amblyopia, a disorder in which vision through one of the eyes is degraded, arises because of deficient processing of information by the visual system. Amblyopia often develops in humans after early misalignment of the eyes (strabismus), and can be simulated in macaque monkeys by artificially inducing strabismus. In such amblyopic animals, single-unit responses in primary visual cortex (V1) are appreciably reduced when evoked by the amblyopic eye compared to the other (fellow) eye. However, this degradation in single V1 neuron responsivity is not commensurate with the marked losses in visual sensitivity and resolution measured behaviorally. Therefore, in this study we explored the idea that changes in the pattern of coordinated activity across a population of V1 neurons may additionally contribute to degraded visual representations in amblyopia, potentially making it more difficult to read out visually evoked activity to support perceptual decisions. We recorded the activity of V1 neuronal populations in three macaques (*M. nemestrina*) with strabismic amblyopia, and in one control. As reported previously, overall activity evoked through the amblyopic eye was diminished. We studied the functional interactions among V1 neurons responding to fellow or amblyopic eye stimulation by measuring spike count correlation in responses of pairs of neurons to identical visual stimuli. We found elevated correlation in neuronal responses to stimuli shown to the amblyopic eye that was independent of contrast level, unlike the fellow eye or typical cortex. Furthermore, the magnitude of this difference in correlation varied with the tuning and eye preferences of the neurons. As expected, these changes in strength and pattern of correlated activity diminished the ability of a standard decoding analysis to correctly identify visual stimuli. Overall, our results suggest that a part of the diminished visual capacity of amblyopes may be due to changes in the patterns of functional interaction among neurons in the primary visual cortex.

Introduction

Normal visual system development is dependent on having unobstructed and balanced binocular visual experience during early life. Amblyopia is a disorder of the visual system which often arises when visual input through the two eyes is imbalanced, most commonly through a misalignment of the two eyes (strabismus) or anisometropia (unilateral blur), during a critical window for development. Amblyopic individuals show major impairments in basic spatial vision in the affected eye, including decreased visual acuity and diminished contrast sensitivity that is particularly acute at high spatial frequencies (*Hess & Howell, 1977; Levi & Harwerth 1977; Bradley & Freeman, 1981; McKee et al., 2003; Levi, 2013*). Furthermore, several studies suggest that amblyopia is detrimental to cognitive processes that rely on higher visual system function, namely contour integration, global motion sensitivity, visual decision-making, and visual attention (*Farzin & Norcia, 2011; Hou et al., 2016; Kozma & Kiorpes 2003; Kiorpes, Tang & Movshon, 2006; Levi & Rislove, 2007; Meier et al., 2016; Pham et al., 2018; for review see Kiorpes, 2006 and Hamm et al., 2014*). Deficits in amblyopic vision originate from altered neural activity in the primary visual cortex (V1), and cortical areas downstream of V1, rather than from abnormalities in the eye or the visual thalamus (*Kiorpes et al., 1998; Blakemore & Vital-Durand, 1986; Levitt, et al., 2001; Movshon et al., 1987; Bi et al. 2011; Shooner et al., 2015; for review see Levi, 2013 and Kiorpes 2016*).

Previous studies using animal models of amblyopia provide evidence for some functional reorganization of ocular dominance in amblyopic V1 (*Adams et al., 2013 & 2015; Horton, Hocking & Kiorpes, 1997; Hendrickson et al, 1987; Fenstemaker et al. 1997; Levay, Wiesel & Hubel, 1980*), including a significant loss in the proportion of binocularly activated cells and – in severe amblyopia – a reduced proportion of neurons that respond to amblyopic eye stimulation (*Crawford et al., 1996; Smith et al., 1997; Kiorpes et al. 1998; Crawford & Harwerth 2004; Schröder et al., 2002; Shooner et al., 2015)*. Additionally, several studies report changes in spatial frequency tuning, as well as a loss of contrast sensitivity in some V1 neurons that receive input from amblyopic eye in monkeys (*Movshon et al., 1987; Kiorpes et al., 1998*) and in cats (*Crewther & Crewther 1990; Chino et al., 1983).* Overall, these changes in the functional properties of V1 neurons suggest that the representation of visual input from the amblyopic eye across the cortical neuronal population is distorted.

Early studies on the neural basis of amblyopia hypothesized that the perceptual deficits in amblyopes arise directly from corresponding losses in responsivity of single neurons in primary visual cortex. However, it is now clear that the magnitude of these single neuron changes cannot account for the entirety of spatial vision

deficits revealed by behavioral assessments of amblyopes (*Kiorpes et al., 1998; Shooner et al., 2015*). There are two additional neurophysiological mechanisms that could contribute to amblyopia: (1) neural deficits more profound than those seen in V1 may arise in downstream visual areas (*Kiorpes et al. 1998; Kiorpes 2016; El-Shamayleh et al., 2010; Bi et al., 2011; Wang et al.,* 2017) and (2) impaired visual representation might result from changes in the structure of activity in populations of V1 neurons (*Shooner et al., 2015; Kiorpes, 2016; Roelfsema et al., 1994*).

Here we seek evidence for this second mechanism, and investigate whether activity correlations between neurons are altered in amblyopic V1 during visual stimulus processing. We recorded from populations of V1 neurons in macaque monkeys that had developed amblyopia as a result of surgically-induced strabismus (*as in Kiorpes et al., 1998*). We measured correlation in the trial-to-trial variability (hereafter referred to as "correlation") in the responses of pairs of neurons to an identical visual stimulus presented to either the non-amblyopic (fellow) or amblyopic, deviating eye. Similar to the firing rate of single neurons, the strength of correlated variability in normal visual cortex has been shown to change due to a number of factors, including the contrast of a visual stimulus (*Smith & Kohn 2005*), the animal's attentional state (*Cohen & Maunsell, 2009; Mitchell et al., 2009; Snyder et al., 2016*), and over the course of perceptual learning (*Gu et al., 2011; Ni et al., 2018).* In our experiments, comparing correlation measurements for stimuli presented to the two eyes allowed us to determine whether the functional circuitry used for processing amblyopic eye visual input is altered compared to that supporting fellow eye processing. We found that correlation indeed changes depending on which eye receives the visual stimulus, an effect that was not present in a control animal. Overall, stimuli presented to the amblyopic eye evoked correlations that were more prominent in pairs of neurons with similar orientation tuning and eye preference. When stimulus contrast was increased, pairs of neurons driven through the fellow eye tended to decorrelate, whereas the high levels of correlation remained elevated for neurons driven by the affected eye. Our findings are consistent with the hypothesis that the abnormalities in amblyopic vision may in part be explained by changes in the strength and pattern of functional interactions among neurons in primary visual cortex.

Materials and Methods

Subjects. We studied four adult macaque monkeys (*Macaca nemestrina*), three female and one male. One animal remained a visually normal, untreated control while three of the animals developed strabismic amblyopia as a result of surgical intervention at 2-3 weeks of age. Specifically we resected the medial rectus muscle and transected the lateral rectus muscle of one eye in order to induce strabismus. All of the animals underwent behavioral testing to verify the presence or absence of amblyopia. All procedures were approved by the Institutional Animal Care and Use Committee of New York University and were in compliance with the guidelines set forth in the United States Public Health Service Guide for the Care and Use of Laboratory Animals.

Behavioral testing. We tested the visual sensitivity of each animal by evaluating their performance on a spatial two-alternative forced-choice detection task. Behavioral testing was conducted at the age of 1.5 years or older, and the acute experiments took place at the age of 7 years or older. On each trial in this task, a sinusoidal grating was presented on the left or the right side of a computer screen while the animal freely viewed the screen. The animal had to correctly indicate the location of the grating stimulus by pressing the corresponding lever in order to receive a juice reward. The gratings varied in spatial frequency and contrast level: we tested 5 contrast levels at each of 3-6 different spatial frequencies and collected at least 40 repeats of each stimulus combination. For each eye, we then determined the lowest contrast the animal could detect at each spatial frequency (threshold contrast) and constructed contrast sensitivity functions for each animal's right and left eyes. A detailed account of the procedures we used for behavioral assessment in this study can be found in previous reports (*Kiorpes, Tang & Movshon, 1999; Kozma & Kiorpes, 2003*).

Electrophysiological recording. The techniques we used for acute physiological recordings have been described in detail previously (*Smith and Kohn, 2008*). Briefly, anesthesia was induced with ketamine HCl (10 mg/kg) and animals were maintained during preparatory surgery with isoflurane (1.5-2.5% in 95% O2). Anesthesia during recordings was maintained with continuous administration of sufentanil citrate (6-18 µg/kg/hr, adjusted as needed for each animal). Vecuronium bromide (Norcuron, 0.1 mg/kg/hr) was used to suppress eye movements and ensure stable eye position during visual stimulation and recordings. Drugs were administrated in normosol with dextrose (2.5%) to maintain physiological ion balance. Physiological signs (ECG, blood pressure, SpO2, end-tidal CO2, EEG, temperature, and urinary output and osmolarity) were continuously monitored to ensure adequate anesthesia and animal well-being. Temperature was maintained at 36-37 C°.

Recordings of neural activity were made from 100-electrode "Utah" arrays (Blackrock Microsystems) using methods reported previously (*Kelly et al., 2007; Smith & Kohn, 2008*). Each array was composed of a 10x10 grid of 1 mm long silicon microelectrodes, spaced by 400 um (16 mm^2 recording area). Each microelectrode in the array typically had an impedance of 200-800 kOhm (measured with a 1 kHz sinusoidal current), and signals were amplified and bandpass filtered (250 Hz to 7.5 kHz) by a Blackrock Microsystems Cerebus system. The arrays were inserted 0.6 mm into cortex using a pneumatic insertion device (*Rousche & Normann 1992*).

Our full data set consisted of acute recordings from 7 microelectrode arrays across 3 amblyopic macaque monkeys and 1 control monkey. One of the amblyopic animals had 4 array implants; one had 2 array implants, and the third had 1 array implant. The control animal had a single implant. For animals with multiple implants in a single hemisphere, the array was removed and shifted to a different, non-overlapping region of cortex prior to reimplantation. Arrays were inserted within a 10 mm craniotomy made in the skull, centered 10 mm lateral to the midline and 10 mm posterior to the lunate sulcus. The resulting receptive fields lay within 5° of the fovea.

Visual stimulation. We presented stimuli on a gamma-corrected CRT monitor (Eizo T966), with spatial resolution 1280 x 960 pixels, temporal resolution 120 Hz, and mean luminance 40 cd/m^2. Viewing distance was 1.14 m or 2.28 m. Stimuli were generated using an Apple Macintosh computer running Expo (http://corevision.cns.nyu.edu).

We used a binocular mirror system to align each eye's fovea on separate locations on the display monitor, so that stimuli presented in the field of view of one eye did not encroach on the field of view of the other eye. This setup enabled us to show stimuli to the receptive fields for the right and left eye independently. We mapped the neurons' spatial receptive fields by presenting small, drifting gratings (0.6 degrees; 250 ms duration) at a range of spatial positions in order to ensure accurate placement of visual stimuli within the recorded neurons' receptive fields. During experimental sessions, we presented full-contrast drifting sinusoidal gratings at 12 orientations spaced equally (30˚) in the field of view of either the right or the left eye on alternating trials. Each stimulus was 8–10 deg in diameter and was presented within a circular aperture surrounded by a gray field of mean luminance. Each stimulus orientation was repeated 100 times for each eye. Periods of stimulus presentation lasted 1.28 seconds and were separated by 1.5 s intervals during which we presented a homogeneous gray screen of mean luminance. In one of the amblyopic animals (4 separate array implants) and

the control animal, we presented the drifting sinusoidal gratings at 12 orientations and 3 contrast levels (100%, 50%, 12%). In these cases, stimuli were presented for 1 second and each stimulus orientation was repeated 50 times at each of three contrasts. The spatial frequency (1.3 c/deg) and drift rate (6.25 Hz) values for the grating stimuli were chosen to correspond to the typical preference of parafoveal V1 neurons (*DeValois et al., 1982; Foster et al., 1985; Smith et al., 2002*) and to be well within the spatial frequency range where we could behaviorally demonstrate contrast sensitivity in both eyes.

Spike sorting and analysis criteria. Our spike sorting procedures have been described in detail previously (Smith & Kohn, 2008). In brief, waveform segments exceeding a threshold (based on a multiple of the r.m.s. noise on each channel) were digitized at 30 kHz and stored for offline analysis. We first employed an automated algorithm to cluster similarly shaped waveforms (*Shoham et al., 2003*) and then manually refined the algorithm's output for each electrode. This manual process took into account the waveform shape, principal component analysis, and inter-spike interval distribution using custom spike sorting software written in Matlab (https://github.com/smithlabvision/spikesort). After offline sorting, we computed a signal to noise ratio metric for each candidate unit (*Kelly et al., 2007*) and discarded any candidate units with SNR below 2.75 as multi-unit recordings. We also eliminated neurons for which even the best grating stimulus evoked a response of less than 1 spike/second. We considered the remaining candidate waveforms (240 units total across sessions) to be high-quality, well isolated single units and we included these units in all further analyses.

Measures of correlation. Here we provide a brief description of correlation analyses performed for this study. A detailed discussion can be found in two previous publications (*Kohn and Smith, 2005; Smith and Kohn, 2008*). The r_{sc}, also known as spike count correlation or noise correlation, captures the degree to which trial-to-trial fluctuations in responses are shared by two neurons. Quantifying the magnitude of the correlation in trial-to-trial response variability is achieved by computing the Pearson correlation coefficient of evoked spike counts of two cells to many presentations of an identical stimulus. For each session, we paired each neuron with all of the other simultaneously recorded neurons, but excluded any pairs of neurons from the same electrode. We then combined all the pairs from all of the recording sessions in the amblyopic animals, and separately, the control animal. This resulted in 4630 pairs across the 3 amblyopic animals and 155 pairs in one control animal. For each stimulus orientation, we normalized the response to a mean of zero and unit variance (Z-score), and calculated r_{sc} after combining responses to all stimuli. We removed trials on which the response of either neuron

was > 3 SDs different from its mean (*Zohary et al., 1994*) to avoid contamination by outlier responses. We also compared our measures of response correlation to the tuning similarity of the two neurons, which we calculated as the Pearson correlation between the mean response of each cell to each of the tested orientations (termed r_{signal}). For neurons with similar orientation tuning r_{signal} is closer to 1, while neurons with dissimilar tuning have r_{signal} values approaching −1.

Ocular dominance analysis: For each unit, we first obtained the average firing rate response to each of the 12 orientations of high contrast gratings, then subtracted the baseline firing rate measured during the interstimulus intervals. Next, we determined each unit's eye preference by comparing the maximum mean response elicited by visual stimulation of the fellow eye (R_f) with the same unit's maximum response to visual stimulation of the amblyopic eye (R_a). Specifically, we computed an ocular dominance index (ODI) defined as ODI = $(R_f – R_a)/(R_f + R_a)$. The ODI values ranged from -1 to 1, with more negative values signifying a cell's preference for amblyopic eye stimulation, and more positive values indicating a preference for the fellow eye. For the pairwise analyses, we measured the difference between the ODI values of the cells constituting each pair, such that cells with a very similar eye preference had an ODI difference close to 0, and cells preferring opposite eyes had an ODI difference close to 2.

Statistical significance tests: All indications of variation in the graphs and text are standard errors of the mean (s.e.m.). The statistical significance of all results was evaluated with paired t-tests, unless otherwise noted.

We used a bootstrapping method for statistical testing of the relationships between r_{sc} and r_{signal}. Specifically, for 1000 iterations, we sampled with replacement from a pool of matched r_{sc} and r_{signal} values computed for each pair of neurons, separately for each eye condition. Using the "polyfit" function in Matlab, we then computed the slope of a line fit through the scatter of r_{sc} values plotted against the corresponding r_{signal} values for the neuronal pairs used on each sampling iteration. Thus, for each eye stimulation condition, we collected 1000 estimates of the slope of the linear relationship between r_{sc} and r_{signal}. We then looked at confidence interval bounds to test for a statistically significant difference between the bootstrapped distributions of slope values computed for amblyopic vs. fellow eye stimulation. We also performed the same bootstrapping procedure to assess whether the relationship between r_{sc} and eye preference was significantly different between fellow and amblyopic eye conditions. We used non-smoothed data for this statistical analysis.

We also used bootstrapping for statistical testing of the interocular difference in delta $r_{sc.}$ Briefly, we calculated Δr_{sc} in our data set by subtracting the high contrast r_{sc} value of each neuronal pair from the low contrast r_{sc} value attained for the same pair of neurons. We then performed 1000 iterations of randomly sampling with replacement from the pool of pairs of neurons (1381 pairs total). Each pair of neurons was associated with a high contrast and low contrast r_{sc} value that we could use to compute $\Delta r_{sc.}$ For each eye condition, on each iteration, we computed the average of the sample of Δr_{sc} values. In the end we collected a distribution of 1000 average Δr_{sc} values for each eye condition. We compared these distributions of Δr_{sc} values using confidence interval bounds.

Decoding stimulus orientation. Within 4 separate recording sessions, we randomly subdivided the spiking data in our two eye conditions such that a subset of the trials was used to train the classifier and the held-out trials were used to assess classification performance. We did 3 rounds of cross-validation such that 3 different random subsets of trials were used for training the classifier. For 3 of the recording sessions, we show the average performance of 20 classifiers each trained and tested on the responses of 30 randomly selected V1 neurons in each session. In the fourth session, we only recorded from 30 neurons in total, and thus we assessed performance of just one classifier for this session. The remaining three of the total seven sessions had comparatively few simultaneously recorded cells (~10) and thus were not included in this decoding analysis.

As we had a total of 12 stimulus orientations, for each testing trial, a trained multi-class classifier was tasked with deciding which one of 12 orientations (classes) was most fitting given the V1 population activity on that trial. We used the Error-Correcting Output Coding method (ECOC) which decomposed our multi-class classification problem into many binary classification tasks solved by binary SVM classifiers. In the ECOC framework, the final decision about the class label for a piece of data is achieved by considering the output/"vote" of each subservient binary classifier.

Results

The overall goal of our study was to examine whether neuronal interactions are altered within primary visual cortex of strabismic amblyopes. To this end, we recorded from populations of V1 neurons using 100-electrode "Utah" arrays while a visual stimulus was separately presented to the amblyopic or the fellow, non-amblyopic eye of anesthetized macaque monkeys. We then evaluated the strength and pattern of correlation in the recorded populations in order to determine if functional interactions among neurons differed during visual stimulation of each eye.

Behavioral deficits in amblyopic monkeys

Prior to the neural recordings, we characterized the behavioral extent of the amblyopic visual deficits by constructing spatial contrast sensitivity functions for each eye in each animal. The fitted curves were used to estimate the optimal spatial frequency and peak contrast sensitivity. For the three strabismic amblyopes, reduced contrast sensitivity and spatial resolution in the amblyopic eye was evident from the reduced peak and spatial extent of the fitted curve (Fig 1). The control animal was tested binocularly and confirmed to be visually normal (Fig 1). Based on these behavioral assessments, we concluded that all three of our experimental animals had severe strabismic amblyopia.

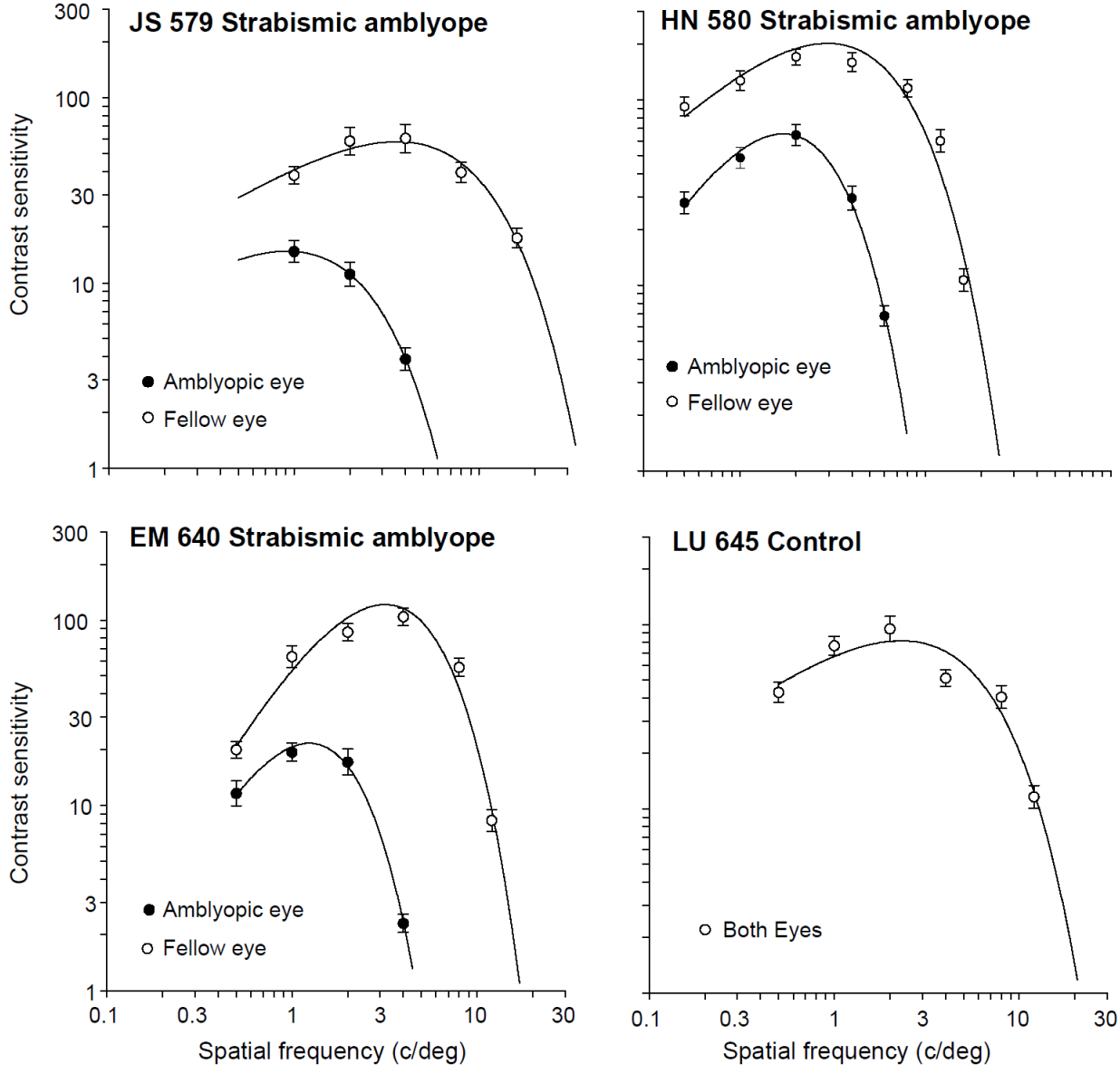

Figure 1. Spatial contrast sensitivity functions, plotted separately for the amblyopic eye (filled symbols) and fellow eye (unoperated, normal eye; open symbols). The four panels show plots for 3 strabismic amblyopes and 1 control, visually normal animal. Behavioral sensitivity loss in the amblyopic eye was observed for all 3 amblyopes: the peak contrast sensitivity was both decreased and shifted to lower spatial frequencies for the amblyopic eyes compared to the fellow eyes.

Amblyopia affects individual neuronal responsivity

We first studied the changes in single neuron responses in amblyopic primary visual cortex. We recorded from "Utah" arrays while a drifting sinusoidal grating was presented to either the fellow or amblyopic eye of an anesthesized monkey. We presented full-contrast gratings of 12 different orientations to either the amblyopic or fellow eye of three monkeys. For comparison, we also analyzed neural responses to the full-contrast stimuli shown to the right or left eye of the control animal.

We found that most V1 neuronal firing rates were substantially lower during amblyopic eye stimulation compared to fellow eye stimulation (Fig 2A-B). For the example in Figure 2A, the peak response was about 1.5 times greater for stimulation of the fellow eye than for the amblyopic eye. Over the whole population of recorded neurons, the mean maximum response to stimuli presented to the fellow eye was 15.08 sp/s, compared to 9.56 sp/s for the same stimuli presented to the amblyopic eye ($p<0.0001$, Fig 2B). In the control animal, considering all the recorded neurons, there was no statistically significant difference in maximum evoked firing rates for left versus right eye stimulation (Fig 2C, 9.61 vs. 9.65 sp/s, $p=0.92$).

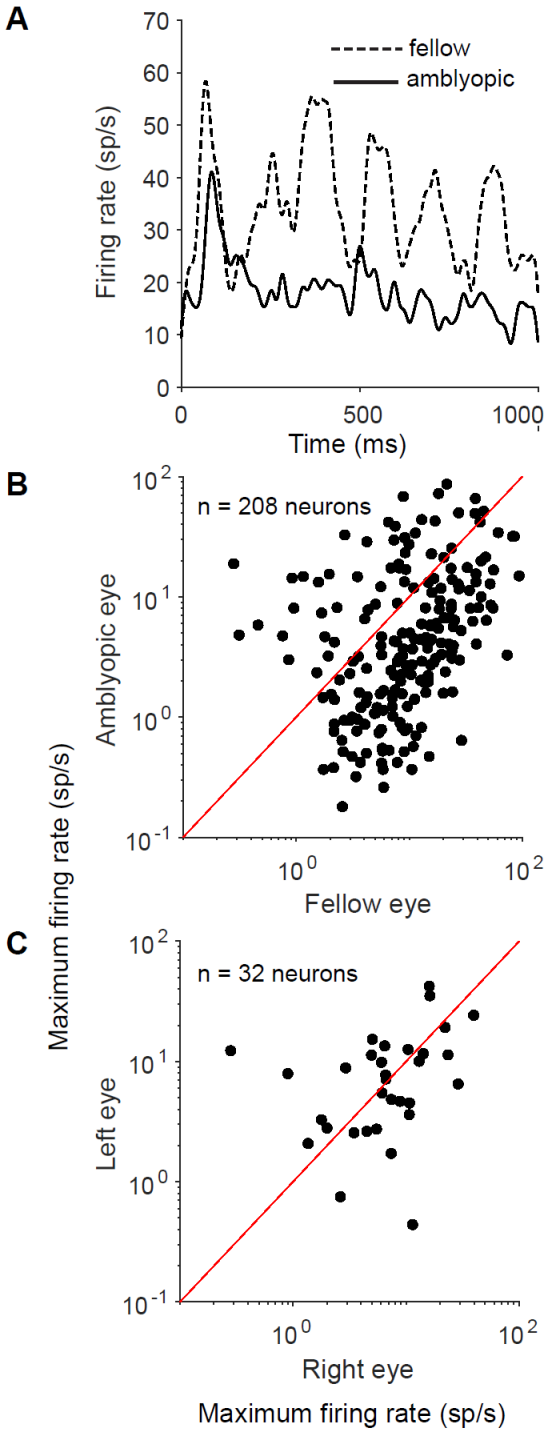

Figure 2. Comparison of neuronal responses to normal and amblyopic eye stimulation. (A) An example neuron's firing rate responses to separate stimulation of the fellow (dashed) and amblyopic (solid) eyes with an identical sinusoidal grating, drifting in the neuron's preferred orientation. Upon amblyopic eye stimulation, the neuron's firing rate was diminished. (B) Each point in the scatter diagram represents the maximum firing rate of each recorded neuron across 12 tested orientations of drifting gratings. The maximum firing rates in response to stimulation of the fellow eye are plotted against the maximum firing rates evoked by amblyopic eye stimulation. The majority of recorded neurons showed decreased responsivity to amblyopic eye stimulation as compared to fellow eye stimulation. Combined across animals, a total of 208 neurons were recorded from V1 of amblyopic animals. (C) Same as in (B), except data for the control animal are shown. A total of 32 neurons were recorded in the control, visually normal animal. There was no observed difference in the maximum firing rates elicited by stimulation of normal right and left eyes.

Amblyopia alters coordinated population activity

Numerous recent studies have been devoted to understanding how stimulus information is embedded in the population code. In particular, the pattern of correlated variability and its dependence on the stimulus-response structure have been shown in theoretical studies to have potential importance for the information in the population code (*Averbeck et al., 2006; Kohn et al., 2016*). We reasoned that amblyopia could alter the activity pattern and level of interaction in networks of V1 neurons, and might thereby influence information encoding and behavioral performance.

We measured the correlated variability of neural responses to quantify the interactions in pairs of simultaneously recorded V1 neurons. It is well established that neurons respond with variable strength to repeated presentations of identical stimuli *(Tolhurst et al. 1983; Shadlen & Newsome 1998).* A small portion of this variability, or noise, is shared between neighboring neurons in cortex. The degree to which trial-to-trial fluctuations in responses are shared by two neurons can be quantified by computing the Pearson correlation of spike count responses to many presentations of the same stimulus (termed spike count correlation, r_{sc}, or noise correlation). In Figure 3A, the scatterplot depicts the spike count responses of two example recorded V1 neurons to an identical stimulus presented to the fellow eye on many trials. The depicted pair of neurons has a positive r_{sc} of 0.31, indicating that responses of these two neurons tend to fluctuate up and down together across trials. We measured correlations over the entire stimulus window (1.28 s), for all pairs of neurons recorded either during amblyopic or fellow eye stimulation (*see Materials and Methods*).

Correlations for pairs of neurons were significantly larger when a stimulus was presented to the amblyopic eye compared to the fellow eye (Fig 3B; mean r_{sc} 0.21 vs 0.16; paired t-test, $p<0.00001$). Because we randomized the visual stimulus between the eyes across trials, we were able to make this comparison directly in the same neurons. Thus, the observed difference in r_{sc} between amblyopic and fellow eye stimulation provides evidence for altered functional interactions in the same population of neurons. There was no statistically significant inter-ocular difference in r_{sc} in the control animal (Fig 3C, paired t-test, $p=0.76$).

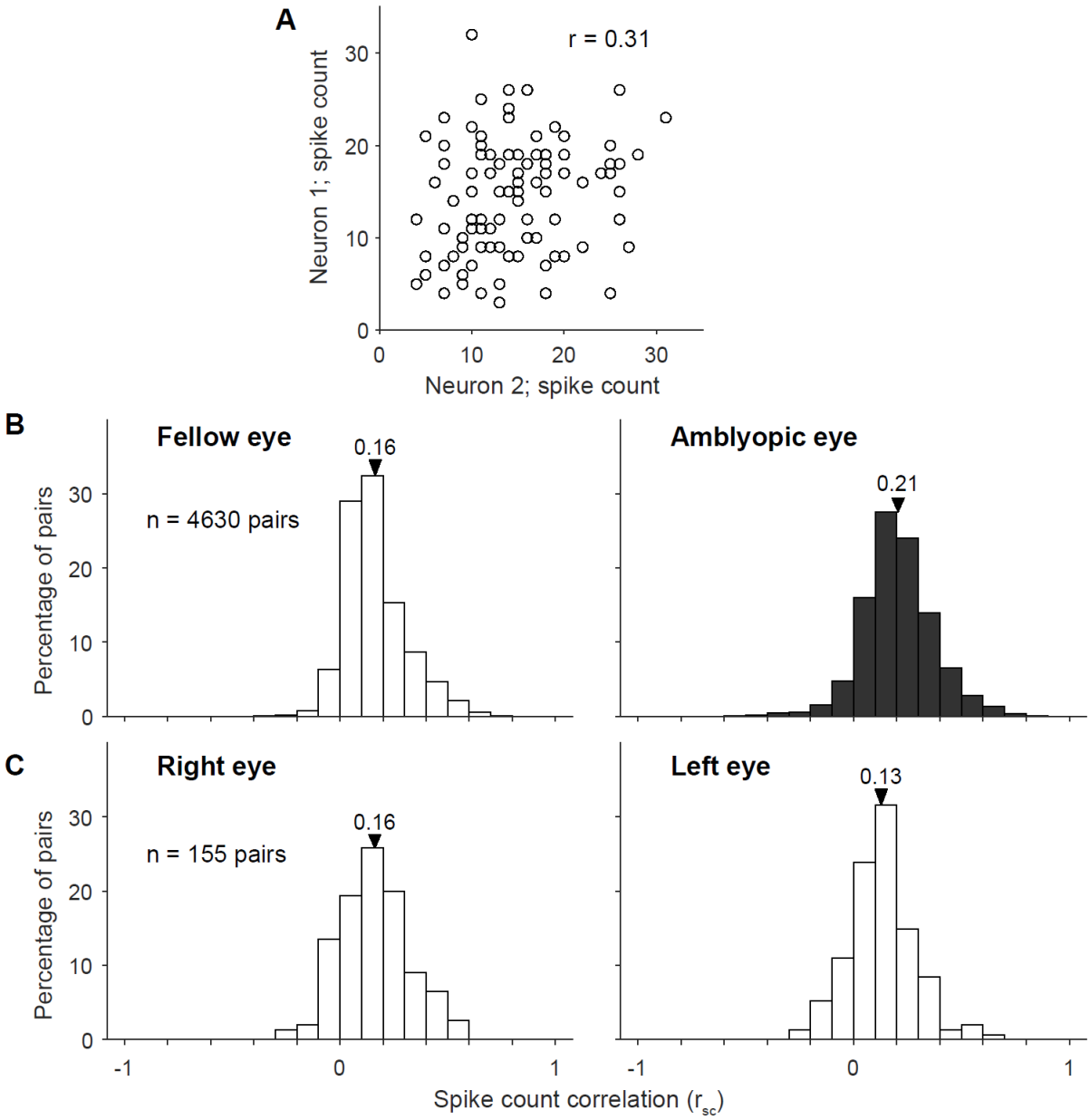

Figure 3. Effect of amblyopia on correlated variability of responses in a population of V1 neurons**.** (A) The scatter plot shows the aggregate single trial responses of an example pair of recorded V1 neurons to 100 repeat presentations of a single identical stimulus. Both of the neurons' responses were 'noisy', varying from trial to trial. Spike count correlation (r_{sc}), also known as noise correlation, is computed as the Pearson's correlation coefficient (r) of the responses of two cells to repeated presentations of an identical stimulus. (B) Spike count correlation was significantly increased for pairs of neurons responding to amblyopic eye stimulation, compared to fellow eye stimulation ($p<0.00001$). Shown are the distributions of r_{sc} computed across 4630 pairs of neurons. Spike count correlation was computed separately for neuronal responses evoked by visual stimulation of the amblyopic (filled) and fellow (white) eyes. For each neuronal pair, we calculated the average r_{sc} measured across all stimulus orientations. (C) Same as in (B), except r_{sc} was computed for pairs of neurons in the control, visually normal animal when either the right or the left eye were stimulated. There was no inter-ocular difference in spike count correlation in the control animal ($p=0.76$).

Stimulus-dependent correlation structure is modified in amblyopic V1

Several experimental and theoretical studies suggest that the structure of correlations – the dependence of correlations on the functional properties and physical location of neurons – can have a strong influence on the information encoded by the population (*see Averbeck et al., 2006 and Kohn et al., 2016 for reviews*). Previous work in normal macaque V1 and V4 has shown that correlations are highest for pairs of neurons that are near

each other and that have similar orientation tuning preferences *(Kohn & Smith, 2005; Smith & Kohn, 2008; Smith & Sommer, 2013).* Here, we investigated whether the correlation structure observed in visual cortex of normal animals is maintained in the cortex of amblyopes. To do this, we first examined if r_{sc} measurements differed depending on the distance between the neurons in each pair. We found that r_{sc} was largest for pairs of neurons near each other, compared to pairs of neurons farther apart, for both fellow and amblyopic eye stimulation (Fig 4A & C). Thus, for cortical processing of visual information received through the amblyopic eye, correlations were increased for all pairs of neurons, regardless of the distance between them.

We next investigated whether the relationship between tuning similarity and the magnitude of correlations was altered in the cortex of amblyopes. We used sinusoidal gratings of 12 different orientations to engage neurons with varied orientation preferences, which enabled us to assess the tuning similarity of each pair of neurons. Tuning similarity was quantified by calculating r_{signal}, the Pearson correlation of the mean responses of two neurons to each of 12 stimulus orientations. To test how functional interactions varied among neurons with different tuning preferences, we calculated r_{sc} as a function of r_{signal}. As in previous studies, we found that r_{sc} was highest for neurons with similar tuning (large, positive r_{signal}), and lowest for neurons with opposite tuning preferences (negative r_{signal}), for both fellow and amblyopic eye stimulation (Fig 4B & C). However, for the amblyopic eye, the relationship between r_{sc} and r_{signal} was significantly stronger compared to the fellow eye ($p < 0.05$; *see Methods* for details of bootstrapping and statistical testing), such that pairs of similarly tuned neurons exhibited the largest difference in r_{sc} between the amblyopic and fellow eye stimulation conditions (Fig 4B&C). That is, pairs of similarly tuned neurons show the largest increase in r_{sc} between fellow and amblyopic eye stimulation. So, both raw correlation for stimulation of each eye as well as the difference in correlation between activity evoked by stimulation of the two eyes depend on tuning similarity of a pair of neurons. In the control animal, we found that r_{sc} was highest for neurons with similar tuning and lowest for neurons with opposite tuning preferences, for both left and right eye stimulation, as previously reported in normal animals. Overall, our results suggest that amblyopia affects not only the overall level of correlation, but also the extent to which neurons interact with their neighbors of both similar and dissimilar stimulus preferences.

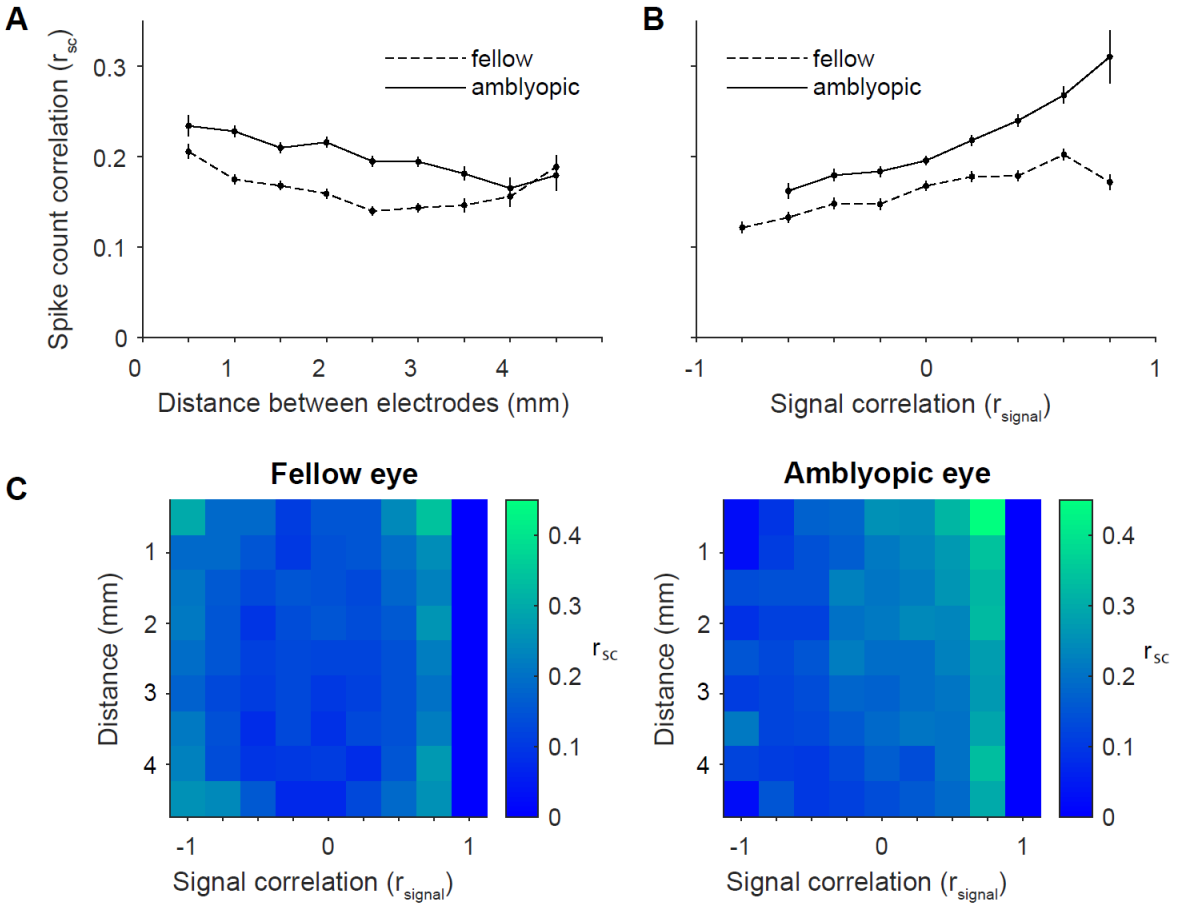

Figure 4. Dependence of r_{sc} on distance and tuning similarity in amblyopic V1. (A) Stimuli presented to the amblyopic eye (solid line) resulted in higher spike count correlation over all possible distances between recorded neurons, as compared to fellow eye stimulation (dashed line). Mean spike count correlation is plotted as a function of the distance between the array electrodes that contain the neurons in each assessed pair. The distance bins start at 0 mm and extend to 4.5 mm in 0.5 mm increments. The average of the r_{sc} values for neuronal pairs included in each bin is plotted at the end value for each bin. Error bars represent s.e.m. (B) For fellow and amblyopic eye stimulation, mean spike count correlation is plotted as a function of signal correlation, which can be thought of as similarity in orientation tuning of the two neurons. The r_{signal} bins start at -1.0 and extend to 1.0 in 0.2 increments. The average of the r_{sc} values for neuronal pairs included in each bin is plotted at the start value for each bin. As has been reported previously, spike count correlation increased with signal correlation. Furthermore, for the amblyopic eye, the relationship between r_{sc} and r_{signal} was significantly stronger compared to the fellow eye ($p<0.05$), indicating that similarly tuned neurons exhibit the largest increase in shared trial-to-trial variability. Error bars represent s.e.m. (C) Summary color maps illustrate the relationships between distance, spike count correlation and signal correlation for fellow vs. amblyopic eye stimulation. The scale of the colors is indicated by the bar on the right. r_{signal} bins start at -1 and extend to 1 in 0.25 increments.

Increased correlations predominate among amblyopic V1 neurons that preferentially respond to fellow eye

In amblyopes, binocular organization in V1 is disrupted, such that the ocular dominance distribution becomes U-shaped with a significant reduction in binocularly activated cells (*Baker et al. 1974; Crawford & von Noorden, 1979; Fenstemaker* et al. *1997; Smith et al.,1997; Kiorpes et al., 1998)*. Additionally, several studies report a decrease in the number of cortical neurons that preferentially respond to visual stimulation through the amblyopic over the fellow eye (e.g. *Adams et al., 2013; Hubel & Wiesel, 1965; Kiorpes et al., 1998; Crawford &*

Harwerth 2004; Shooner et al., 2015; (in cat) Schröder et al., 2002). Specific changes in the circuitry underlying the eye preference and binocular responsivity of V1 neurons could be reflected in an altered pattern of pairwise interactions in the population. Therefore, we next examined whether our observed changes in spike count correlation were associated with eye preference changes of individual neurons in amblyopic V1.

For each cell, we first computed an ocular dominance index (ODI) as a measure of the cell's eye preference. ODI distributions in each amblyopic animal ranged between the values of -1 and 1, with more negative and positive values indicating higher responsivity to visual stimuli viewed through the amblyopic or fellow eye, respectively. Figure 5A shows a distribution of ODI values for 208 neurons recorded from the 3 amblyopic animals. We observed an ocular dominance bias toward positive values, indicating that the majority of cells fired more strongly in response to visual stimulation of the fellow eye than the amblyopic eye (141 neurons with ODI value > 0.2 and 36 neurons with ODI value < -0.2). There were relatively few binocularly activated V1 neurons in our amblyopic animals (31 neurons with ODI values within +/- 0.2 of 0).

We next investigated whether the magnitude of spiking correlations was dependent on the eye from which each neuron received its dominant input. In this analysis, we measured correlations in pairs of neurons as a function of the difference in eye preference between the cells in each pair, termed ODI difference. Differences in ODI ranged from 0 to 2, where cells that preferred the same eye had an ODI difference of 0, while cells that preferred opposite eyes had an ODI difference of 2. Because of the ocular dominance bias in our neuronal population, the majority of neuronal pairs with an ODI difference close to 0 preferred the fellow eye. We first analyzed the magnitude of correlation as a function of the ODI difference, and found that there was a negative relationship in both the fellow (Fig 5B) and amblyopic (Fig 5C) eye. This effect could be due simply to the lower mean firing rates among pairs of neurons that preferred quite dissimilar stimuli. For the fellow eye, this was indeed the case – the correlation tracked the geometric mean firing rate of the pairs of neurons. However, for the amblyopic eye there was a particularly high level of correlation among neurons that received input from the same eye (ODI difference < 0.8) that could not be explained by the firing rates. Accordingly, we found that the relationship between eye preference similarity and the magnitude of correlations in pairs of neurons was significantly different between the two eyes (stronger for the amblyopic eye, $p<0.05$; *see Methods* for details on bootstrapping and statistical testing). These results are consistent with the idea that the circuit plasticity that

underlies eye preference changes in single neurons in amblyopic V1 also leads to changes in the pattern of interactions among monocular and binocular neurons within and across ocular dominance columns.

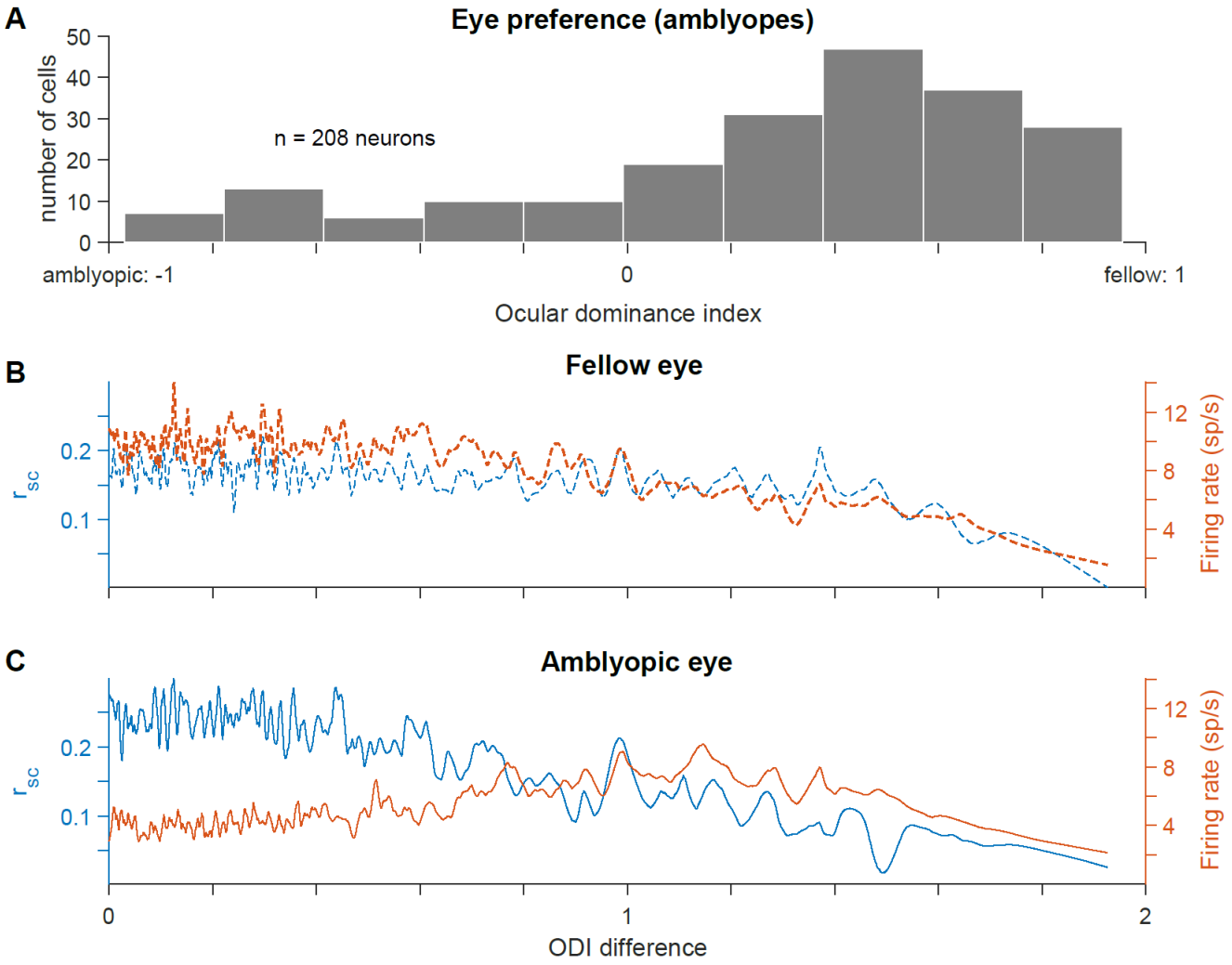

Figure 5. Relationship between ocular dominance changes and increased correlations in amblyopic V1. (A) A histogram showing the ocular dominance index (ODI) values for all 208 neurons recorded across the 3 amblyopic animals. Neurons with ODI values closer to -1 preferentially responded to visual input through the amblyopic eye, while neurons with ODI values closer to 1 had higher responsivity to fellow eye visual stimulation. The ODI values were unevenly distributed, and biased toward the fellow eye (ODI < -0.2: 36 neurons; -0.2<ODI<0.2: 31 neurons; ODI>0.2: 141 neurons). (B) For fellow eye visual stimulation, spike count correlation values (left y-axis) and firing rates (right y-axis) are plotted as a function of the difference in ODI values of the neurons in each pair. An ODI difference closer to 0 indicates that the neurons composing the pair have the same ocular preference. The traces shown were produced by smoothing over the data points with a sliding window (size of window = 15 data points). (C) same as in (B), but considering V1 responses to visual stimulation through the amblyopic eye. Neurons with similar ODIs had higher correlations during amblyopic eye stimulation, compared to the level of correlations in the same neuron pairs during fellow eye stimulation ($p < 0.05$).

Decoding stimulus orientation from amblyopic V1 population activity

The modifications in pattern and strength of functional interactions that we observed in amblyopic V1 could degrade the encoding of stimuli presented to the amblyopic eye. Therefore, we compared how well the recorded network of V1 neurons represented stimulus information when high contrast visual input was delivered

through the amblyopic versus the fellow eye. We used a statistical classification method to decode stimulus orientation from the activity of simultaneously recorded V1 neurons (see *Methods* for details). As we had a total of 12 stimulus orientations, for each testing trial, a trained multi-class classifier was tasked with deciding which one of 12 possible classes was most consistent with the V1 population activity on that trial. Using this classification analysis, we explored whether visual stimulus information was harder to read out from V1 population activity when the amblyopic eye provided the input.

We found that classification accuracy was substantially decreased when a classifier was trained and tested on neuronal responses during amblyopic eye stimulation compared to training and testing on V1 responses to fellow eye stimulation. Figure 6 shows decoding accuracy for fellow versus amblyopic eye stimulation trials for four different recording sessions across 3 animals. While decoding performance remained above chance (8.33%) for both of the eyes in all four examined sessions, accuracy was consistently reduced when decoding from neural responses to amblyopic eye visual input.

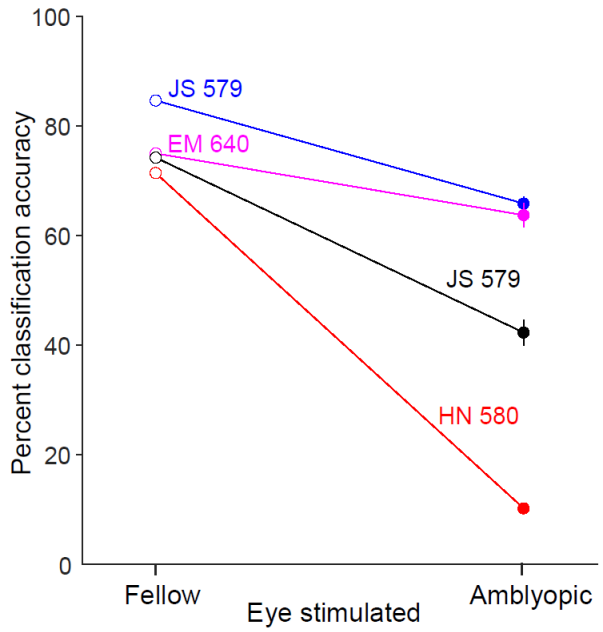

Figure 6. Decoding grating orientation from fellow or amblyopic eye stimulation. When trained and tested on neuronal responses during amblyopic eye stimulation, the decoding accuracy was decreased compared to when a decoder is trained and tested on responses to fellow eye stimulation. The four colors correspond to decoding results from neuronal responses on 4 different array implants across 3 animals.

Effect of stimulus contrast on correlated variability in amblyopic V1

Despite previous work, our understanding of the neural basis for diminished contrast sensitivity in amblyopes remains incomplete. It is possible that in amblyopia, a deficit in global network responsivity to contrast is more pronounced than individual neuron response deficits. Importantly, studies in visually normal animals

have shown that stimulus contrast can affect the level of interactions in a neuronal population. For instance, correlations in pairs of V1 neurons depend on stimulus contrast, such that r_{sc} is significantly larger for low contrast stimuli than high contrast stimuli (*Kohn & Smith, 2005*). This suggests that spontaneous cortical activity has a considerable amount of inherent correlated variability which can be reduced by strong stimulus drive (also see *Churchland et al. 2010*). Developmental abnormalities in the visual cortex of amblyopes could affect how networks of cortical neurons interpret the strength of stimulus drive provided by high vs. low contrast stimuli. Based on these observations in normal animals, we wondered how the amount of stimulus drive to the amblyopic eye affects the strength of correlated variability in V1?

We presented full (100%), medium (50%) and low (12%) contrast gratings of 12 different orientations, separately to the amblyopic or fellow eye of one of the amblyopic monkeys. We then measured the correlation in response variability of 1381 neuronal pairs in the recorded neuronal population for each stimulus contrast presented to each of the two eyes. Because r_{sc} values for neuronal pairs are known to depend on the firing rates of constituent neurons (see *Cohen & Kohn 2011*), for this analysis, we binned the computed r_{sc} values by geometric mean firing rate of neuronal pairs. This method allowed us to study the effect of stimulus contrast on correlated variability in amblyopic V1 while accounting for the wide range of responsivity observed across the recorded individual neurons (Fig 2B).

In agreement with the results of *Kohn & Smith (2005),* when we analyzed the V1 population response on trials with fellow eye stimulation, lowering stimulus contrast significantly increased mean r_{sc} for all neural pairs regardless of their geometric mean firing rate (Fig 7A). Interestingly, for stimuli presented to the amblyopic eye, r_{sc} was relatively insensitive to the level of contrast (Fig 7B). That is, a full contrast stimulus viewed by the amblyopic eye did not substantially reduce the amount of correlated variability in most V1 neurons (except those with very high firing rates) compared to a lower contrast stimulus. This is apparent when viewing a contrast response function for correlation (Fig 8), where the relatively flat lines in low-firing rate pairs of neurons for amblyopic eye stimulation indicate a lack of contrast sensitivity of correlation.

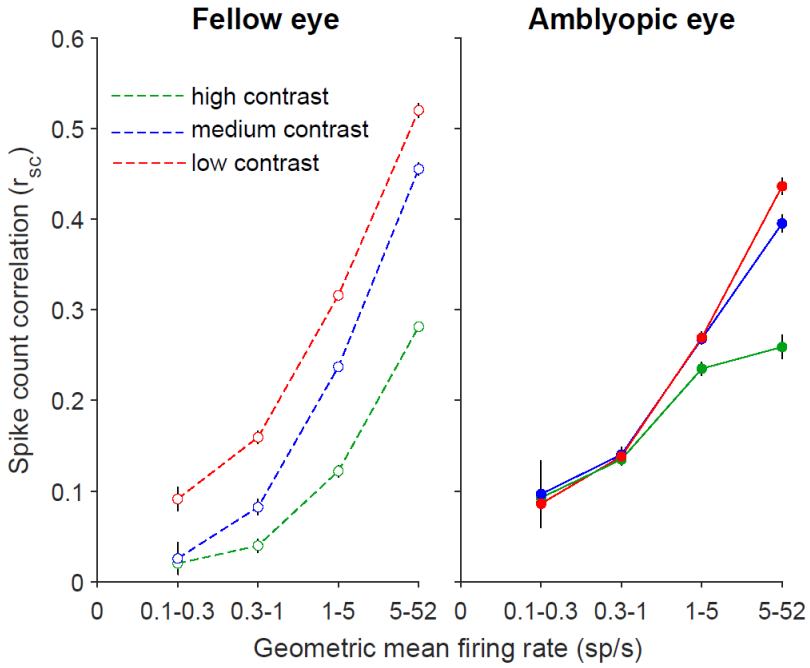

Figure 7. The average of the r_{sc} values for neuronal pairs in each geometric mean firing rate bin is plotted, for grating stimuli of high (green, 100%), medium (blue, 50%), and low (red, 12%) contrasts. Error bars represent s.e.m. For the fellow eye, lowering stimulus contrast significantly increased mean r_{sc} at all firing rates, while with amblyopic eye stimulation, r_{sc} was relatively unaffected by stimulus contrast. Computing the difference in r_{sc} between high and low contrast (Δr_{sc}) for all 1381 neuron pairs revealed a significant inter-ocular disparity in Δr_{sc} in the amblyopic animal ($p<0.05$; based on confidence intervals of bootstrapped, mean Δr_{sc} distributions).

We next quantified the differential effect of stimulus contrast on the amount of correlated variability for the fellow versus the amblyopic eye. We computed the difference in r_{sc} between high and low contrast (Δr_{sc}) for all neuron pairs separately for each eye condition. Since Δr_{sc} is computed by subtracting high contrast r_{sc} values from low contrast r_{sc} values, the closer Δr_{sc} is to 0, the more similar are the r_{sc} values computed during high and low contrast stimulation. This metric revealed that indeed, the Δr_{sc} distribution for amblyopic eye stimulation was shifted closer to 0, and was significantly different from the Δr_{sc} distribution computed for fellow eye stimulation (amblyopic mean = -0.1017, fellow mean = -0.1523; $p<0.05$; based on confidence intervals of bootstrapped, mean Δr_{sc} distributions). Furthermore, we also found a significant difference in the strength of this interocular disparity between the amblyopes and the control animal ($p<0.0001$). Thus, for stimulus processing in the amblyopic eye, neurons have not only impaired contrast sensitivity measured one cell at a time (*Movshon et al., 1987*; *Kiorpes et al., 1998*), but also maintain high levels of correlated variability even in the presence of strong stimulus input.

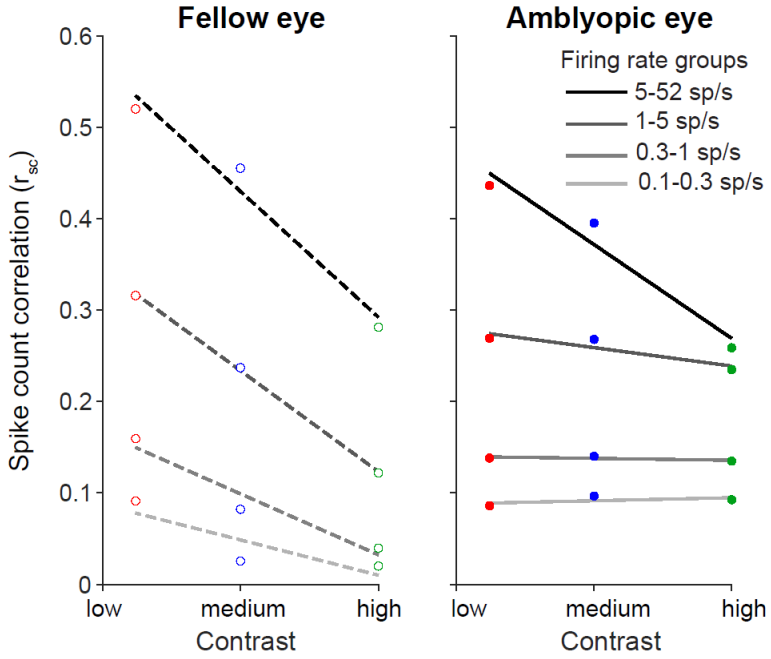

Figure 8. Dependence of spike count correlation on stimulus contrast. Amblyopic eye stimulation resulted in similar r_{sc} across three stimulus contrasts (100%, 50% and 12%). r_{sc} values are binned according to the mean firing rate for each neuronal pair, and the average r_{sc} value per firing rate bin is plotted as a function of contrast.

Discussion

Our goal in this study was to gain insight into the neural basis of amblyopia by exposing abnormalities beyond those already known to affect individual neuronal responses. We recorded simultaneously from tens of neurons in primary visual cortex of monkeys with strabismic amblyopia, which allowed us to measure the functional interactions between pairs of neurons during visual stimulation of the fellow, non-amblyopic versus the amblyopic eye of each animal. Our primary finding was that the structure of correlated trial-to-trial response variability among V1 neurons is altered in amblyopic compared to fellow eye stimulation. Specifically, stimulation of the amblyopic eye resulted in larger levels of correlation that were restricted to neurons with similar orientation tuning and similar ocular dominance preference, and these correlations were relatively insensitive to stimulus drive. To examine the consequence of these changes in amblyopic cortex on stimulus representation in networks of V1 neurons, we decoded grating orientation from simultaneously recorded populations of neurons, and found that the accuracy of decoding stimulus orientation for amblyopic eye stimulation was reduced compared to decoding the same stimuli from neural activity in response to fellow eye stimulation. Taken together, these results constitute profound shifts in the functional response properties and interactions among neurons in amblyopic cortex that manifest when a stimulus is presented to the amblyopic eye.

Altered circuitry in V1 of amblyopes

What do our observed differences in r_{sc} between the two eyes suggest about circuits of V1 neurons that process visual information received from amblyopic eye? To answer this question, it is first necessary to consider the physiological sources of correlated variability (*for review see Doiron et al., 2016*). Correlations in pairs of neurons are generally thought to arise from common sensory afferent projections to two neurons (*Shadlen & Newsome, 1998*). More recent theoretical and experimental work suggests that correlations can also arise from feedback (top down) signals (*Cumming & Nienborg 2016*), feedforward processing of stimuli (*Kanitscheider, Coen-Cagli & Pouget, 2015*), recurrent connectivity in local circuits (*Doiron et al., 2016*), or sources of noise at the synapse, such as vesicle release dynamics *(Doiron et al., 2016*). Thus, changes in correlated variability can reflect reorganization in the underlying circuitry and accordingly, correlation analysis has previously proven useful for assessing changes in functional connectivity (*Greschner et al., 2011; Reid & Alonso, 1995; Cohen & Newsome, 2008*).

In our study of amblyopic V1, we found that during amblyopic eye stimulation, there was heightened co-fluctuation in V1 neuronal responses, and that the amount of correlated variability in the recorded population remains unchanged across low, medium and high stimulus drive to the amblyopic eye. Collectively, our results suggest that in amblyopic visual systems, networks of V1 neurons have altered connectivity and may function abnormally when processing visual information received through the amblyopic eye. In particular, our observation that increased correlation persists across a range of stimulus intensities shown to the amblyopic eye suggests that V1 neurons may not fully engage in processing stimulus information received through an amblyopic eye. One well supported possibility is that the visual stimuli received through the amblyopic eye have a weaker influence in the visual cortex due to both single-neuron and network level changes following a shift in ocular dominance towards the fellow eye.

In the amblyopic animals of this study, the majority of the recorded V1 neurons preferentially responded to stimulus drive through the fellow eye, and there were few binocularly responsive neurons. Furthermore, we observed that the difference in correlated variability and firing rates between amblyopic and fellow eye stimulation was restricted to pairs of cells that had the same eye preference. Together, these results are consistent with a re-wiring scheme in which a substantial portion of the neurons lose amblyopic eye inputs but gain or retain fellow eye inputs following strabismus induction. Anatomically, the representation of the amblyopic eye in pairs of V1 neurons could decline as a result of altered lateral connections in V1, from reduced thalamocortical projections

that carry amblyopic eye information, or both. Studies of horizontal connections in amblyopic macaques and cats have reported reduced connectivity between cells located in right and left ocular dominance columns in the superficial layers of V1 (*Tychsen & Burkhalter, 1992; Lowel & Singer, 1992*). In contrast, the structure of thalamocortical inputs remains largely normal in amblyopic monkeys (*Hendrickson et al 1987; Horton, Hocking, Kiorpes, 1996; Adams et al, 2013-2015; Fenstemaker et al., 1997*). However, even with structurally intact thalamocortical projections, the effectiveness of thalamocortical drive to V1 could be reduced specifically for inputs from the amblyopic eye due to changes in how the cortical architecture receives and processes those inputs. To that point, we recently described local circuit changes in V1, in particular, reduction in excitatory drive to amblyopic eye neurons resulting in a change in E/I balance, that could explain the abnormal response to contrast variation during amblyopic eye viewing (*Hallum et al., 2017; Shooner et al., 2015*). Overall we conclude that it is necessary to consider both the prevalence and functional connectivity of the neurons that reliably activate in response to each eye, in order to pinpoint why stimulus processing through the amblyopic eye is degraded.

When considering changes across the entire population of neurons, it is evident that the effect of amblyopia is heterogenous across the V1 population. For instance, although most neurons exhibited a higher level of correlations and lower firing rates for amblyopic eye stimulation, a subgroup of neurons retained normal responsivity and continued to respond well to stimulation of the amblyopic eye. Specifically, neuronal pairs with the highest firing rates did not show an increase in correlation compared to the same high firing neuronal pairs responding to fellow eye stimulation (Figs 5 and 7). This observation is consistent with prior reports that some neurons in amblyopic cortex retain normal response properties. For example, some neurons in amblyopic cortex in monkeys maintained high responsivity to high spatial frequencies while other neurons had altered responsivity (*Movshon et al., 1987; Kiorpes et al., 1998*). This co-existence of normally responsive and altered cells in amblyopic V1 highlights the importance of considering pairwise interactions in the context of the properties of the cells in each pair, which can reveal subgroups of neurons (and types of visual stimulus information) that are particularly affected.

Implications for behavior

A number of studies suggest that correlated variability between sensory neurons might be especially important for encoding of stimulus information in populations of neurons (*Abbott & Dayan, 1999; Averbeck,*

Latham & Pouget 2006; Cohen & Maunsell 2009; Cohen & Kohn 2011). Furthermore, there is some evidence for a direct link between changes in correlated variability and shifts in psychophysical performance (*Cohen & Maunsell 2009; Beaman & Dragoi 2017, Zohary et al., 1994*). Importantly, it's not just changes in the amount of correlated variability in a given network that matter for stimulus representation, but also specifically which neurons exhibit altered interactions. Here, we found that the increase in correlations between amblyopic and fellow eye stimulation is the highest for pairs of similarly tuned neurons. A common finding of theoretical and experimental studies is that an increase in amount of shared noise between similarly tuned neurons is detrimental for population coding (*Averbeck, Latham & Pouget 2006; Jeanne et al., 2013; Ecker et al., 2011).* Our results thus indicate that stimulus representation is degraded in populations of V1 neurons that process visual stimuli shown to the amblyopic eye, more than would be expected simply from the reduced responses observed in individual neurons.

Our decoding analysis demonstrates that, as expected, stimulus information is harder to read out from V1 population activity when amblyopic eye rather than the fellow, non-amblyopic eye provides the visual information. We found that classification accuracy was consistently reduced when decoding stimulus orientation from neural responses to amblyopic vs fellow eye stimulation. This result is very much in line with the idea that stimulus representation in V1 is impaired for amblyopic eye visual inputs, creating potential for downstream errors in visual information processing. Interestingly, amblyopic observers have global perceptual deficits that are not simply predicted by single neuron changes in V1 (*Kozma & Kiorpes*, 2003). For instance, strabismic amblyopes have impaired performance in contour integration, a task that requires mentally tracing a curve that is embedded in a noisy background (*Kozma & Kiorpes 2003; Levi & Rislove, 2007)*. In this study we found a larger increase in correlations between similarly tuned neurons compared to neurons with dissimilar tuning during amblyopic eye stimulation. It is therefore possible that deficits in contour integration in amblyopia arise from decreased accuracy in coordination of neighboring, similarly oriented pieces of the contour in V1. Overall, our findings indicate that to more conclusively define the neurophysiological correlates of visual deficits in amblyopia, it is important to consider population-level processing of visual information and not just the properties of single neurons.

Theories for the neural basis of amblyopia

Previous work provides evidence for several possible neurophysiological correlates of amblyopic visual deficits. Some well-studied hypotheses for the neural basis of amblyopia include 1) altered responsivity and tuning of single neurons in V1, 2) neural changes in visual areas downstream of V1, 3) reduced cortical representation of the amblyopic eye ("undersampling") and 4) topographical jitter, or disorder in neural map of visual space (*Kiorpes et al., 1998; Kiorpes, 2006 & 2016; Levi, 2013; Wang et al., 2016).* In this study we found that the strength and pattern of functional interactions in pairs of neurons in the primary visual cortex was different when processing of amblyopic eye and fellow eye inputs. We conclude that abnormalities in visual information processing at the level of V1 neuron populations also likely contribute to amblyopic visual deficits. What remains to be explored is whether these changes in coordinated activity contribute to the amblyopic deficit directly, or do so by altering the mechanisms by which downstream areas might read out activity in primary visual cortex.

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