Title: Premature vision drives aberrant development of response properties in primary visual cortex

Abbreviated Title: Premature vision drives aberrant development

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ABSTRACT:

Development of the mammalian visual system is thought to proceed in two stages. In the first stage, before birth in primates and before eye opening in altricial mammals, spontaneous activity generated by the retina and cortex shapes visual brain circuits in an activity-dependent but experience-independent manner. In the second stage, visual activity generated by sensory experience refines receptive fields. Here we investigated the consequences of altering this sequence of events by prematurely opening one or both eyes of ferrets and examining visual receptive fields in monocular cortex after the closure of the critical period for ocular dominance plasticity. We observed that many cells in animals with prematurely-opened eyes exhibited low-pass temporal frequency tuning and increased temporal frequency bandwidths, and these cells showed slightly increased orientation and direction selectivity index values. Spontaneous activity was greatly elevated in both hemispheres following the premature opening of one or both eyes, suggesting a global change in circuit excitability that was not restricted to cells that viewed the world through the prematurely opened eye. No major changes were noted in spatial frequency tuning. These results suggest that premature visual experience alters circuit excitability and visual receptive fields, in particular with respect to temporal processing. We speculate that closed lids in altricial mammals serve to prevent visual experience until circuits are initially established and are ready to be refined by visual experience.

INTRODUCTION

The proper development of visual cortical circuits depends on both experience-independent (Katz and Shatz 1996, Wong 1999) and experience-dependent (Huberman et al 2008, Wang et al., 2010) processes. Classically, these mechanisms have been divided into two sequential stages: an early stage, before the onset of visual experience, in which molecular cues and spontaneous activity in retina and cortex guide initial circuit formation (Katz and Shatz 1996, Wong 1999), followed by a period in which activity driven by visual experience refines circuit function (Huberman et al 2008, Li et al,. 2006, Wang et al., 2010). The sequential nature of these two phases presumably ensures a developmental trajectory in which circuits achieve a state of maturation that provides proper support for the onset of experience-driven mechanisms that finalize the construction process.

Given the sequential nature of visual development, it is interesting to ask if there are any positive or negative consequences of violating this sequence by introducing patterned visual stimulation at earlier time points. Are there significant changes that cannot be reversed even with subsequent visual experience? These questions are especially important to address in light of the rising population of human infants born very prematurely (Crump et al., 2019), who receive visual stimulation during what is typically a presensory period (Colonnese et al. 2010).

To address these questions, we have examined the impact of premature visual experience on receptive fields in visual cortex of the ferret. Ferrets undergo a long postnatal developmental period and have a history of foundational developmental studies in vision. Ferrets are born with their eyes closed – a condition that is maintained for 30-35 days (Issa et al., 1999) – making it possible to introduce inappropriately early visual experience by opening the lids with forceps,

without introducing factors related to immature birth. We opened zero, one, or both eyes early, and evaluated receptive fields in primary visual cortex electrophysiologically after the closure of the critical periods for direction selectivity and ocular dominance. We studied monocular receptive fields only, so that we could be sure of the developmental condition of the eye, necessarily the contralateral eye, that was driving the receptive field properties we observed.

We observed substantial changes in temporal frequency tuning in monocular cells that observed the world through an early-opened eye. These cells, on average, exhibited strikingly broad tuning for temporal frequency with markedly enhanced responses at low temporal frequencies. These major alterations in visual selectivity were not present in all receptive field properties, as orientation and direction tuning in these cells were only slightly altered. By contrast, we observed substantial changes in spontaneous firing rates in both hemispheres after either or both eyes were opened early, suggesting that premature vision has a more global impact on the establishment of a firing rate set point in cortex (Turrigiano and Nelson, 2004; Hengen et al. 2013).

In all, these results suggest that premature visual experience causes lasting changes in temporal processing and in the baseline tone of cortical circuits. The changes in temporal frequency tuning are likely to have an impact on motion perception. To perceive a moving object, an animal must have knowledge of the object's direction and speed. The ratio of the temporal frequency of a stimulus to its spatial frequency is its speed, so temporal frequency tuning provides critical information about stimulus speed. Human babies that are born very prematurely are a heterogenous group with a wide variety of visual deficits (Kozeis 2010, Dutton 2013, Sakki et al., 2018), but even when one excludes cases of known brain or retinal damage,

very premature babies exhibit increased thresholds for motion perception later in life (Taylor et al., 2009, Hou et al., 2011). Our results in ferret raise the possibility that inappropriately early visual experience could be an important factor that contributes to lasting motion processing deficits in humans born very prematurely.

Part of this work appeared as the PhD thesis of SVG (Griswold, 2024).

METHODS

All experimental procedures were approved by the Brandeis University's Institutional Animal Care and Use Committee (IACUC) and performed in compliance with National Institutes of Health guidelines.

Animal source and housing: Ferrets (*Mustelo putorius furo*) were obtained from Marshall Bio-Resources. Litters of 4 or more kits arrived with a jill between postnatal days (P) 12-21. Animals were housed in a room with timed lights (12 h on, 12 h off) in a custom stainless-steel cage (60 cm × 60 cm × 35 cm) with a hammock and small toys. For the entire study, a total of 27 female ferrets were used and all experimental procedures were carried out between postnatal days P55–68. Female ferrets were used because housing mature male ferrets in the same room with mature female ferrets causes stress to the female ferrets.

Facilitating premature visual experience: We divided animals into three experimental groups. The first group of animals had one of their eyes gently opened with forceps at P25, while the other eye was left closed to open naturally, and time of natural eye opening was noted. We used the label early Eye Opening One (henceforth EO1) to indicate neurons in the monocular visual cortex that viewed the world through the eye that was opened early, and early Eye Opening

111 Ipsilateral (henceforth EOIPS) to indicate neurons in the monocular visual cortex that viewed the
112 world through the eye that opened on time. In the second group of animals, both eyes were
113 opened at P25, and neurons from the monocular visual cortex that viewed the world through
114 either of these eyes were labeled early Eye Opening 2 (henceforth EO2). Finally, the third group
115 of animals were two eye controls, and were allowed to open both eyes normally, with time of
116 natural eye opening noted. Ferrets frequently open one eye up to a day before the other, and any
117 disparity in the time of opening between the eyes was noted. Ferret kits are actively kept in their
118 nests by their mothers prior to eye opening, so in order to ensure that animals with early-opened
119 eyes actually had patterned visual experience, animals were brought to the lab for 2 hours a day
120 for 4 consecutive days beginning at P25. These ferret kits were placed in a rat cage atop a
121 heating pad, and gently manipulated to maintain wakefulness during this natural, unguided
122 viewing. We studied 17 animals that had one eye prematurely opened, 4 animals that had both
123 eyes were opened, and 11 control.

124 *Surgical preparation for terminal physiology experiments P55-68*: The ferret was sedated with
125 ketamine (20 mg kg−1 im). Atropine (0.16–0.8 mg kg−1 im) and dexamethasone (0.5 mg kg−1
126 im) were administered to reduce bronchial and salivary secretion and to reduce inflammation,
127 respectively. The animal was next anesthetized with a mixture of isoflurane, oxygen, and nitrous
128 oxide through a mask and a tracheostomy was performed. The animal was then ventilated with
129 1.5–3% isoflurane in a 2:1 mixture of nitrous oxide and oxygen. A cannula was inserted into the
130 intraperitoneal (ip) cavity for delivery of neuromuscular blockers and Ringer solution (3 ml kg−1
131 h−1), and the animal was inserted in a custom stereotaxic frame that did not obstruct vision. All
132 wound margins were infused with bupivacaine. A suture was made in the scalp and the skin
133 resected over the posterior half of the skull. A small opening in the cranium was drilled over V1

134 with a dental drill (Medidenta). The dura covering the brain at the craniotomy site was removed
135 over a 1 mm × 1 mm area to allow for electrode placement. Craniotomies were made over V1 of
136 each hemisphere. The eyelids were sutured open, and contact lenses were placed on the eyes to
137 prevent corneal damage. Before visual stimulation commenced, the ferret was paralyzed with the
138 neuromuscular blocker gallamine triethiodide (10–30 mg kg−1 h−1) through the ip cannula to
139 suppress spontaneous eye movements, and the nitrous oxide oxygen mixture was adjusted to 1:1.
140 The animal's ECG was continuously monitored to ensure adequate anesthesia, and the
141 percentage of isoflurane was increased if the ECG indicated any distress. Body temperature was
142 maintained at 37 °C. At the conclusion of the experiment, the animal was killed with an overdose
143 of sodium pentobarbitol (200 mg/kg, IP) and transcardially perfused to retrieve the brain for
144 histology.

145 *Electrophysiological recordings*: 32 channel electrodes (Plexon S probes, 50um inter-tetrode
146 spacing; 50um intra-tetrode spacing) were used for all recordings. The signal was amplified
147 using the RHD2000 amplifying/ digitizing chip and USB interface board (Intan Technologies).
148 Stimulus timing information was acquired using a Micro1401 acquisition board and Spike2
149 software (Cambridge Electronic Design). Spike sorting was performed off-line using JRClust
150 running in Matlab (Jun et al., 2017). An electrode was inserted into the brain using a Sutter
151 Instruments MP-285 manipulator. To reduce sampling bias, we recorded from any site that had a
152 signal-to- noise ratio sufficient for isolation and had a response that appeared to be modulated by
153 the presentation of drifting gratings. Data are reported from all units that are responsive enough
154 to be included in analysis (see below). After finishing the recording at one site, the electrode was
155 lowered at least 640 microns before attempting to identify a suitable subsequent recording site.

156 The experiment was concluded when successful recordings were made from one or both
157 hemispheres.

158 *Locating Monocular Neurons*: After placing the electrode at a minimum depth of 200 μm in the
159 brain, entering the brain at an angle of 30-45 degrees, the search for monocular neurons
160 commenced. The electrode was driven into the brain until monocular neurons were discovered.
161 A population of neurons was deemed monocular if their receptive fields were in the periphery of
162 the eye contralateral to the recording hemisphere. Monocularity was ensured by determining
163 whether movement in the central visual and ipsilateral visual fields evoked a response; any such
164 responses indicated binocularity. If no purely monocular cells were found in a given penetration,
165 the electrode was removed and placed and another penetration was made elsewhere in the brain.

166 *Locating the Optic Disk*: An indirect ophthalmoscope (Heine Omega 600) and handheld 78 or
167 90D lens (Volk) were used to locate the optic disk and determine the orientation of the eye. This
168 was necessary as the orientation of the eye is necessary for determining the true eccentricity of
169 receptive fields. When one investigator had the optic disk in the center of view of the indirect
170 ophthalmoscope, another investigator introduced a wooden rod into the line of sight and moved
171 it until the end of the rod was centered on the image of the optic disk (also the center of view).
172 The position of the end of the rod was then measured in X, Y, and Z relative to the animal's eye
173 to make the optic disk direction.

174 *Visual Stimuli*: Visual stimuli were created in MATLAB (MathWorks) using the Psychophysics
175 Toolbox (Brainard 1997, Pelli 1997) and displayed on a 21-inch flat face CRT monitor (GDM-
176 520, Sony) with a resolution of 800 × 600 and a refresh rate of 100 Hz. We manually mapped
177 receptive fields by displaying circular patches of drifting sinusoidal gratings at different positions

178 and moving the monitor to accommodate different eccentricities while listening to the responses
179 on a loudspeaker.

180 Drifting grating stimuli were full-field, drifting sinusoidal gratings (4 s duration; 3.5 s
181 interstimulus interval) presented pseudorandomly, with direction of motion (in steps of 45°) in
182 either of the two directions orthogonal to the axis of orientation. We ran two sets of stimuli
183 where multiple grating parameters were covaried in order to sample a wide variety of receptive
184 field properties in our multi-neuron recordings. In the first set, orientation (angles 0°/horizontal,
185 45°, 90°/vertical, 135°) was co-varied with stimuli consisting of drifting sinusoidal gratings at 8
186 different spatial frequencies (0.04, 0.08, 0.16, 0.24, 0.32, 0.64, 0.90, and 1.25), and 6 different
187 contrasts (0.04, 0.08, 0.16, 0.32, 0.64, and 1), while temporal frequency was held constant at 4
188 Hz. In this first set of stimuli, gratings drifted back and forth every 4 cycles; for example,
189 horizontal stimuli drifted upward and then downward. In a second set of stimuli, direction (0°/up,
190 45°, 90°/right, 135°, 180°/down, 225°, 270°/left, 315°) was co-varied with stimuli of 7 different
191 temporal frequencies (0.5, 1, 2, 4, 8, 16, and 32 Hz) at 100% contrast at 100% contrast and a
192 fixed spatial frequency of 0.1 cycles/° visual angle, In this second set of stimuli, gratings drifted
193 in a single direction and did not move back and forth. Each stimulus set had a blank, control
194 stimulus that was the same duration as the other stimuli where the screen did not change. The
195 first set of stimuli was repeated 5 times, and the second set 7 times.

196 *Data analysis*: Responses were determined by examining either the mean response during the
197 entire stimulus or by taking the F1 component of the response. The same analysis (mean, or F1 at
198 the temporal frequency of the stimulus of interest) was performed for the closest blank (control)
199 stimulus and the response to the control stimulus was subtracted to yield the stimulus-driven

response. For each tuning curve for orientation, direction, and spatial frequency analyses, we examined whether the mean or the F1 response was higher, and used those responses for analysis and fits. For temporal frequency analysis, we only used mean responses because we found a profound response suppression in many cells.

Orientation selectivity was examined in the first set of stimuli at the preferred spatial frequency for each cell. Circular variance was calculated in orientation space (Ringach et al., 2002, Mazurek et al., 2014) with the equation V = 1 - |R |, where R is the resultant calculated as:

$$R = \frac{\sum_k r_k e^{i2\theta_k}}{\sum_k r_k}$$

Where rk was the mean spike rate in response to a grating drifting with angle θk.

Tuning curves from cells that showed significant variation across orientation stimuli and blank (ANOVA test, (Mazurek et al., 2014)) were fit with a double gaussian to obtain the angle preference.

Direction selectivity was examined in the second set of stimuli for the preferred temporal frequency of each cell (unless noted). Circular variance was calculated in direction space with the following equation:

$$1 - DirCirVar = \left| \frac{\sum_k R(\theta_k) \exp(i\theta_k)}{\sum_k R(\theta_k)} \right|$$

Preferred spatial frequency was determined by responses to the first stimulus battery at the preferred orientation at 100% contrast. Preferred temporal frequency was determined by responses to the second stimulus battery at the preferred direction. Each was fitted with a model due to Movshon et al. 2005: $R(f) = k * \exp\left(-\left(\frac{f}{fc}\right)^2\right)/[1 + (\frac{fh}{f})^{\beta}]$.

Low frequency cut-offs were determined by following the fit from its peak to lower frequencies until the first frequency where the response dropped to half its maximum; high frequency cut-offs were determined by the same procedure, except that the fit was followed from the peak towards higher frequencies (Moore et al. 2005, Heimel et al., 2005). If the response never dropped below half its maximum, then the low frequency cut off was said to be 0 or the high frequency cut off was said to be infinity. Temporal frequency tuning bandwidth was defined as log2(H50/L50).

Contrast responses were fit with Naka-Rushton functions as described in (Peirce 2007) and sensitivity determined by the reciprocal of the contrast for which the response exceeds 5 standard deviations of the response to a blank screen. The Naka-Rushton function is defined as:

$$R = R_{max} \frac{c^n}{c^n_{50} + c^n} + B$$

232 Where Rmax is the maximum response of the neuron, c50 is the contrast at which the
233 response is halfway between baseline and maximum, c is the contrast of the stimulus presented
234 to the neuron, and B is the baseline response of the neuron. n is a factor simply referred to as the
235 exponent.

236 *Statistics*: Index values were examined with linear mixed effects models in Matlab (function:
237 fitlme), where treatment condition (control, EO1, EO2, EOIPS) were fixed effects and animal
238 identities were random effects.

239 *Immunohistochemistry*: Upon completion of experiments, an electrode coated in the fluorescent
240 dye DiI (DiCarlo et al., 1996) was inserted at the location and depth and left in place for 20
241 minutes. Animals were then transcardially perfused and the brain was placed in 4%
242 paraformaldehyde in 0.1M PBS at 4°C for 24 hours and then moved to 10% sucrose in PBS for
243 24-48 h. This was followed by placement in 30% sucrose in PBS at 4°C until sectioning. The
244 brain was sectioned sagittally into 100 µm sections using a sliding microtome (Leica SM2010R).
245 We washed sections in 0.1M PBS 3×5 min and permeabilized in 0.3% Triton-X 100 diluted in
246 PBS for 2 hours at room temperature on a shaker. Then slices were incubated in fluorophore-
247 conjugated anti-NeuN antibody (Alexa Fluor 488 Rabbit anti NeuN, Millipore ABN78A4) at a
248 1:300 dilution overnight (>12 hours) at room temperature on a shaker. Sections were then
249 washed 3×5 min in PBS and mounted on slides and allowed to air dry. Slides were then cover-
250 slipped with Fluoromount-G media (Electron Microscopy Sciences, Ft. Washington, PA) and
251 edges were sealed using nail polish. Histological sections were viewed using a fluorescent
252 microscope (Keyence BX-Z 710) and electrode tracks were reconstructed using DiI dye traces.

253 **RESULTS**

254 Our primary goal was to explore the influence of premature vision on the parameters of
255 receptive fields in V1. We reared ferrets under three conditions in order to examine the impact of
256 premature vision through one or both eyes in comparison with controls (**Figure 1**): in one group,
257 we opened one eye early; in a second group, we opened both eyes early; and a third, control
258 group were allowed to open their eyes naturally. Animals in both of the premature eye opening
259 groups experienced early vision beginning on postnatal day 25, a developmental timepoint when
260 retinal waves are still occurring (Meister et al., 1991, Wong et al., 1993), yet V1 is also
261 responsive to visual input through the closed lids (Krug et al., 2001, Akerman et al., 2002). This
262 ensured interaction between spontaneous, endogenously generated activity and patterned visual
263 input. We hypothesized that this interaction may drive aberrant development of cortical receptive
264 fields, as it is known that visual input is capable of initiating retinal waves through the closed lids
265 (Tiriac et al., 2018). Following premature eye opening, animals were brought to the lab for 2
266 hours a day of unguided visual exposure over 4 days, for a total of 8 hours of visual exposure.
267 Visual exposure consisted of gentle handling to prevent the young kits from sleeping thus
268 ensuring a sufficient amount of visual experience through the prematurely opened eye(s).
269 Animals received no other intervention between the end of visual stimulus training on P28 and
270 terminal electrophysiology experiments which occurred between P55-68.

271 We made multichannel recordings at a developmental timepoint when past studies have
272 shown that V1 receptive fields are largely mature. By postnatal day 42, contrast sensitivity (Li et
273 al., 2006), orientation (Chapman and Stryker 1993), direction, temporal frequency, and spatial
274 frequency (Li et al., 2006) tuning have reached adult-like levels and ocular dominance plasticity
275 is greatly reduced (Issa 1999). Thus, if premature vision causes permanent changes to receptive
276 field properties, we ought to be able to see them at P55-68.

We recorded responses to long batteries of visual stimulation with sinusoidal gratings where multiple parameters were co-varied in order to assess a wide variety of possible receptive field differences between control animals and animals that had their eyes opened prematurely. In this study, all recordings were performed in the monocular visual cortex in order to simplify the interpretation of these changes without needing to consider interactions between the two eyes. We labeled cells as E01 (monocular neurons contralateral to a single early-opened eye), EOIPS (monocular neurons ipsilateral to a single early-opened eye), E02 (monocular neurons contralateral to an early opened eye where both eyes were opened early), and control (monocular neurons in control animals). E01 and E02 cells observed the world through early-opened eyes, while EOIPS neurons observed the world through eyes that opened on time but were ipsilateral to early-opened eyes.

Orientation and direction tuning index values are slightly increased by premature experience

Cells in all animals exhibited some degree of orientation and direction selectivity. Orientation selectivity was assessed for stimuli that moved back and forth in two opposite directions at each cell's preferred spatial frequency. Direction selectivity was assessed at the neuron's optimal temporal frequency and a spatial frequency of 0.1. Example responses for each group are shown in Fig. 2A-H. Control animals exhibited a baseline average orientation index value (1-CV) of 0.42, and this value was not significantly elevated in EOIPS neurons (0.45, $p<0.54$, Linear Mixed Effects Model). However, orientation selectivity was slightly elevated in E01 neurons (0.52, $p<0.024$) and E02 neurons (0.54, $p<0.016$, LMEM). Direction selectivity as assessed by 1-DCV was slightly reduced in EOIPS neurons (0.24, $p<0.027$, LMEM) as

compared to control values (0.29), and 1-DCV values were not significantly different in E01 neurons (0.29, $p < 0.296$) or E02 neurons (0.33, $p<0.169$, LMEM) . The overall distribution of direction preferences in 45° bins did not significantly differ across the groups (chi-square test, p = 0.11), nor did the distribution of orientation angle preferences in 45° bins (chi-square test, 5.3 x 10-2). Therefore, we observed only minor long-term changes in orientation and direction tuning between animals with premature vision and control animals.

Temporal frequency tuning is aberrant in animals with premature visual experience

We were struck by the unusual temporal frequency tuning curves that we observed in animals whose eyes were opened prematurely. Many EO1 cells exhibited strong responses at the lowest temporal frequency tested (Fig. 3A), and we observed a trend for this in EO2 cells as well (Fig. 3B). Further, several cells also showed evidence of a suppression of the response below baseline. Tuning curves from E0IPS cells (Fig. 3C) superficially looked more like curves from control animals (Fig. 3D), although quantitative analyses uncovered small differences. Most cell types exhibited similar peak temporal frequency values (Fig. 3E), except that EOIPS cells exhibited slightly higher temporal frequency preferences ($p<0.021$, LMEM). To quantify the response to the lowest temporal frequency tested, we calculated a low pass index, defined as the ratio of the response to the lowest temporal frequency tested to the largest temporal frequency response observed (Fig. 3F). Temporal frequency low pass index values of control cells were 0.20 on average, while EO1 cells showed low pass index values that averaged 0.35 ($p< 0.039$, LMEM) and EO2 cells showed empirically elevated values of 0.33 that were not significantly different from control ($p< 0.142$, LMEM). High pass index values, determined by calculating the

320 response at the highest temporal frequency tested divided by the maximum response, did not
321 differ across these animals (Fig. 3G).

322 In order to assess tuning bandwidth, we calculated low- and high-frequency cut off values
323 by identifying the low and high frequency values where the response dropped below half the
324 maximum response value. If this never occurred, the cell was considered to be low-pass (if this
325 never occurred on the low frequency side) or high-pass (if this never occurred on the high
326 frequency side). We then calculated the bandwidth between this low and high value in octaves. If
327 a cell was low-pass or high-pass or both, the cell was said to have infinite bandwidth. In Fig. 3H,
328 we show bandwidth computed from rectified responses, and saw a empirically elevated
329 bandwidths in E01 cells (2.33 octaves, $p< 0.07$) and E02 cells (2.33 octaves, $p<0.08$) compared
330 to control cells (1.95 octaves) or EOIPS cells (1.91 octaves, $p<.937$). Many cells exhibited
331 suppression, where the response fell below the response to a control stimulus, and we took the
332 absolute value of the response in calculating the absolute bandwidth so that both positive and
333 negative responses were considered. The median absolute bandwidth (Fig. 3I) of control cells
334 (4.1 octaves) was narrower than any of the cells in animals whose eyes were opened early,
335 including EOIPS cells (4.7 octaves, $p<0.0013$), EO1 cells (4.8 octaves, $p<0.002$), and EO2 cells
336 (5.1 octaves, $p<0.00015$, LMEM).

337 **Spatial frequency tuning is relatively unaffected by premature visual experience**

338 Spatial frequency tuning was hardly influenced by early eye opening. We assessed spatial
339 frequency at a cell's preferred orientation, as determined by responses to drifting gratings that
340 moved back and forth in opposite directions. Example tuning curves are shown in Fig 4A-D.

In linear mixed effect modeling, no significant differences were observed in peak spatial frequency preferences across these groups (control: 0.031 cpd; EOIPS: 0.045 cpd, $p<0.19$; EO1: 0.031 cpd, $p<0.949$; EO2: 0.042 cpd, $p<0.362$, LMEM). Similarly, median spatial frequency low pass index values were very similar, with a slightly significant change noted for EOIPS animals (control: 0.86; EOIPS: 0.76, $p<0.0499$; EO1: 0.85, $p<0.928$; EO2: 0.79, $p<0.390$, LMEM). We observed slightly higher spatial frequency high pass index values in EO2 cells, but effects were modest: (control: 0.02; EOIPS: 0.02, $p<0.857$; EO1: 0.04, $p<0.090$; EO2: 0.06, $p<0.0323$, LMEM).

We observed no significant effects with respect to spatial frequency bandwidth, either when measured with responses that were greater than 0 or measuring the absolute response (that is, interpreting responses below baseline as positive responses). Bandwidths of individual cells were often infinite, given the large preponderance of low-pass cells, and so we analyzed the data in rank order instead of the raw values. Median values for both positive-only responses and absolute responses were always above the ranks of cells with finite bandwidths, indicating that the typical cell in all groups had infinite bandwidth. Differences from control were not significant for positive-only responses (EOIPS: $p<0.310$, EO1: 0.622, EO2: $p<0.898$, LMEM) or absolute responses (EOIPS: $p<0.06$, EO1: $p<0.597$, EO2: $p<0.385$, LMEM).

In short, we found very little evidence of substantial changes to spatial frequency tuning in these monocularly-driven cells.

Spontaneous firing rates and response suppression are increased in animals that have had premature visual experience

362 Hebbian and homeostatic mechanisms are active early in development (Turrigiano and
363 Nelson, 2004), and may be critical for setting response gains and the background excitability of
364 neural circuits (Roy et al., 2018; Roy et al. 2020a). To examine whether response gains or
365 excitability were impacted by premature vision, we quantified maximum firing rates in response
366 to visual stimuli, response suppression, and background firing rates.

367 The peak mean responses of neurons to visual stimuli (Fig. 5A) did not differ among the
368 experimental groups. Control neurons exhibited average peak responses of 7.0 Hz; EOIPS
369 neurons did not differ significantly (6.4 Hz, $P<0.600$), nor did EO1 neurons (10.1 Hz, $p<0.518$)
370 or EO2 neurons (10.5 Hz, $p<0.295$).

371 In contrast to peak responses, response suppression below background levels was
372 pronounced in animals with prematurely opened eyes (Fig. 5B). We calculated all responses by
373 subtracting the background rate measured during control stimuli (gray screen), and took response
374 suppression for each cell to be the maximum amount of suppression below background rates for
375 the average response to any visual stimulus. Suppression was rarely observed in control cells
376 (average: 2.1 Hz), but was substantially elevated in EOIPS cells (7.0 Hz, $p<1.59e-9$) and slightly
377 elevated in EO1 cells (3.4 Hz, $p<0.022$) and EO2 cells (2.8 Hz, $p<0.035$).

378 Finally, background firing rates were significantly higher in animals whose eyes were
379 opened early (Fig. 5C). Spontaneous firing rates were low in control animals (2.6 Hz), and were
380 markedly increased in EOIPS hemispheres (11.1 Hz, $p<1.09e-4$), EO1 hemispheres (6.6 Hz,
381 $p<0.0132$) and EO2 hemispheres (6.6 Hz, $p<0.0248$). Therefore, early opening produced a long-
382 lasting effect on spontaneous firing rates after the critical period.

In all, early eye opening induced changes in response suppression and background firing rates that were still evident at the time of our measurements several weeks later. We observed these changes in both hemispheres, which indicates that the differences in direct visual drive to visual receptive fields are not underlying these differences but instead are the result of some more global process. These results are consistent with the idea that early eye opening induces long-term changes to circuit-level excitability that are not corrected during the remainder of development.

DISCUSSION

We explored the impact of premature vision on the development of a number of V1 RF properties in ferret. We found small increases in direction and orientation tuning in cells that viewed the world through prematurely-opened eyes. We observed profound changes in temporal frequency tuning: cells recorded from animals that had their eyes opened prematurely exhibited more low-pass temporal frequency tuning curves and broader temporal frequency bandwidths compared to controls. Spatial frequency preferences were not substantially altered. Finally, cells in either hemisphere in animals with prematurely-opened eyes had higher spontaneous firing rates and exhibited marked suppression below this spontaneous firing rate in response to some visual stimuli.

A novel temporal frequency tuning deficit with possible implications for motion processing

We found that ferrets with premature visual experience exhibited a pronounced broadening of temporal frequency tuning curves and increases in the fraction of low- pass neurons. The alterations in temporal frequency tuning identified in ferrets following premature

404 eye opening are strongly suggestive of a deficit in motion processing. The broadening of
405 temporal frequency tuning curves and increase in the proportion of low pass cells in V1 could
406 translate to a decrease in the animal's ability to distinguish the temporal frequency (and perhaps
407 the speed) of a moving visual stimulus.

408 Altered rearing has been shown to influence the subsequent development of motion
409 processing in various ways. Dark-reared cats and ferrets exhibit poor direction selectivity (Imbert
410 and Buisseret 1975, Li et al., 2006), but dark-reared ferrets do not show strong deficits in
411 temporal frequency processing. Overall responses after dark-rearing are reduced, but temporal
412 frequency tuning is only slightly narrowed (Li et al., 2006). Cats raised in a strobe-light
413 environment (mostly after eye opening) exhibited strong changes in subsequent direction
414 selectivity (Kennedy and Orban 1983, Humphrey and Saul 1998), but temporal frequency tuning
415 of these animals has not been reported in detail. Kennedy and Orban (1983) report a reduction in
416 high-pass velocity-tuned cells, but not an increase in low-pass cells; Humphrey and Saul (1998)
417 do not report temporal frequency tuning across their population but their example cell does
418 appear to be broadly tuned and low-pass. Temporal frequency tuning is not subject to rapid
419 modification shortly after eye opening, as Ritter and colleagues demonstrated that providing
420 ferrets that had just opened their eyes naturally with 6-9 hours of visual stimulation of a single
421 TF did not elicit a shift in TF tuning (Ritter et al., 2017). The same stimulation causes a dramatic
422 increase in direction selectivity (Ritter et al., 2017) that normally develops in the first week to 10
423 days after eye opening and requires visual experience (Li et al., 2006, Li et al., 2008, Van Hooser
424 et al., 2012). The only manipulation we know of in the literature that has been shown to modify
425 temporal frequency properties of developing animals is prey capture: mice that learned to hunt

426 crickets in the critical period for ocular dominance plasticity exhibit lower low-pass index values
427 (Bissen et al. 2025).

428 In sum, the deficits in temporal frequency tuning we observed are unlike those reported
429 previously. Premature vision produces permanent alteration of temporal frequency tuning curves,
430 while dark-rearing does not and comparable results from strobe rearing are not available.

431 **Mechanisms underlying altered receptive fields**

432 One way that premature patterned vision could alter the development of the brain is by
433 altering the character of retinal waves. Low resolution visual input before natural eye opening is
434 capable of driving activity in the visual circuit (Huttenlocher 1967, Chapman and Stryker 1993,
435 Krug et al., 2001, Akerman et al., 2002, Akerman et al., 2004), and evidence shows that this
436 early form of low resolution visual experience plays a role in the development of ON-OFF
437 segregation in dLGN (Akerman et al., 2002) and the initiation of retinal waves (Tiriac et al.,
438 2018). Propagation of high luminance, high contrast, and high spatial frequency input through
439 the developing retina may alter or disrupt the typical retinal wave formation and propagation,
440 and thus may have deleterious effects on developmental processes driven by endogenous
441 activity. Alternatively, high contrast signals may not interrupt retinal waves but may contribute
442 independent activity that, through experience-dependent plasticity mechanisms, produces the
443 alterations in receptive field properties that we observed.

444 Several other basic mechanistic questions remain unanswered. It is unclear where in the
445 visual circuit cascade these deficits first arise. Does the lateral geniculate nucleus or retina
446 exhibit altered temporal frequency tuning? Is the influence of the patterned visual stimulation

447 instructive, so that if one provided premature stimulation with only certain temporal frequencies,
448 one would see selectivity for those temporal frequencies, or would tuning always be broad?
449 Future studies will be needed to address these questions.

450 The broad tuning in temporal frequency and elevated spontaneous firing rates that we
451 observed could reflect a deficit in cortical inhibition in animals that experienced premature
452 vision. Yet selectivity was not entirely destroyed, as neurons still exhibited selectivity for
453 orientation and direction. Selectivity can be achieved with a combination of amplification of
454 appropriate excitatory signals and inhibitory suppression that is either selective or broad (Ben-
455 Yishai et al., 1995, Rubin et al., 2015, Somers et al., 1995, Troyer et al., 1998), so it is unclear
456 how the circuit has changed. The amount and timing of inhibition, whether feed-forward or
457 feedback, could be altered.

458 **Alterations in ipsilateral receptive fields**

459 One of our most surprising findings was a difference in the receptive fields and firing
460 properties of cells that were ipsilateral to the early opened eye. It is straightforward to imagine
461 how Hebbian mechanisms might influence monocular cells that are contralateral to the early-
462 opened eye, but one would have to imagine different and possibly more global mechanisms to
463 explain changes in monocular cells that view the world through the eye that opened naturally.

464 Homeostatic mechanisms such as synaptic scaling (Desai et al., 2008, Turrigiano et al.,
465 1998), and regulation of intrinsic excitability (Desai et al., 1998, Lambo and Turrigiano, 2013)
466 operate during the critical period for ocular dominance plasticity and serve to keep ongoing
467 firing rates within a cell-defined range (Hengen et al., 2013, Hengen et al., 2016). It is possible

468 that these homeostatic mechanisms are not yet operating in the presensory period, and that the
469 extra activity causes an increase in excitatory forces (whether synaptic or intrinsic) relative to
470 inhibitory forces.

471 Alternatively, opening a single eye early may still influence feed-forward activity in the
472 ipsilateral hemisphere. Work in ferrets and rats suggests a role for retinal waves in the
473 development of interhemispheric connectivity; bilateral enucleation of ferrets induces anomalies
474 in the distribution of callosal cells in primary visual cortex (Bock et al., 2012), and results in
475 callosal projections connecting topographically mismatched loci in VC in P4-6 rats (Olavarria
476 and Hiroi 2003). Further, retinal waves demonstrate coordinated activity between both
477 hemispheres in mice and ferrets (Weliky and Katz 1999, Ackman et al., 2012). Recent findings
478 describe a transient retina to retina connection in mice and ferret, which exists during the period
479 of retinal waves (Murcia-Belmonte et al., 2019). This connection provides a plausible
480 mechanism for the theorized inter- retinal coordination of waves thought to be necessary to drive
481 development of bilateral topographic maps (Adams and Horton 2003, Murcia-Belmonte et al.,
482 2019). Given that light is capable of initiating retinal waves (Tiriac et al., 2018), it is feasible that
483 exposure to light through a single, prematurely opened eye would initiate retinal waves capable
484 of propagating to the closed eye. Given the qualitative differences between vision through a
485 closed lid vs open eye, initiation and propagation of retinal waves would be both asymmetric and
486 mutually influential between retinas, potentially accounting for the differences in RFs observed
487 between EOIPS and control hemispheres.

488 **Comparison with prior studies**

There have been only a few animal studies that have sought to introduce inappropriately early vision. Lichliter and colleagues (2018) prematurely opened the shells of bobwhite quail eggs and provided visual experience to the chick, and found a subsequent loss of visual selectivity to bobwhite hens vs. hens of another species (Sleigh and Lickliter 1995). Further, they demonstrated multi-modal impacts on auditory processing after premature visual experience, in that animals failed to eventually become responsive to cross-species hen calls. In behavioral studies of rats whose eyes were prematurely opened 7 days early, investigators found that opening a single eye (but not opening both eyes early) caused a deficit in pivoting locomotor reactions on the side of the early-opened eye; that is, rats pivoted more frequently towards stimuli viewed through the eye that opened on time (Foreman and Altaha 1991). To our knowledge, the present work is the first to study cortical receptive fields after premature sensory experience. All of these studies, including our own, have noted deficits after premature experience.

Premature vision as a risk factor for visual disfunction

Very premature human babies exhibit a variety of visual deficits later in life that are not explained by the condition of the eye, broadly termed Cortical/Cerebral Visual Impairment (CVI) (Kozeis 2010, Dutton 2013, Sakki et al., 2018). These very premature babies are a heterogenous population. Some of these infants have suffered clear brain injuries (Slidsborg et al., 2012, Dutton 2013) of varies types, such as hypoxia, brain bleeding, or periventricular leukomalacia (Gallo and Lennerstrand 1991, Hokken and Krabbendam 2023, Kozeis 2010), and these injuries clearly have a direct impact on subsequent visual deficits that go beyond any influence of early experience. But, studies that have excluded individuals with known brain

damage or retinal problems (or analyzed these populations separately) have also found that extreme prematurity itself has an impact on later vision, particularly on motion perception (Atkinson and Braddick, 2007, Benassi et al., 2018, Guzzetta et al., 2009, Hou et al., 2011, MacKay et al., 2005) and sometimes lowered visual acuity (Jain et al. 2022). Previous investigators have speculated that inappropriately early visual stimulation may contribute to these deficits, as in Taylor et al (2009): "Why the dorsal stream should be particularly vulnerable in this population is not completely understood. One possibility is that the unusually early visual stimulation that very premature infants are exposed to may, in itself, have a differential effect on the functional development of the dorsal and ventral streams". Our data are consistent with the idea that inappropriately early visual stimulation contributes to deficits in motion processing. A moving object has both a speed and direction, and temporal frequency is critical to determine an object's speed. The major temporal frequency tuning deficits we have observed in receptive fields are consistent with a motion deficit.

Premature vision as a cause of visual plasticity

Regardless of whether premature patterned vision has a clinically relevant role for human vision, the experiments here demonstrate clearly that premature patterned vision has a long-lasting impact on the development of receptive fields in the visual cortex. The results suggest that the evolved late eye opening of many rodents and carnivores, and the prolonged prenatal period of primates, may help to protect the visual system from exposure to high luminance, high contrast, and high spatial frequency stimulation until the visual system is ready for this type of stimulation. This shielding of the developing visual system is not found in all vertebrates, as tadpoles and zebrafish have transparent eyelids that permit patterned vision from very early

533 stages (Avitan et al., 2017, Demas et al., 2012). By altering premature patterned vision, it may be
534 possible to uncover the plasticity rules that are at play in the developing mammalian visual
535 system before the natural onset of vision.

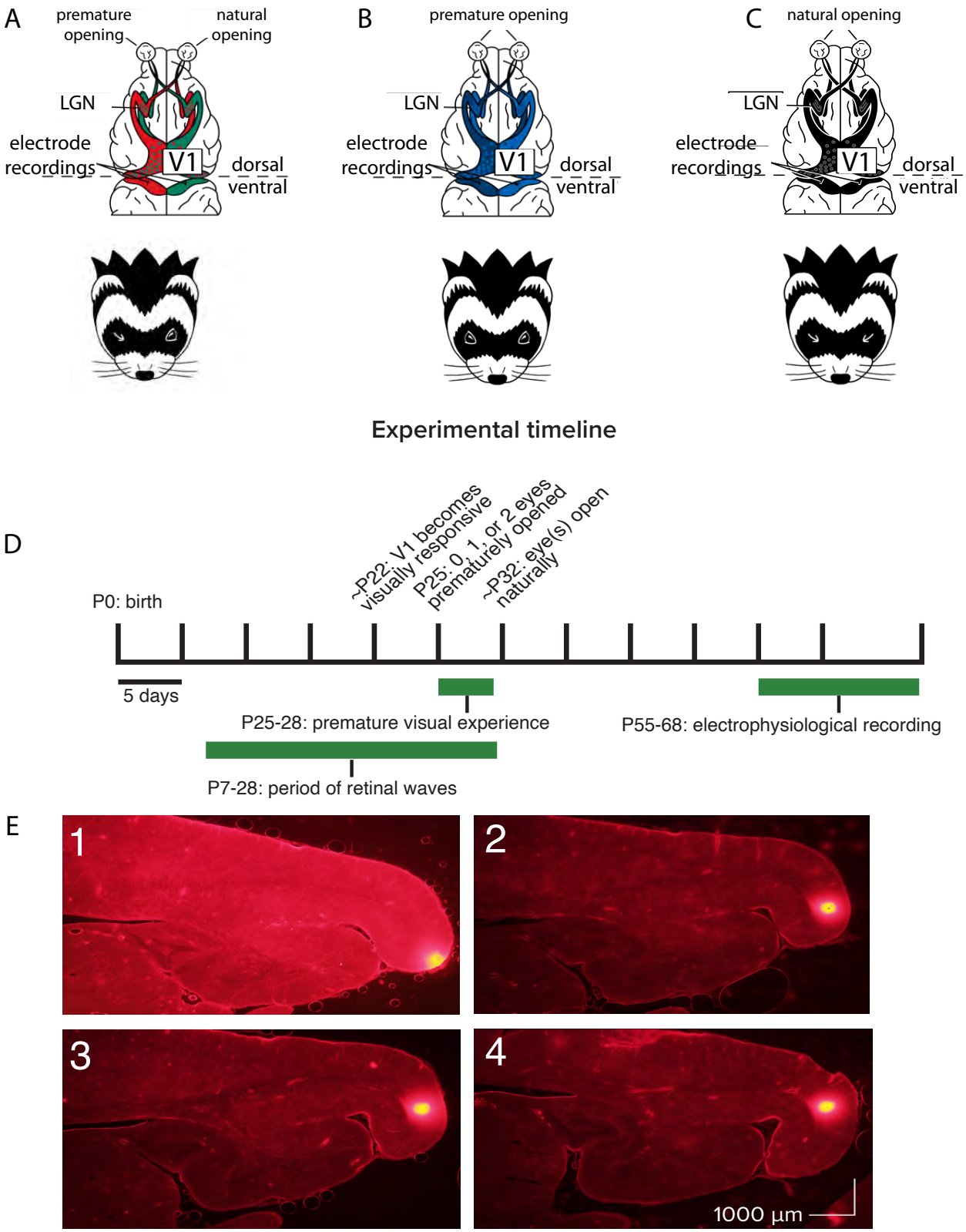


Figure 1: Recording schematics, experimental timeline, and electrode tract reconstructions.

538 A: Recording schematics: EO1 cells were those recorded in monocular cortex contralateral to a
539 single prematurely-opened eye. EOIPS cells were those recorded in monocular cortex ipsilateral
540 to a single prematurely-opened eye. B: EO2 cells were those recorded in monocular cortex after
541 both eyes were opened prematurely. C: Control cells were those recorded in monocular cortex
542 after both eyes were allowed to open naturally. D: Experimental timeline. Animals that
543 experienced premature vision had one eye or both eyes opened on P25. All animals experienced a
544 period outside of the nest in the form of daily 2 hour handling sessions beginning on P25 and
545 ending on P28, allowing unguided viewing of the laboratory environment through prematurely
546 opened eyes or low resolution experience through closed lids. Electrophysiological recording took
547 place between P55-68, at a time when the critical period for ocular dominance was closing or
548 closed (Issa et al. 1999). E: Electrode track reconstructions showing penetrations along the
549 posterior cortical surface, in monocular V1 (Law et al., 1988; White et al. 1999). Following
550 recording, the recording electrode was removed and replaced with a marking electrode coated in
551 DiI.

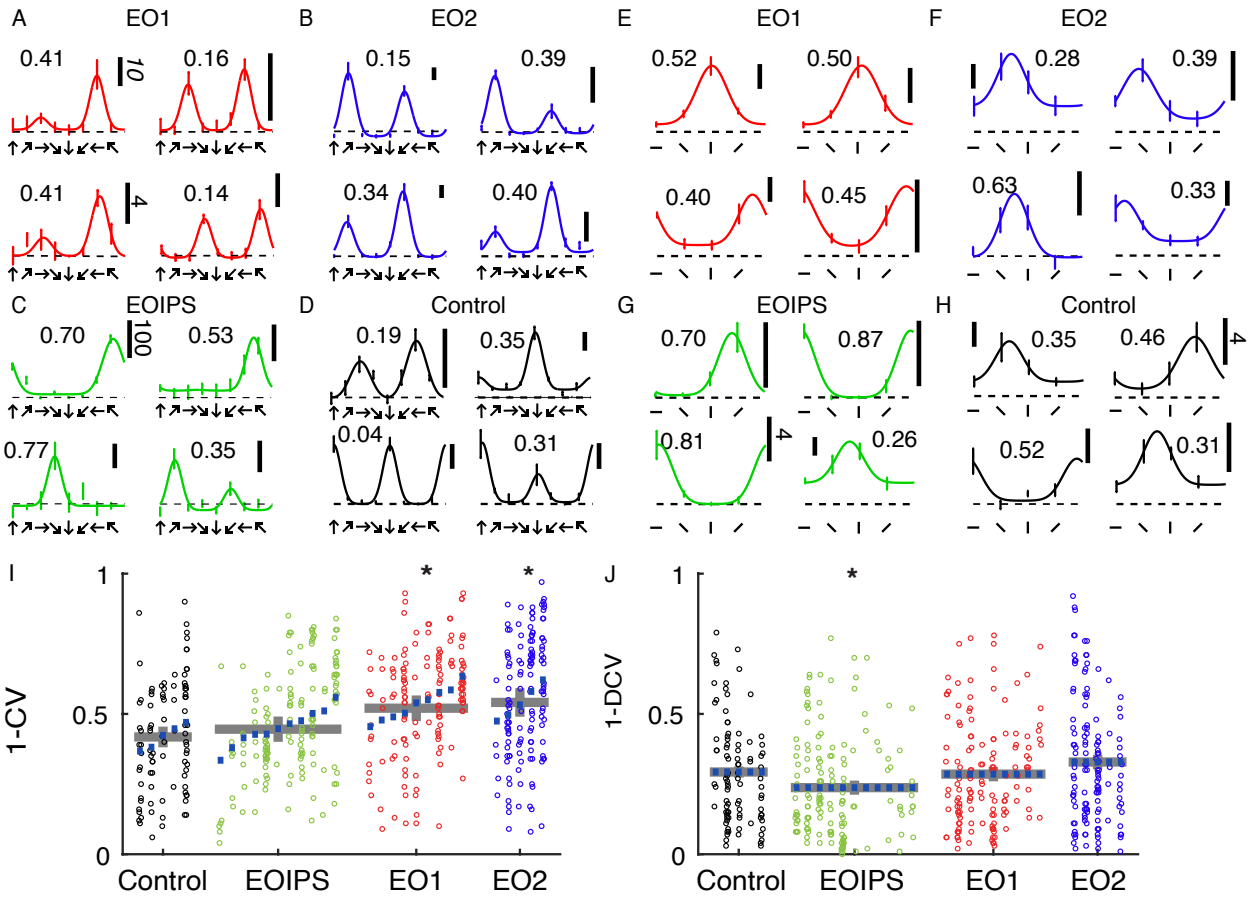
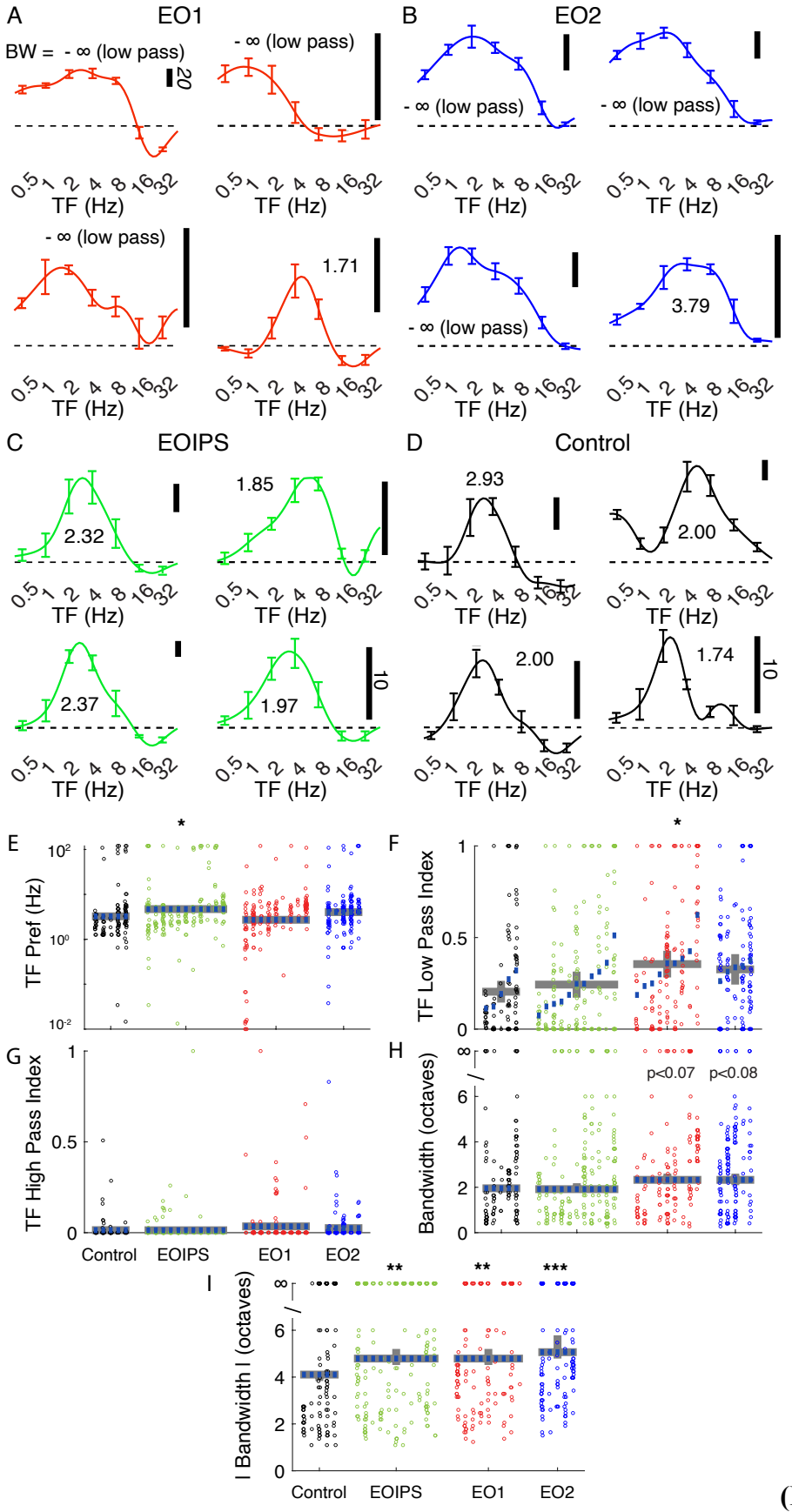


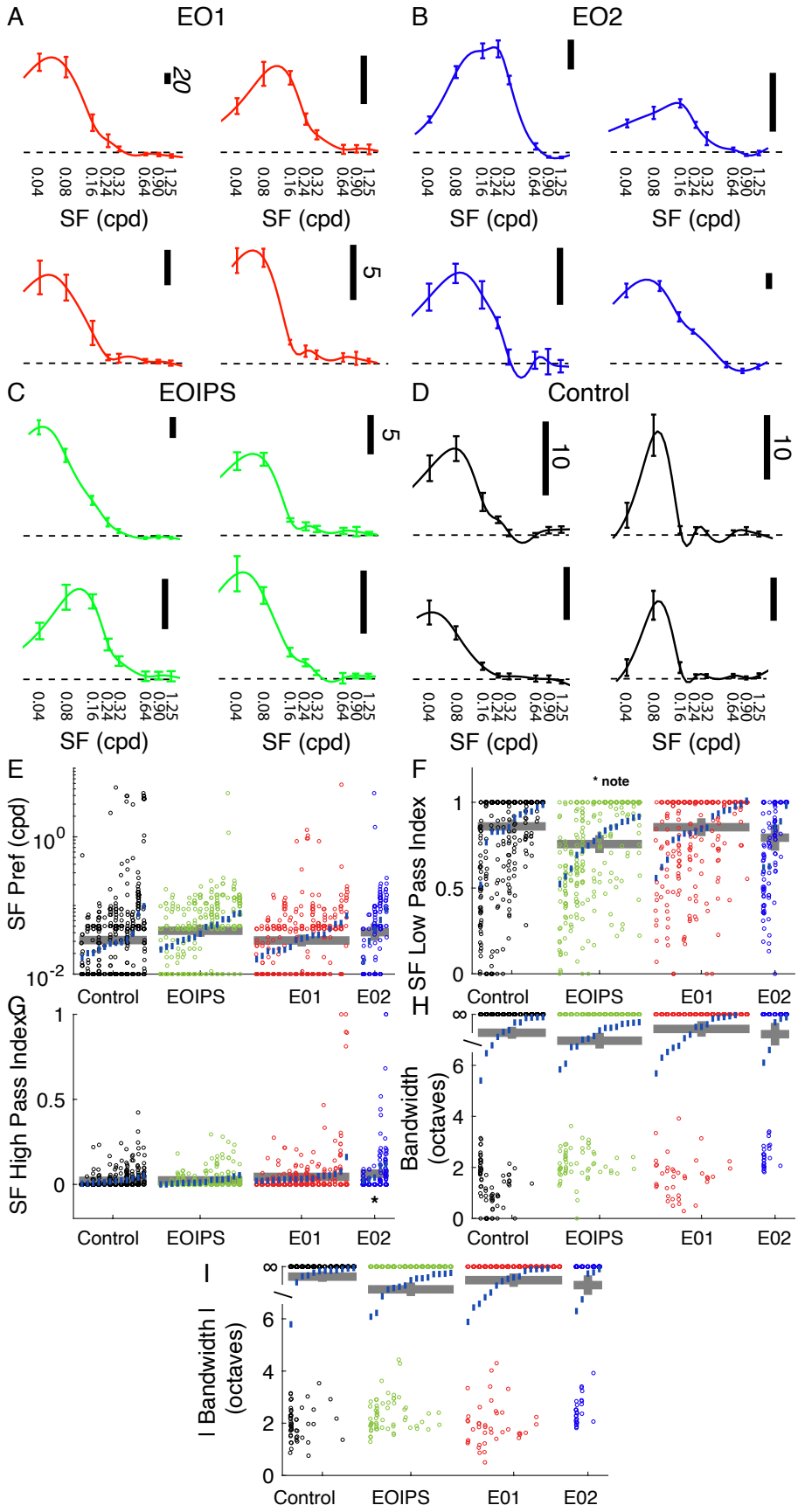
Figure 2: Early eye opening produced only minor changes in orientation and direction selectivity index values: A: Example direction tuning curves of individual EO1 cells measured after the close of the critical period. Direction tuning curves are shown for stimulation at the optimal temporal frequency. Direction tuning curves look coarsely normal. Horizontal scale bar represents 10 spikes per second unless otherwise indicated. Dashed line shows mean response to blank / control stimuli. Number indicates 1-DCV value. B: Same, for EO2 cells C: Same, for EOIPS cells: D: Same, for control cells E: Orientation tuning curves of individual EO1 cells, measured in different epochs and in some different animals than the direction tuning curves. Temporal frequency was 2 Hz, and the spatial frequency optimal for each cell. Numbers indicate orientation selectivity index values 1-CV. F: EO2 cells G: EOIPS cells H: control cells I: Results of a linear mixed effects analysis of orientation selectivity index values (1-CV) for all cells and

conditions in the study. Each small column shows the cells for an individual animal. Purple lines indicate random effect values for each animal. Gray lines indicate condition means and standard errors of the mean from the linear mixed effect model. Animals within a group have been sorted by mean index value. Condition coefficients that differ significantly from 0 are indicated with * ($p<0.05$). See text for P values. J: Same for direction selectivity index values, as assessed by (1-DCV). E01 and E02 cells exhibited slightly higher orientation selectivity index values than control animals, while EOIPS cells exhibited slightly lower direction selectivity values than other conditions.


A
EO1
BW = - ∞ (low pass)
- ∞ (low pass)
20
B
EO2
- ∞ (low pass)
- ∞ (low pass)
- ∞ (low pass)
1.71
- ∞ (low pass)
3.79
TF (Hz)
C
EOIPS
D
Control
2.32
1.85
2.93
2.00
2.37
1.97
2.00
1.74
10
E
TF Pref (Hz)
F
TF Low Pass Index
G
TF High Pass Index
H
Bandwidth (octaves)
p<0.07
p<0.08
Control
EOIPS
EO1
EO2
I
I Bandwidth I (octaves)

572 **(Figure 3)**

Figure 3: Premature eye opening altered temporal frequency tuning after maturity: Representative temporal frequency tuning curves recorded from single cells: A: EO1: cells contralateral to a single prematurely opened eye. Several cells exhibited strong responses at the lowest temporal frequency tested (that is, several exhibited low-pass tuning). Temporal frequency reported at each cell's overall preferred direction (assessed over all temporal frequencies). Number indicates bandwidth in octaves. -∞ is low pass. B: EO2: cells recorded in an animal with both eyes prematurely opened. Again, many cells exhibited low-pass responses. C: EOIPS: cells ipsilateral to a single prematurely opened eye. D: Control: cells recorded in animals that opened both eyes naturally. E: Linear mixed effects model plot of median TF preference; linear mixed effects plotted as in **Figure 2**. Median TF preference was slightly higher in EOIPS cells than other cells. F: TF low pass index values were significantly elevated in EO1 cells, indicating stronger responses to the lowest temporal frequency tested. G: No differences were observed in high pass index values. H. Bandwidth of the rectified response. I: Bandwidth of the absolute value of responses. Cells in animals that experienced early eye opening exhibited wider bandwidths (less selectivity) than control animals. See text for numbers and p-values.


A
EO1
B
EO2
C
EOIPS
D
Control
SF (cpd)
0.04
0.08
0.16
0.32
0.24
0.64
1.25
0.90
20
5
10
E
SF Pref (cpd)
F
SF Low Pass Index
* note
G
SF High Pass Index
H
Bandwidth (octaves)
I
I Bandwidth I (octaves)
Control
EOIPS
E01
E02

588 **(Figure 4)**

589 **Figure 4: Premature eye opening had very small impacts on spatial frequency tuning. A:**
590 Example spatial frequency tuning curves in EO1 cells. B: Same for EO2 cells. C: Same for
591 EOIPS cells. D: Same for control cells. E: Spatial frequency peak preferences for all cells,
592 animals, and experimental groups (same linear mixed effect model plot layout as Fig. 2). F:
593 Spatial frequency low pass index values. EOIPS cells exhibit a slightly significant ($p<0.499$)
594 decrease in low pass index but differences across groups were small. G: High pass index values
595 for spatial frequency; differences were modest across groups although cells with strong high-pass
596 responses were more common in E02 cells. H: Spatial frequency bandwidth, in octaves. Most
597 cells exhibited low-pass profiles and had infinite bandwidth, and no differences were noted
598 across the groups. I: Spatial frequency bandwidth for absolute response.

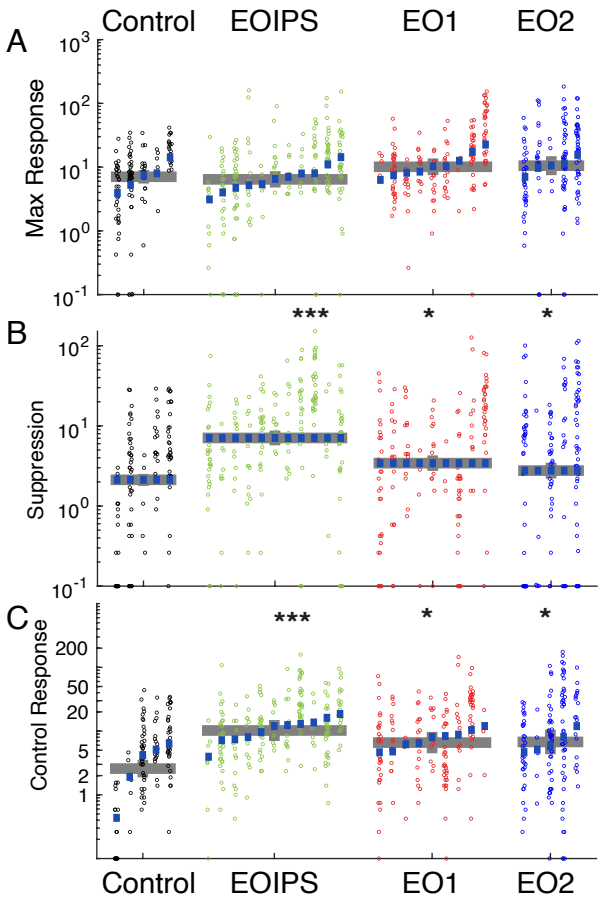


Figure 5: Premature eye opening altered response suppression below baseline and spontaneous activity of V1 neurons: A: Maximum firing rates of cells to visual stimulation were unchanged across experimental conditions. B: Response suppression rates, defined as the largest reduction in responses to visual stimulation below background firing rates, were substantially bigger in EOIPS, EO1, and EO2 cells, indicating that responses below baseline were features of the stimulus response in many of these cells. C: Background firing rates. Responses of cells during presentation of control stimuli, where the screen remained gray for the same duration as our typical visual stimuli. EOIPS, EO1, and EO2 cells showed greatly and significantly elevated firing rates compared to controls. See text for numbers.

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