

1 **Title:** Development of cross-orientation suppression and size tuning and the role of
2 experience

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4 **Abbreviated title:** Development of cross-orientation suppression and size tuning

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36 SDV performed data analysis, and wrote the article, with feedback from all
37 authors.

38

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40 development

41 **Abstract**

42
43 Many sensory neural circuits exhibit response normalization, which occurs when
44 the response of a neuron to a combination of multiple stimuli is less than the sum
45 of the responses to the individual stimuli presented alone. In the visual cortex,
46 normalization takes the forms of cross-orientation suppression and surround
47 suppression. At the onset of visual experience, visual circuits are partially
48 developed and exhibit some mature features such as orientation selectivity, but it is
49 unknown whether cross-orientation suppression or surround suppression are
50 present at the onset of visual experience or require visual experience for their
51 emergence. We characterized the development of these properties and their
52 dependence on visual experience in ferrets. Visual experience was varied across
53 three conditions: typical rearing, dark rearing, and dark rearing with daily exposure
54 to simple sinusoidal gratings (14-16 hours total). Cross-orientation suppression and
55 surround suppression were noted in the earliest observations, and did not vary
56 considerably with experience. We also observed evidence of continued maturation
57 of receptive field properties in the second month of visual experience: substantial
58 length summation was observed only in the oldest animals (postnatal day 90);
59 evoked firing rates were greatly increased in older animals; and direction
60 selectivity required experience, but declined slightly in older animals. These results
61 constrain the space of possible circuit implementations of these features.

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64

65 **Significance Statement**

66
67 The development of the brain depends on both nature – factors that are
68 independent of the experience of an individual animal – and nurture – factors that
69 depend on experience. While orientation selectivity, one of the major response
70 properties of neurons in visual cortex, is already present at the onset of visual
71 experience, it is unknown if response properties that depend on interactions among
72 multiple stimuli develop without experience. We find that the properties of cross-
73 orientation suppression and surround suppression are present at eye opening, and
74 do not depend on visual experience. Our results are consistent with the idea that a
75 majority of the basic properties of sensory neurons in primary visual cortex are
76 derived independent of the experience of an individual animal.

77
78

79 **Introduction (target: 650 words, including references)**

80
81 One of the most ubiquitous features of sensory receptive fields across species, modalities, and
82 cortical hierarchies is the property of divisive normalization: cells exhibit responses to
83 combinations of stimuli that are less than the sum of the responses to the individual stimuli
84 (Heeger, 1992; Carandini et al., 1997; Tolhurst and Heeger, 1997; Simoncelli and Heeger, 1998;
85 Britten and Heuer, 1999; Reynolds and Heeger, 2009; Olsen et al., 2010; Ohshiro et al., 2011;
86 Ruff et al., 2016). In the primary visual cortex, the most-studied form of normalization is cross-
87 orientation suppression, which occurs when the response of a neuron to an optimally oriented
88 grating stimulus is suppressed by a superimposed orthogonal grating (plaid stimulus) that does
89 not, by itself, elicit a response (Adelson and Movshon, 1982; Morrone et al., 1982; Morrone et
90 al., 1987; DeAngelis et al., 1992). In addition, some models also posit that other contextual
91 interactions – such as size tuning – are simply forms of normalization (Rubin et al., 2015). Size
92 tuning includes surround suppression (Hubel and Wiesel, 1965; Gilbert, 1977; Bolz and Gilbert,
93 1986; DeAngelis et al., 1994) and length summation (Bolz and Gilbert, 1989; Chisum et al.,
94 2003; Van Hooser et al., 2006). Despite the importance of normalization in sensory computation,
95 it remains unknown whether the development of normalization manifested as cross-orientation
96 suppression or size tuning requires sensory experience or, rather, is formed without sensory
97 experience.

98
99 The proper development of most neural circuits is contingent on both experience-independent
100 and experience-dependent factors. Some response properties of sensory neurons are present
101 before sensory experience. At the onset of visual experience, neurons in carnivore V1 already
102 exhibit tuning for stimulus orientation, spatial frequency, and temporal frequency, and this
103 tuning is elaborated or altered by experience-dependent processes (Chapman and Stryker, 1993;
104 White et al., 2001; Li et al., 2006). Other response properties require experience for their
105 expression. For example, direction selectivity is very weak at the onset of visual experience, and
106 develops rapidly when the ferret experiences moving visual stimuli (Li et al., 2006; Li et al.,
107 2008; Van Hooser et al., 2012; Smith et al., 2015).

108
109 To study the influence of experience on cross-orientation suppression and size tuning, we
110 compared visual receptive field properties in dark-reared animals and typically-reared animals at
111 several ages. Additionally, we exposed some dark-reared animals to several hours of viewing
112 artificial stimuli – large gratings of single orientations. These impoverished stimuli lacked the
113 simultaneous presentation of multiple orientations, spatial, and temporal frequencies as well as
114 variation in size typical of natural images. This allowed us to further explore the influence of the
115 quality of visual experience on the emergence of cross-orientation suppression and size tuning.

116
117 We found that cross-orientation suppression and surround suppression were present in both dark-
118 reared animals and in experienced animals, although the magnitude of this tuning varied slightly
119 with experience and age. Cross-orientation suppression and surround suppression in animals
120 whose experience was limited to large gratings of single orientations did not differ from that of
121 typically reared animals, suggesting that experience is not critical for the emergence of these
122 properties.

123

124 Finally, we uncovered unexpected evidence that basic visual cortical response properties
125 continue to mature even after a month of visual experience. In typically-reared ferrets, direction
126 selectivity reached a peak about a week after eye opening and was reduced later, suggesting that
127 some receptive field features may change with age in a non-monotonic fashion. In addition,
128 evoked firing rates and length summation increased substantially during the second month of
129 visual experience. These changes occurred after the outgrowth of the long-range horizontal
130 connections within visual cortex (Durack and Katz, 1996; Ruthazer and Stryker, 1996; White et
131 al., 2001), but closely follow the growth of synaptic density to its peak at about 90 days of age
132 (Erisir and Harris, 2003; White and Fitzpatrick, 2007).
133

134 **Materials and Methods**

135
136 All experimental procedures were approved by the Brandeis University Animal Care and Use
137 Committee and performed in compliance with National Institutes of Health guidelines.
138

139 *Experimental groups*

140 Female sable ferrets (*Mustela putorius furo*) used in the experiment were split into five study
141 groups (**Figure 1**):
142

143 **1 Dark-reared (n=5):** The animals were reared with 3-5 littermates and their jill in complete
144 darkness starting 1-3 days before eye opening (postnatal day 27-30) until the experiment at age
145 P40-P42. The kits were nursed by their jill until spontaneous weaning; water and soft diet were
146 available ad libitum. These animals were also used in an unrelated study; we took advantage of
147 the opportunity to make additional discoveries with animals that were being initially studied for
148 other purposes. As a part of this unrelated experiment, at P30 (with eyes still closed) the ferrets
149 were implanted with chronic microelectrode arrays in left V1, and at P33 and P37 they were
150 subject to two 80 min long, head-fixed recording sessions. Stimuli consisted of 20 minutes of a
151 greyscale natural movie, 20 minutes of drifting gratings, 20 minutes of block noise and 20
152 minutes of a dark screen (Berkes et al., 2011). While it would have been ideal (for the study
153 discussed here) to have had access to animals that did not include this procedure, our previous
154 research has found that <3 hours of visual experience does not cause a substantial increase in
155 direction selectivity, so we did not expect substantial influence of the experience that occurs
156 during these measurements (Clemens et al., 2012; Roy et al., 2016; Ritter et al., 2017). During the
157 post-operative recovery they were additionally fed milk replacement (KMR, PetAg) with a
158 syringe. The need for additional syringe feeding was not related to dark rearing – it did not differ
159 from that observed in typically-reared ferrets of corresponding age after surgery. Ferrets were
160 observed and their weight was monitored daily using night vision goggles with an infrared light
161 source. No effects of dark rearing on the animals' general health and behavior were observed.
162

163 **2 Dark-reared, trained (n=7):** The animals were reared with 3-5 littermates and their jill in
164 complete darkness starting 1-3 days before eye opening (postnatal day 27-30) until the
165 experiment at age P40-P42. As a part of the previously described unrelated experiment, at P30
166 they were implanted with chronic microelectrode arrays in left V1 and had headposts affixed,
167 and at P33 and P37 they were subject to two 80 min-long recording sessions. Between P33 and
168 P37 the ferrets were exposed to controlled visual experience. Awake ferrets were head-fixed and

169 placed in front of a screen inside a dark box for two 1.5hr long sessions daily with a 1.5hr break
170 in between the sessions adding to a total of 14-16 hours. The training stimuli consisted of
171 bidirectionally drifting sinusoidal gratings of varying orientation (from horizontal to vertical in
172 22.5° steps) at 0.1 cycle/degree spatial frequency, 4Hz temporal frequency, and 100% contrast in
173 20 minute blocks separated with 10 min of mean luminance. Other than the daily training
174 sessions the rearing conditions for ferrets in this experimental group were identical to those in
175 the dark-reared group. Efforts were made to keep the dark-reared ferret kits awake during the
176 period of visual stimulation (gentle tapping or gentle hand clapping), although these very young
177 animals frequently dozed for several minutes during the visual exposure.

178
179 **3 Typically-reared, P40 (n=8):** The animals were reared with 3-5 littermates and jill in a 12 h
180 light/dark cycle environment until the experiment at age P40-P42. As a part of the previously
181 described unrelated experiment, at P30 they were implanted with chronic microelectrode arrays
182 in left V1 and had headposts affixed, and at P33 and P37 they were subject to two 80 min-long
183 recording sessions.

184
185 **4 Typically-reared, P60 (n=4):** The animals were reared in a 12 h light/dark cycle environment
186 until the experiment at age P59-P66.

187
188 **5 Typically-reared, P90 (n=6):** The animals were reared in a 12 h light/dark cycle environment
189 until the experiment at age P90-P92.

190 *Survival surgery*

191
192
193 All the ferrets in the dark-reared, dark-reared trained, and typically-reared ~P40 group were also
194 used in an unrelated chronic recording experiment. For this experiment, ferrets had a 2×8
195 microwire electrode array implanted into V1 in the left hemisphere at age P30, while their eyes
196 were still closed. Immediately before the surgery and up to 48 hours after surgery, ferrets were
197 intramuscularly (IM) administered analgesic ketoprofen (1mg/kg) and antibiotic penicillin
198 (27mg/kg) and orally administered analgesic tramadol (2mg/kg). During the surgery, ferrets were
199 anesthetized with an intramuscular injection of ketamine-xylazine cocktail (20mg/kg and
200 2mg/kg, respectively), and given atropine (0.04mg/kg) to reduce secretions. Surgical margins
201 were infused with 0.2 ml of the local analgesic bupivacaine. At the end of surgery, anesthesia
202 was reversed using the xylazine antidote yohimbine (0.5mg/kg). Importantly, the last dose of
203 analgesics was given 24hrs before the start of training. Body temperature was maintained at
204 37°C using a thermostatically controlled heating pad, heart rate was continuously monitored, and
205 hydration was maintained throughout by subcutaneous injections of lactated Ringer's solution (3
206 ml/kg/h). The cranium was exposed and a 4mm×4mm craniotomy made over V1. A durotomy
207 was performed with a 31-gauge needle before placing the electrode array into the brain. The
208 brain was sealed with a low toxicity silicone elastomere (Kwik-Cast, World Precision
209 Instruments) and the electrode and headpost were affixed to the skull using 6 skull screws and
210 light cured dental composite (Flow-It ALC, Pentron). After the animals were ambulatory, they
211 were transferred back to the cage with their littermates and jill.

212 *Acute surgical procedures*

213
214

215 Ferrets were sedated with ketamine (20 mg/kg IM). Atropine (0.16–0.8 mg/kg IM) was
216 administered to prevent bradycardia and reduce bronchial and salivary secretion and
217 dexamethasone (0.5 mg/kg IM) administered to reduce inflammation and swelling. The animal
218 was deeply anesthetized with a mixture of isoflurane, oxygen, and nitrous oxide through a face
219 mask while tracheotomy was performed. Once the tracheotomy was done, the animal was
220 ventilated with 1–2% isoflurane in a 2:1 mixture of nitrous oxide and oxygen. A cannula was
221 inserted into the intraperitoneal (IP) cavity for delivery of 5% dextrose in lactated Ringers
222 solution (3 ml/kg/h). Body temperature was maintained at 37°C using a thermostatically
223 controlled heating pad. End-tidal CO₂ levels and respiration rate were monitored and kept within
224 the appropriate physiological range (3.5–4%). The animal was held in place by a custom
225 stereotaxic frame. All wound margins were infused with bupivacaine. Silicone oil was placed on
226 the eyes to prevent damage to the cornea. A 4×4 mm craniotomy was made over V1 in the right
227 hemisphere, and the dura was removed with a 31-gauge needle.

228
229 Before the start of recording, ferrets were paralyzed using a neuromuscular blocker (gallamine
230 triethiodide 10 - 30 mg/h/kg), delivered through the IP cannula, in order to suppress spontaneous
231 eye movements. The nitrous oxide to oxygen ratio was adjusted to 1:1. Adequate anesthesia was
232 maintained by continuously monitoring the animals' EKG and adjusting the isoflurane
233 concentration. At the conclusion of the experiment the animal was killed and transcardially
234 perfused to retrieve the brain for histology.

235 236 *Electrophysiological recordings*

237
238 Carbon fiber electrodes (Carbostar-1, Kation Scientific) were used for all recordings. The signal
239 was amplified using the RHD2000 amplifying/digitizing chip and USB interface board (Intan
240 Technologies) and acquired and clustered using a Micro1401 acquisition board and Spike2
241 software (Cambridge Electronic Design, LLC). Spike sorting was done manually using Spike 2
242 software.

243
244 An electrode was inserted into the brain using a Sutter Instruments MP-285 manipulator. In order
245 to reduce sampling bias, we recorded from any site that had a signal to noise ratio sufficient for
246 isolation and had a response that appeared to be modulated by presentation of drifting gratings.
247 Data are reported from all units that are responsive enough to be included in analysis (see
248 below). After finishing the recording at one site, the electrode was lowered at least 40µm before
249 attempting to identify a suitable subsequent recording site. The experiment was concluded once
250 white matter was reached or once the animal's physiological indicators became unstable.

251 252 *Visual stimulation*

253
254 Visual stimuli were created in Matlab using the Psychophysics Toolbox (Brainard, 1997; Pelli,
255 1997) and displayed on a 21" flat face CRT monitor (Sony GDM-520) with a resolution of
256 800×600 and a refresh rate of 100Hz. The monitor was positioned 20cm away from the animals'
257 eyes, such that it was subtending 63°×63° of visual angle. For each unit we isolated, we first
258 determined the ocular dominance and occluded the non-dominant eye. We then used circular
259 patches of drifting sinusoidal gratings of varying sizes to manually map receptive fields. We

260 moved the monitor to accommodate all eccentricities without varying the distance of the monitor
 261 from the animal.

262
 263 *Immunohistochemistry*

264
 265 Upon completion of each experiment, electrolytic lesions were made at the final recording site
 266 and at ~300 μ m from the surface of the cortex to enable the reconstruction of the electrode track.
 267 Following a transcardial perfusion, the brain was placed in 4% paraformaldehyde in 0.1 M PBS
 268 at 4°C for 24 h, and then moved to 10% sucrose in PBS at 4°C for 24 – 48 h, followed by 30%
 269 sucrose in PBS at 4°C for 24 – 48 h.

270
 271 *Data analysis*

272
 273 We recorded from a total of 335 V1 neurons of 30 female sable ferrets in 5 experimental
 274 conditions. Cells with a response rate below 2 spikes/sec were excluded during analysis, but
 275 were still recorded from if they appeared to be modulated by the stimuli during the experiment.
 276 The actual number of cells included in analysis varied across conditions (**Table 1**). Additional
 277 exclusion criteria for specific analyses are discussed in separate sections below.
 278

	dark-reared P40	dark-reared trained P40	typically- reared P40	typically- reared P60	typically- reared P90
ages	2x40, 3x42	1x39, 2x40, 4x42	2x40, 2x41, 4x42	2x59, 1x61, 1x66	4x90, 1x91, 1x92
# animals	5	7	8	4	6
# cells	71	77	79	45	63
# cells included					
DS	50	54	47	29	49
SF	66	73	53	43	59
TF	69	71	55	42	55
contrast	67	70	40	39	58
size	44	37	31	32	45
Cross-orientation suppression	54	52	55	40	60

279 **Table 1 Number of cells analyzed per condition**

280
 281 *Orientation and direction tuning*

282
 283 We characterized the orientation and direction selectivity of all cells using bidirectionally
 284 drifting sinusoidal grating stimuli of varying direction (22.5° steps) at 0.1 cycle/degree spatial

285 frequency, 4Hz temporal frequency and 100% contrast. Orientation/direction tuning curves were
 286 fit with a mixture of two Gaussians in circular space, forced to peak 180° apart and to have the
 287 same width σ (Carandini & Ferster, 2000):

$$R(\theta) = R_0 + R_{pref} e^{-\frac{(\theta - \theta_{pref})^2}{2\sigma^2}} + R_{pref+180} e^{-\frac{(\theta - \theta_{pref} + 180)^2}{2\sigma^2}}$$

288 where θ is the stimulus direction in circular space (0°-360°), R_0 is a constant offset, θ_{pref} is the
 289 preferred orientation, the tuning width, (R_{pref}) is the increment above offset to the preferred
 290 direction, ($R_{pref+180}$) is the increment above offset to the opposite direction, and the tuning

291 width (half-width at half height) is given by $\sigma\sqrt{\log(4)}$.

292

293 To ensure good fitting, we constrained the fitting parameters: $\sigma \geq \alpha/2$, where α is the stimulus
 294 angle step size (22.5°); $-R_{max} \leq R_0 \leq R_{max}$, where is R_{max} the highest observed response for
 295 any stimulus; $0 \leq R_{pref}$, $R_{pref+180} \leq 3R_{max}$. We initiated iterative fitting at parameter values
 296 expected to produce a good fit: $\theta_{pref} = \theta_{R_{max}}$; $R_{pref} = R_{pref+180} = R_{max}$; $R_0 = 0$. We
 297 performed fitting for $\sigma \equiv (\alpha/2, \alpha, 40^\circ, 60^\circ, 90^\circ)$ and selected the fit with the lowest least squared
 298 error. Finally, we eliminated from further analysis cells that did not exhibit significant
 299 orientation tuning as quantified by Hotelling's T^2 test performed on orientation vector for each
 300 trial. This was done because the fitting method has been shown to produce large errors in θ_{pref}
 301 at low OI values (Mazurek et al., 2014).

302

303 Orientation selectivity was quantified using circular variance (Batschelet, 1981). Direction
 304 selectivity was quantified using direction index (DI), a normalized difference between the
 305 responses for the preferred and direction of motion and its opposite:

$$DI = \frac{R(\theta_{pref}) - R(\theta_{pref+180^\circ})}{R(\theta_{pref})}$$

306

307 Contrast responses were fit using the Naka-Rushton equation (Naka and Rushton, 1966; Albrecht
 308 and Hamilton, 1982; Heimel et al., 2005):

$$R(c) = R_s + \frac{gc^n}{c_{50}^n + c^n}$$

309

310 where R_s is the spontaneous firing rate, c is contrast, fitting parameters are contrast at half peak
 311 response (c_{50}), gain (g), and exponent (n). Relative maximum gain (RMG) was calculated from
 312 the fits as maximum slope of the contrast response curve when the difference between maximum
 313 firing rate and spontaneous firing rate is normalized to 1. RMG indicates linearity of the contrast
 314 response curve, with 1 being completely linear. The contrast saturation index SI (Peirce, 2007)
 315 was defined to be

$$SI = \frac{R_{max} - R(100\%)}{R_{max} - R(0)}$$

316

317 and indicates the degree of “supersaturation” of the contrast response (that is, the amount the
318 response might be reduced at 100% contrast compared to the contrast that produces the
319 maximum response, which might or might not be 100%).

320 Size tuning responses were fit to a product of two functions that represented the center response
321 and the modulation of the center response, respectively:

$$322 \quad R(r) = R_{center}(r)R_{mod}(r)$$

323 The center response R_{center} is the response of a Gaussian receptive field with the stimulus $S(x,y)$:

$$324 \quad R_{center}(r) = \sum_x \sum_y S(x,y) * A * G(x,y,\mu,\Sigma)$$

325 where A is the amplitude of the response (in spikes/sec), μ is the center position of the stimulus
326 on the screen, and Σ is the covariance matrix. Here, we constrained the Gaussian function to be

$$\Sigma = \begin{vmatrix} c & 0 \\ 0 & c \end{vmatrix}$$

327 circular by defining

328
329 The modulating function $R_{mod}(r)$ takes values between 0 and 2, and is proportional to the
330 overlap of the stimulus and a circle of radius R_{max_stim} :

$$331 \quad R_{mod_circle}(r) = 1 + S_m \frac{r^2}{R_{max_stim}^2}$$

332 When the stimulus was an aperture, the modulating response was:

$$333 \quad R_{mod_aperture}(r) = 1 + S_m \frac{R_{max_stim}^2 - r^2}{R_{max_stim}^2}$$

334 We quantified size tuning using two measurements, the size modulation parameter S_m , and the
335 stimulus size when R_{center} exhibited half of its maximum response. S_m takes positive values for
336 cells that exhibit length summation, and negative values for cells that exhibit surround
337 suppression.

338
339 Cross orientation suppression was characterized in all cells using circular plaid stimuli consisting
340 of two superimposed drifting sinusoidal gratings. One of the component gratings was assigned
341 the previously established preferred orientation of the cell, the other component grating was
342 assigned the orthogonal orientation. The direction of drift for the orthogonal grating was taken to
343 be the preferred direction plus 90°. Response to the plaid stimulus can be related to the linear
344 combination of responses to the component gratings:

$$345 \quad R_{pref+orth} = Pm (R_{pref} + R_{orth})$$

346
347
348 The plaid multiplier, Pm , is used to quantify the magnitude of the suppression of the response to
349 the preferred orientation by the orthogonal orientation. Higher values of the plaid multiplier
350 denote lower values of cross-orientation suppression.

351

352 *Computer code*

353

354 All computer code related to this study is available at [http://github.com/VH-](http://github.com/VH-Lab/vhlab_publishedstudies)
355 [Lab/vhlab_publishedstudies](http://github.com/VH-Lab/vhlab_publishedstudies) and depends on libraries available at
356 <http://code.vhlab.org>.

357

358 **Results**

359 Our primary goal was to examine the influence of visual experience and age on the development
360 of several receptive field properties. In particular, we were interested in uncovering whether
361 cross-orientation suppression and size tuning depend on visual experience. To this end, we raised
362 ferrets under three different conditions that were each designed to test a possible relationship
363 between experience and selectivity. Typically-reared animals received 12 hours of visual
364 experience daily, so they were exposed to complex natural scenes with objects of different sizes
365 and mixtures of stimulus orientations. We recorded from animals living under typical rearing
366 conditions at three different ages: postnatal day 40 (P40), postnatal day 60 (P60), and postnatal
367 day 90 (P90). Dark-reared animals were raised in 24-hour constant darkness that was interrupted
368 by two brief testing sessions (see Methods), and had very impoverished visual experience. A
369 third group of animals was dark-reared but provided with two daily 1.5-hour “training” sessions
370 for 5 days, where the animals were exposed to stimulation with sinusoidal gratings of a single
371 orientation that occupied the full screen. Experience could be important for the development of
372 cross-orientation-suppression or size tuning – furthermore experience with multiple orientations
373 or objects of varying size might be necessary. The third experimental group was designed to test
374 just that - whether the quality of visual experience influences the emergence of cross-orientation-
375 suppression and size tuning.

376

377 We examined the refinement of receptive field properties at times related to the anatomical
378 maturation of the visual cortical circuit (White and Fitzpatrick, 2007). Long-range horizontal
379 connections extending for millimeters across the cortical surface exhibit adult-levels of
380 complexity at around postnatal day 35-45 (Durack and Katz, 1996; Ruthazer and Stryker, 1996;
381 White et al., 2001); volumetric synaptic density achieves adult levels around postnatal day 90
382 (Erisir and Harris, 2003). In principle, either of these anatomical features could underlie the
383 development of cross-orientation suppression or size tuning. This study allowed us to connect
384 these landmark events in the development of the visual cortical circuit to the changes in response
385 properties of V1 neurons. A diagram of all animal groups is shown in **Figure 1**.

386

387 After isolating a cell, we assessed its direction tuning, followed by its spatial frequency tuning
388 and temporal frequency tuning. All subsequent measurements were made with gratings that were
389 aligned to the optimal direction, spatial frequency, and temporal frequency properties of the cell
390 of interest. Then, we examined contrast responses, cross-orientation suppression, and size tuning.
391 To our knowledge, the experience and age dependence of cross-orientation suppression and size
392 tuning have not been examined previously, so we turn our attention to these results first,
393 followed by orientation selectivity, direction selectivity, spatial and temporal frequency tuning,
394 contrast responses, and evoked firing rates.

395

396 *Cross-orientation suppression*

397
398 Cross-orientation suppression was robustly present in all animal groups in our study. We
399 assessed cross-orientation suppression at several contrasts with a stimulus that was 10° by 10° in
400 size. **Figure 2** shows responses from typical cells from animals in each experimental group.
401 Responses to plaid drifting gratings were nearly always smaller than the sum of the individual
402 responses to the two component directions. One of the two component gratings always had the
403 cell's preferred orientation and drifted in the preferred direction, while the other component
404 grating had the orthogonal orientation (**Figure 3**).

405
406 Although cross-orientation suppression was present in all experimental groups, the amount of
407 suppression that we observed varied slightly with age and experience. We quantified cross-
408 orientation suppression with a plaid multiplier P_m , that compared the actual response to a plaid
409 stimulus to the linear sum of the two components (**Figure 4**). A value of 1 would indicate perfect
410 linear summation, and a value less than 1 indicates cross-orientation suppression. The Kruskal-
411 Wallis H test shows a statistically significant effect of experimental condition on the plaid
412 multiplier for all three contrast levels tested (32%: $\chi^2(4) = 22.15, p < 0.005$; 64%: $\chi^2(4) =$
413 $22.23, p < 0.05$; 100%: $\chi^2(4) = 29.09, p < 0.05$). Interestingly, cross-orientation suppression in
414 typically-reared animals showed an increase with experience at P40 (compared to dark-reared
415 animals), but this initial increase in suppression was followed by a subsequent decrease at P60
416 and P90.

417
418 *Size tuning*

419
420 Size tuning is another parameter whose developmental profile has not been examined previously.
421 Studies (Gilbert, 1977; Chisum et al., 2003) have shown that cells can exhibit a wide variety of
422 responses to large stimuli. Some cells merely plateau in response to increasing stimulus size
423 (**Figure 5a**). Other cells exhibit surround suppression, where stimulation outside of the classical
424 receptive field induces weaker responses to central stimulation (**Figure 5b**). Finally, still other
425 cells show length summation, where cells' responses to stimuli that exceed the classical receptive
426 field keep increasing (**Figure 5c**). We observed all of these response types in our animals.

427
428 To evaluate these responses quantitatively, we developed a fit function that included a Gaussian
429 center component that was modulated by a circular surround component (see Methods). The
430 degree of surround modulation was quantified by a single parameter, S_m , that was negative when
431 stimulation of the surround was suppressive and was positive when the stimulation of the
432 surround was enhancing. This parameter took values near 0 when surround stimulation did not
433 influence the firing of the neuron. We examined responses to stimuli of increasing size and
434 annular stimuli of decreasing inner diameter, and both sets of responses were used to establish
435 the fits. Analysis of the responses to the annular stimulus allowed us to delineate the classical
436 receptive field center (where stimulation evokes a response) from the surround that merely
437 modulates responses to the center stimulus.

438
439 We observed plateau responses and surround suppression in all animal groups (**Figure 6a**),
440 indicating that these variants of size tuning do not require visual experience for their expression.
441 The fraction of neurons that exhibited substantial length summation increased in the oldest

442 animals in the study (**Figure 6a**). Because we did not modulate visual experience in the oldest
443 animals in our study, we cannot conclude whether these results are due to age or experience, but
444 these responses do emerge at a time when the horizontal connections across the cortical surface
445 have already reached anatomical maturity (Durack and Katz, 1996; Ruthazer and Stryker, 1996;
446 White et al., 2001).

447
448 Consistent with prior reports, we observed a substantial decrease of receptive field center size in
449 the oldest animals (**Figure 6b**). Median receptive field center sizes dropped from 7.5° in dark-
450 reared animals to 5.4° in the P90 animals. This maturation coincides with the peak synapse
451 density in layer 2/3 in ferret (around P90) (Erisir and Harris, 2003; White and Fitzpatrick, 2007).

452 *Orientation and direction selectivity*

453
454
455 Previous studies have found that orientation selectivity is present at the time of eye opening and
456 that it increases with the onset of visual experience (Chapman and Stryker, 1993; White et al.,
457 2001; Li et al., 2006). Direction selectivity, on the other hand, is almost entirely absent at the
458 time of eye opening, emerges over several days, and requires visual experience (Li et al., 2006).
459 Our results largely recapitulated these prior observations: dark-reared animals exhibited
460 moderately strong orientation selectivity that increased with visual experience, and dark-reared
461 animals exhibited very weak direction selectivity that was also increased by visual experience
462 (**Figure 7**).

463
464 These data also give us a new view of the impact of visual experience with simple grating stimuli
465 on orientation and direction selectivity. Previous work has demonstrated that only a few hours
466 (3-9 hours) of experience with a moving visual stimulus is sufficient to cause the rapid
467 emergence of direction selectivity and a concurrent increase in orientation selectivity (Li et al.,
468 2008; Van Hooser et al., 2012; Ritter et al., 2017). However, for methodological reasons, these
469 experiments only assessed orientation and direction selectivity immediately after exposure to the
470 “training stimulus”, leaving open the possibility that the effects of such visual experience were
471 transient. In this study, recordings were obtained 1-5 days after the last training session, allowing
472 us to address this possibility. Dark-reared and trained animals exhibited direction selectivity that
473 was intermediate between dark-reared animals that did not have training and animals with typical
474 visual experience. P40 dark-reared animals exhibited direction selectivity that was significantly
475 lower than P40 typically-reared animals. A direct comparison between dark-reared animals and
476 trained dark-reared animals did not reach significance ($p=0.09$, Kruskal-Wallis test), but trained
477 and dark-reared animals exhibited direction selectivity that was not different from typically-
478 reared P90 animals (**Figure 7c**; $p<0.05$, Kruskal-Wallis test, Bonferroni correction), which show
479 some substantial direction selectivity. This evidence suggests that the exposure to the training
480 stimulus did produce relatively lasting, if small, changes in receptive field properties.

481
482 Finally, we were surprised to observe that direction selectivity changes non-monotonically with
483 age. We observed the strongest direction selectivity in P40 animals that were typically reared.
484 Direction selectivity index values decreased at P90, but still remained well above the values of
485 visually-naïve animals. This result suggests that selectivity for some features goes through
486 periods of increases and decreases as the animal matures.

487

488 *Spatial and temporal frequency tuning*

489
490 Spatial frequency preference showed a substantial and expected dependency on experience.
491 Spatial frequency was characterized in all cells using drifting sinusoidal grating stimuli of
492 varying spatial frequency ([0.05, 0.1, 0.15, 0.2, 0.3, 0.5, 0.8] cycles per degree visual angle), 4Hz
493 temporal frequency, 100% contrast, and orientation and direction fixed at the previously
494 established optimal value for each cell. As expected from previous reports, cells from animals in
495 the P40 age group prefer lower spatial frequencies regardless of rearing condition (**Figure 8ab**),
496 consistent with the lower resolution of vision in younger animals (Freeman and Marg, 1975;
497 DeAngelis et al., 1993; Tavazoie and Reid, 2000; Heimel et al., 2007). In the two older groups,
498 P60 and P90, spatial frequency preference shifted towards higher frequencies. There was also a
499 noticeable diversification of SF preferences with age – SF preferences of individual cells in
500 younger animals were more tightly clustered. Conversely, in older animals, cells preferred higher
501 SFs, and their preferences had a larger spread.

502
503 Temporal frequency preferences were subject to fewer differences across the experimental
504 groups compared to selectivity to other features. Temporal frequency was characterized in all
505 cells using drifting sinusoidal grating stimuli of varying temporal frequency ([0.5, 1, 2, 4, 8, 16,
506 32] Hz), 100% contrast, and spatial frequency, orientation, and direction fixed at the previously
507 established optimal value for each cell. Cells from animals in the P40 and P60 age groups
508 preferred lower temporal frequencies regardless of rearing condition (**Figure 8cd**). In the P90
509 age group, TF preference shifted slightly towards higher frequencies, but these changes were
510 quite modest.

511
512 *Contrast tuning*

513
514 Contrast tuning was subject to subtle differences across the different animal groups. Contrast
515 responses were examined in all cells using drifting sinusoidal grating stimuli of varying contrast
516 (2%, 4%, 8%, 16%, 32%, 64%, 100%), and with temporal frequency, spatial frequency, and
517 direction fixed at the previously established optimal values for each cell (**Figure 9**). There were
518 no statistically significant differences among relative maximum gain (RMG) for different
519 conditions (**Figure 9b**). There were small but significant differences in the amount of
520 “supersaturation” that was exhibited by neurons in this different groups. The median value for all
521 groups was very close to 0 (no supersaturation) but a few cells were substantially suppressed at
522 the highest contrast (**Figure 9c**). Overall, visual experience and age appeared to have only a
523 modest impact on contrast responses.

524
525 *Firing rate*

526
527 One major parameter that exhibited a large change with age was evoked firing rate. The
528 maximum evoked firing rate was taken to be the strongest trial-averaged response to sinusoidal
529 grating stimulation that we observed – that is, the response measured at the preferred direction,
530 spatial frequency, temporal frequency, and best contrast. Evoked maximum firing rates began at
531 around 10Hz in young animals, but increased substantially in the P90 animals to about 20Hz on
532 average (**Figure 10**). Kruskal-Wallis H test shows a statistically significant effect of
533 experimental condition on firing rate ($\chi^2(4) = 23.00, p < 0.05$). We observed no difference in

534 median evoked firing rate across the three rearing conditions at P40, but large firing rates
535 (>40Hz) were only observed in the two older groups. These findings suggest that the network
536 changes that support high firing rates are still emerging, even after 1 month of visual experience
537 (P60).
538

539 **Discussion**

540
541 We characterized the role of visual experience and age on the development of V1 receptive field
542 properties in ferret. We found that cross-orientation suppression and surround suppression are
543 present regardless of whether the animal has had any experience with visual stimuli. In addition,
544 we found that increases in direction selectivity that are produced by short-term exposures to
545 moving visual stimuli are retained over days. Direction selectivity reached a peak at P40 and
546 decreased slightly in older animals. Finally, we observed that two features, length summation
547 and high evoked firing rates, were primarily found in the oldest animals (P90).
548

549 *Contribution of sensory experience to normalization*

550
551 Normalization and contextual interactions, including cross-orientation suppression and size
552 tuning, are canonical computations of neural circuits (Carandini and Heeger, 2011; Angelucci et
553 al., 2017). Cross-orientation suppression is a form of response normalization that has been
554 observed in a wide variety of cortical areas, including V1 (Gizzi et al., 1990; Ringach et al.,
555 2002), V2 (Rowekamp and Sharpee, 2017), V4 (Reynolds et al., 1999), MT (Britten and Heuer,
556 1999; Heuer and Britten, 2002), and IT (Zoccolan et al., 2005). It is ubiquitous across examined
557 species (Carandini and Heeger, 2011), being found in macaque (Ringach et al., 2002), cat
558 (DeAngelis et al., 1992), mouse (Sato et al., 2016), and even *Drosophila* (Olsen et al., 2010).
559 Brain imaging studies have also found that contrast-dependent suppression is precisely
560 maintained across the entire neural population (Busse et al., 2009; MacEvoy et al., 2009).
561 Surround suppression is also ubiquitous across species, being found in mouse (Van den Bergh et
562 al., 2010; Self et al., 2014), ferret (Rubin et al., 2015), cat (Hubel and Wiesel, 1965; Blakemore
563 and Tobin, 1972; Gilbert, 1977; DeAngelis et al., 1994; Sengpiel et al., 1997), monkey (Hubel
564 and Wiesel, 1968; Sceniak et al., 1999; Jones et al., 2001; Cavanaugh et al., 2002a, b), and
565 human (Williams et al., 2003; Zenger-Landolt and Heeger, 2003).
566

567 Due to the importance of normalization and contextual interactions to selectivity in the presence
568 of multiple stimuli, including in natural scenes (Barlow, 1961, 1972; Bauman and Bonds, 1991;
569 Somers et al., 1995; Carandini and Ringach, 1997; Lauritzen et al., 2001; Vinje and Gallant,
570 2002; David et al., 2004; Nurminen and Angelucci, 2014; Angelucci et al., 2017), it seemed
571 possible that sensory experience with multiple stimuli or objects of various sizes might be
572 necessary for the expression of cross-orientation suppression and surround suppression, or at
573 least its refinement. Our results provide strong evidence that sensory experience is unnecessary
574 for the development of cross-orientation suppression or surround suppression. Like orientation
575 selectivity, these features are robustly present at the onset of visual experience and in dark-reared
576 animals, and were not greatly impacted by varying levels of experience.
577

578 *Cortical circuits and normalization*

579

580 The circuit mechanisms of cross-orientation suppression and size tuning are unknown. Some
581 models posit that local connections within the cortex provide suppression, either via increased
582 inhibition or reduced excitation (Somers et al., 1995; Haider et al., 2010; Sato et al., 2014; Rubin
583 et al., 2015). Other models suggest that cross-orientation suppression reflects reduced
584 synchronized input from lateral geniculate nucleus when multiple stimuli are present (Priebe and
585 Ferster, 2006), or that the inhibition arises via feedback connections from higher cortical areas
586 (Angelucci et al., 2002; Angelucci et al., 2017). Our results do not allow us to choose among
587 these alternatives, but we can make one inference. Dark-reared animals showed strong cross-
588 orientation suppression and typical rates of surround suppression, and prior research has noted
589 that the long-range horizontal connections across the cortical surface are poorly formed in dark-
590 reared animals (White et al., 2001). Therefore, it is unlikely that the long-range horizontal
591 connections are a critical component for cross-orientation or surround suppression.

592
593 We observed the highest percentage of length-summing cells and the highest evoked firing rates
594 in animals that had attained approximately 2 months of visual experience (P90). What circuit
595 properties are modified at this time? The long-range horizontal connections are anatomically
596 established by P35-45 (Durack and Katz, 1996; Ruthazer and Stryker, 1996; White et al., 2001),
597 but excitatory synaptic density in layer 2/3 does not reach its maximum until P80-100 (Erisir and
598 Harris, 2003). Further, feedback connections to V1 from extrastriate areas are present at the time
599 of eye opening, and are pruned from eye opening to P70 (Khalil and Levitt, 2014). The
600 refinement of these circuit elements could contribute to the emergence of normalization related
601 tuning properties.

602 603 *Influence of experience on direction selectivity*

604
605 The development of direction selectivity requires visual experience. Visually-naïve animals do
606 not exhibit strong direction selectivity, and animals that are dark reared throughout an early
607 critical period do not attain direction selectivity even if they are subsequently exposed to light for
608 weeks (Li et al., 2006). Previous experiments have found that just 3-9 hours of visual experience
609 with moving stimuli is sufficient to cause emergence of direction selectivity in visually-naïve,
610 anesthetized ferrets (Li et al., 2008; Van Hooser et al., 2012; Roy et al., 2016; Ritter et al., 2017).
611 Previous experiments were done in acute preparations, and it was unknown if these effects would
612 persist for more than a few hours. We exposed dark-reared animals to 14-16 hours of stimulation
613 with large drifting grating stimuli. Stimulus delivery differed from previous studies in which the
614 anesthetized ferrets were paralyzed to eliminate eye movements. Here, awake animals were
615 head-fixed but were free to move their eyes. Due to their age, the animals often spent tens of
616 minutes of their 80 minute exposures sleeping. Further, trained dark-reared animals spent the
617 vast majority of their total time after eye opening in darkness, which might have degraded any
618 experience-dependent changes.

619
620 Nevertheless, we found that the P40 animals that were dark reared and exposed to large moving
621 gratings exhibited average direction selectivity with a magnitude between those of P40 dark-
622 reared animals and P40 typically-reared animals. While the differences in direction selectivity
623 between P40 dark-reared and dark-reared trained animals did not reach significance, P40 dark-
624 reared and trained animals exhibited direction selectivity that was not different from P90

625 animals, which is evidence of modestly increased selectivity. This is evidence of the persistence
626 of the influence of visual experience on direction selectivity.

627
628 We also found a surprising decline of direction selectivity in the second month of visual
629 experience (approximately P60-P90). Direction selectivity index values peaked at P40, and
630 declined slightly afterwards. This suggests that the changes to direction selectivity over age are
631 non-monotonic, with direction selectivity increasing and decreasing as visual circuitry reaches
632 maturity.

633
634 *Role of experience in development of primary sensory receptive field properties*

635
636 One could imagine two broad ideas about how receptive field properties might be formed in
637 primary sensory areas. Visual circuits could analyze the input statistics and design appropriate
638 filters to encode this information. Indeed, when artificial cortical networks with learning rules
639 are presented with natural scenes, the early filters in these networks resemble those of visual
640 cortical neurons (Olshausen and Field, 1996; Bell and Sejnowski, 1997; van Hateren and van der
641 Schaaf, 1998; Ranzato et al., 2007). Thus, in principle, it is possible that these response
642 properties could be derived purely from experience.

643
644 But an alternative hypothesis – one that posits that efficient receptive field properties have been
645 genetically derived over eons of evolution – seems more consistent with experimental data.
646 Orientation tuning, spatial and temporal frequency tuning, and normalization are present at the
647 onset of the visual experience, and are only modestly altered by normal experience (Chapman
648 and Stryker, 1993; DeAngelis et al., 1993; White et al., 2001; this paper; Li et al., 2006) (though
649 abnormal experience can create highly aberrant receptive field properties, as in Mitchell, 1988;
650 White et al., 2001; Prusky and Douglas, 2003). Experience is necessary for development of
651 cortical direction selectivity (Li et al., 2006), but the tuning parameters that will emerge (angle
652 preference and speed tuning) are already determined, and experience seems only to enhance the
653 selectivity (Li et al., 2008; Roy et al., 2016; Ritter et al., 2017). The major contribution of
654 experience, at least in primary visual cortex, appears to be the alignment of the inputs of the two
655 eyes (Wang et al., 2010), some refinement of spatial frequency preferences (Mitchell, 1988), and
656 the establishment of appropriate gains for selectivity (Turrigiano and Nelson, 2000).

657
658 These results provide one of two possible conclusions. It could be the case that the major
659 properties of V1 neurons (except ocular alignment) are simply established by experience-
660 independent mechanisms, such as molecular cues and modifications due to spontaneous activity
661 (Meister et al., 1991; Ruthazer and Stryker, 1996; Cang et al., 2008). Or, perhaps, there are
662 important experience-dependent modifications, but these modifications are not observable with
663 the stimuli we have used here, and would only be apparent when animals are viewing more
664 natural stimuli (e.g., Berkes et al., 2011).

665
666 Experience is clearly important to the mammalian brain, but whether its influence is instructive
667 may depend considerably on the brain area or, as suggested here, on the type of neural
668 computation. The evidence presented here suggests that cross-orientation suppression and
669 surround suppression are present in ferrets independent of visual experience.

670

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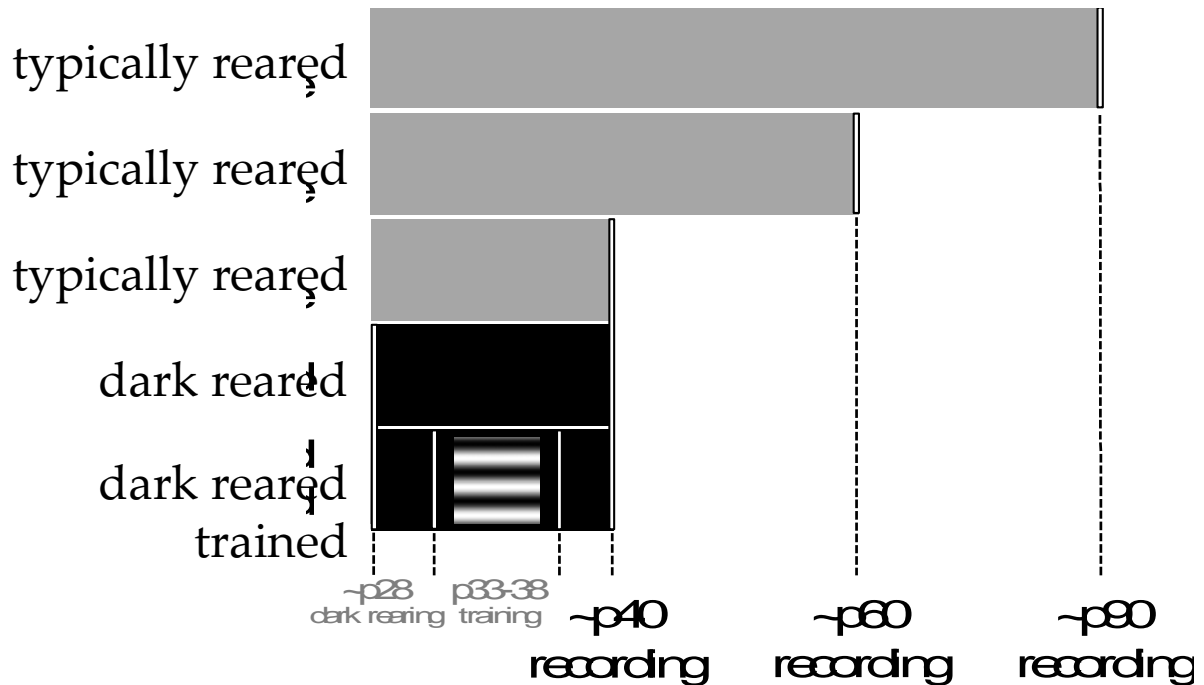


Figure 1. Experimental groups. We studied the development of receptive field properties while varying visual experience and age. We reared three groups of animals until approximately postnatal day 40 (P40, see Methods) according to different protocols. One group (typically-reared, P40) was provided 12 hours of normal light each day. Another group (dark-reared P40) was raised in darkness from P28 (about 3-5 days before normal eye opening) and had very impoverished visual experience. A third group (dark-reared and trained, P40) was raised in the dark from P28 but was provided with 14-16 total hours of experience with simple sinusoidal grating stimuli over several sessions. These groups were compared to animals with approximately 1 month of typical visual experience (typically-reared, P60) and approximately 2 months of visual experience (typically-reared P90).

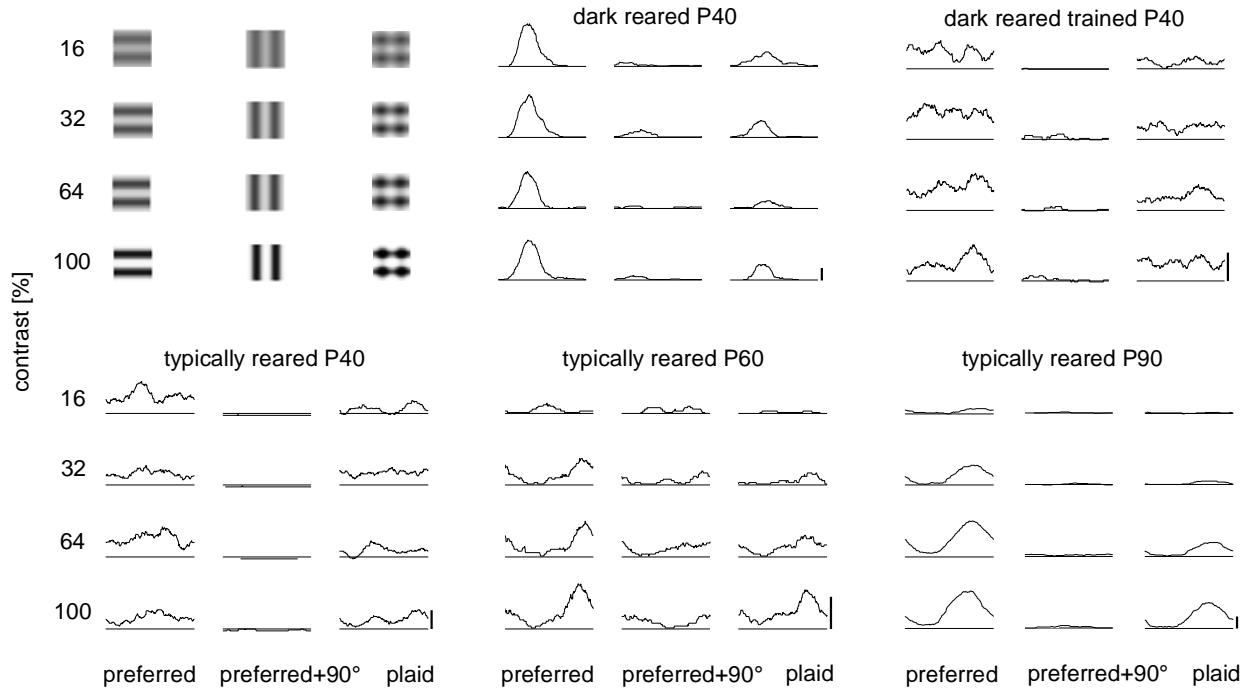


Figure 2. Representative cells in all experimental conditions exhibit cross-orientation suppression. For each cell, cycle-averaged responses to stimulation at the preferred direction, the orthogonal direction, and a plaid combination of the two stimuli are shown, for a variety of stimulus contrasts. Time is on the horizontal axis (showing 1 grating cycle). Vertical axis indicates response; bars denote 10 spikes/sec.

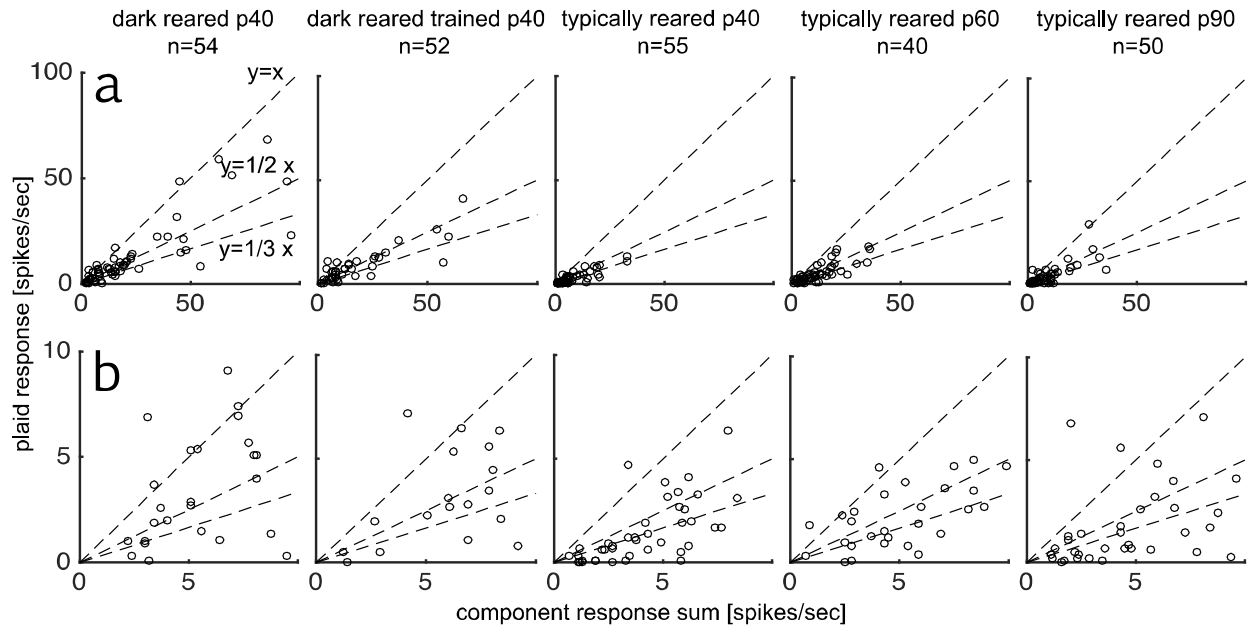


Figure 3. Cells in all animal groups exhibit robust cross-orientation suppression. Scatterplots of responses to plaid stimulation plotted against the linear sum of the response to preferred stimulation and orthogonal stimulation (that is, the component response sum) for stimuli of 100% contrast. Dashed lines show slopes $y = x$, $y = 1/2 x$, and $y = 1/3 x$. **a)** displays full range of data, **b)** displays data in the 0-10 spikes/sec range.

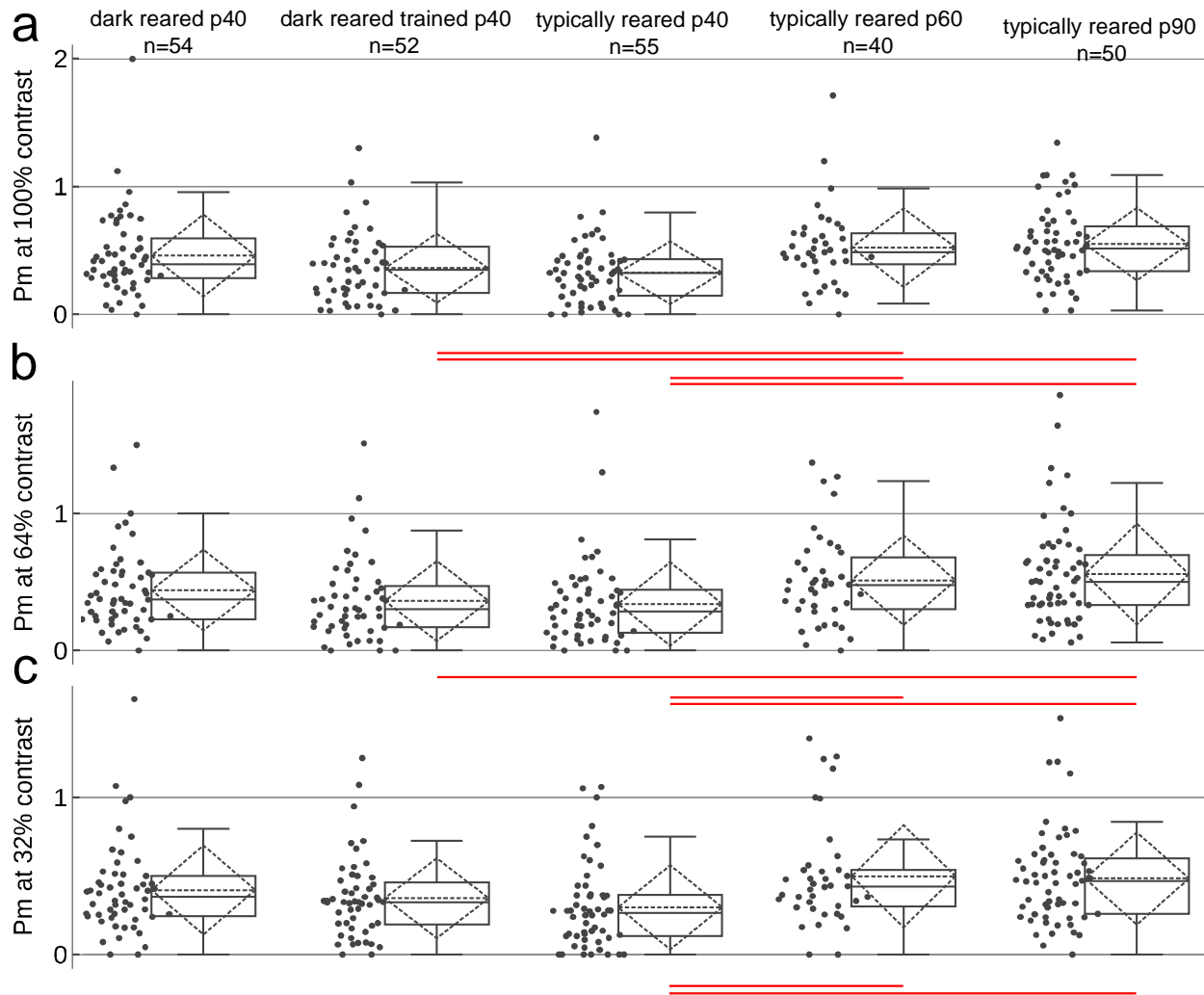


Figure 4. Median cross-orientation suppression varies slightly across age and condition. Plaid multiplier P_m is shown for all cells across all groups at 32%, 64%, and 100% contrast. For each group, all data points are shown at the left, and a box and whisker plot is shown at the right. The horizontal line in the center of each dotted diamond indicates the mean, and the dotted diamond tips are at ± 1 standard deviation. Lower P_m values indicate higher suppression. There is a slight increase in suppression in typically-reared P40 animals at all contrasts, and cross-orientation suppression reduces slightly at P60 and P90. Dashed lines are at 0.5 and 1. Red lines indicate pairwise differences significant at $p < .05$ (Bonferroni-corrected Kruskal-Wallis test).

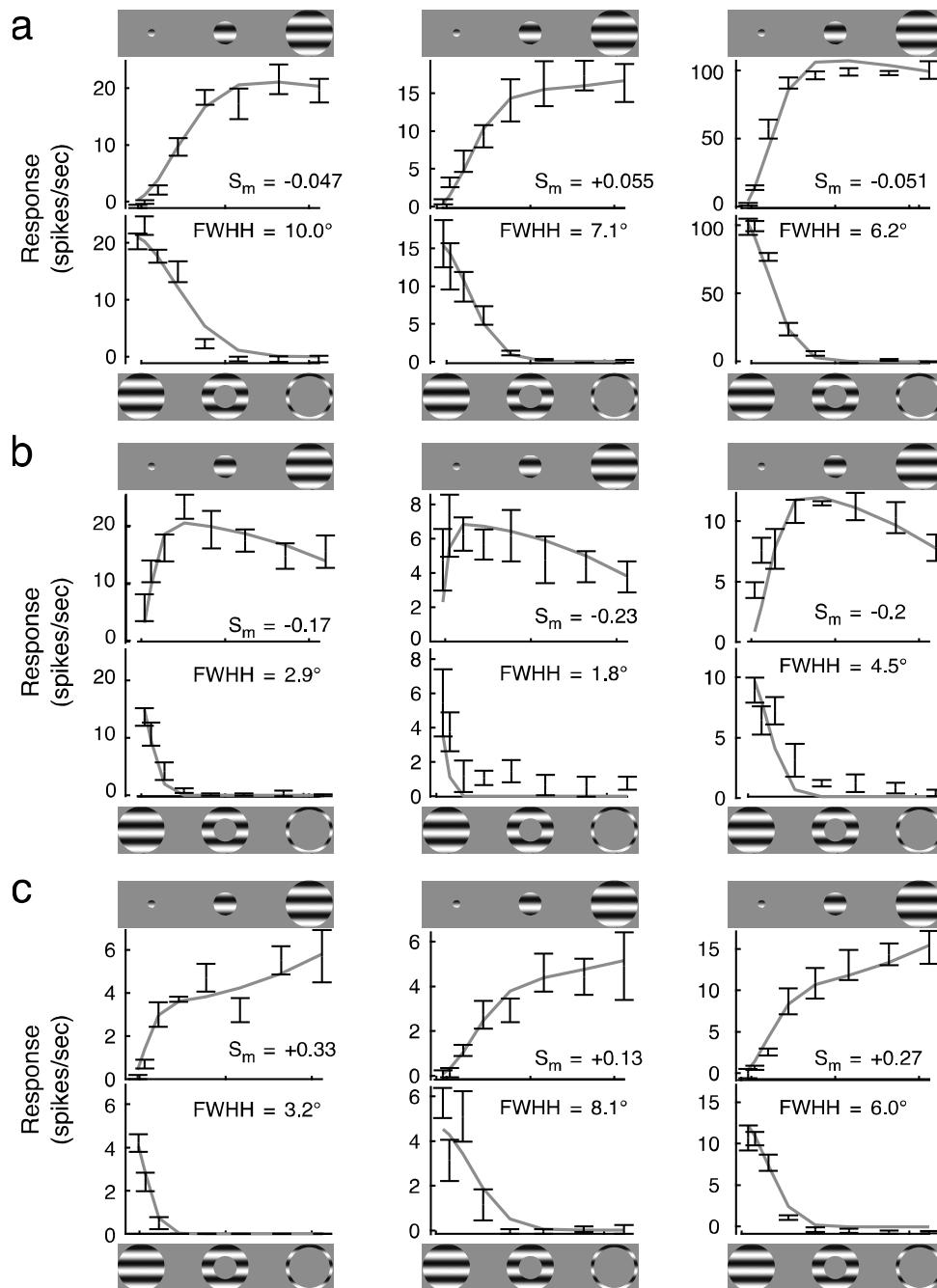


Figure 5. Diversity of size tuning curves in ferret visual cortex. Cells were fit to a Gaussian center and a circular modulating region (see Methods). Size tuning curves and corresponding fits for three broad groups of response categories: a) cells that exhibit a plateau but are not modulated by stimulation in the surround (S_m approximately 0), b) cells that exhibit surround suppression (S_m negative), and c) cells that exhibit length summation (S_m positive). Top panel for each cell shows responses to stimuli of increasing size [3° , 6° , 11° , 19° , 29° , 39° , 48° , 54°] while bottom panel shows responses to an annulus of increasing inner diameter (same sizes). Responses to both classes of stimuli were used to construct the fits. FWHH is full width at half height of the Gaussian center region.

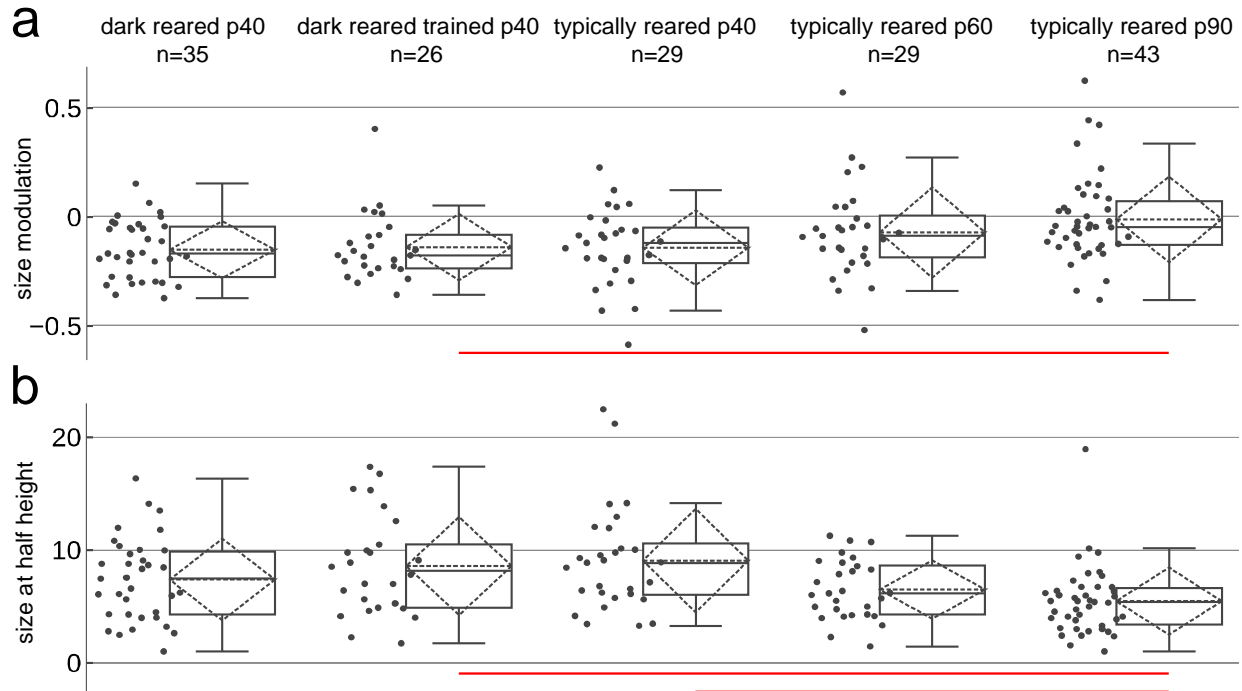


Figure 6. Size tuning properties with age and experience. a) Parameter S_m ; cells that exhibit plateau responses and surround suppression are found in all animals, but cells that exhibited substantial length-summation were found more commonly in the oldest animals. Red lines indicate pairwise differences (Kruskal-Wallis test, Bonferroni corrected) at $p < 0.05$. b) As expected from earlier reports, receptive field size as assessed by the full width at half height (FWHH) of the Gaussian center component exhibited decreases with experience, and was smallest in the oldest animals examined. Red lines indicate pairwise differences (paired t-test with Bonferroni correction) significant at $p < 0.05$. Note that the major reduction of receptive field size occurs after other properties like orientation and direction selectivity have been established.

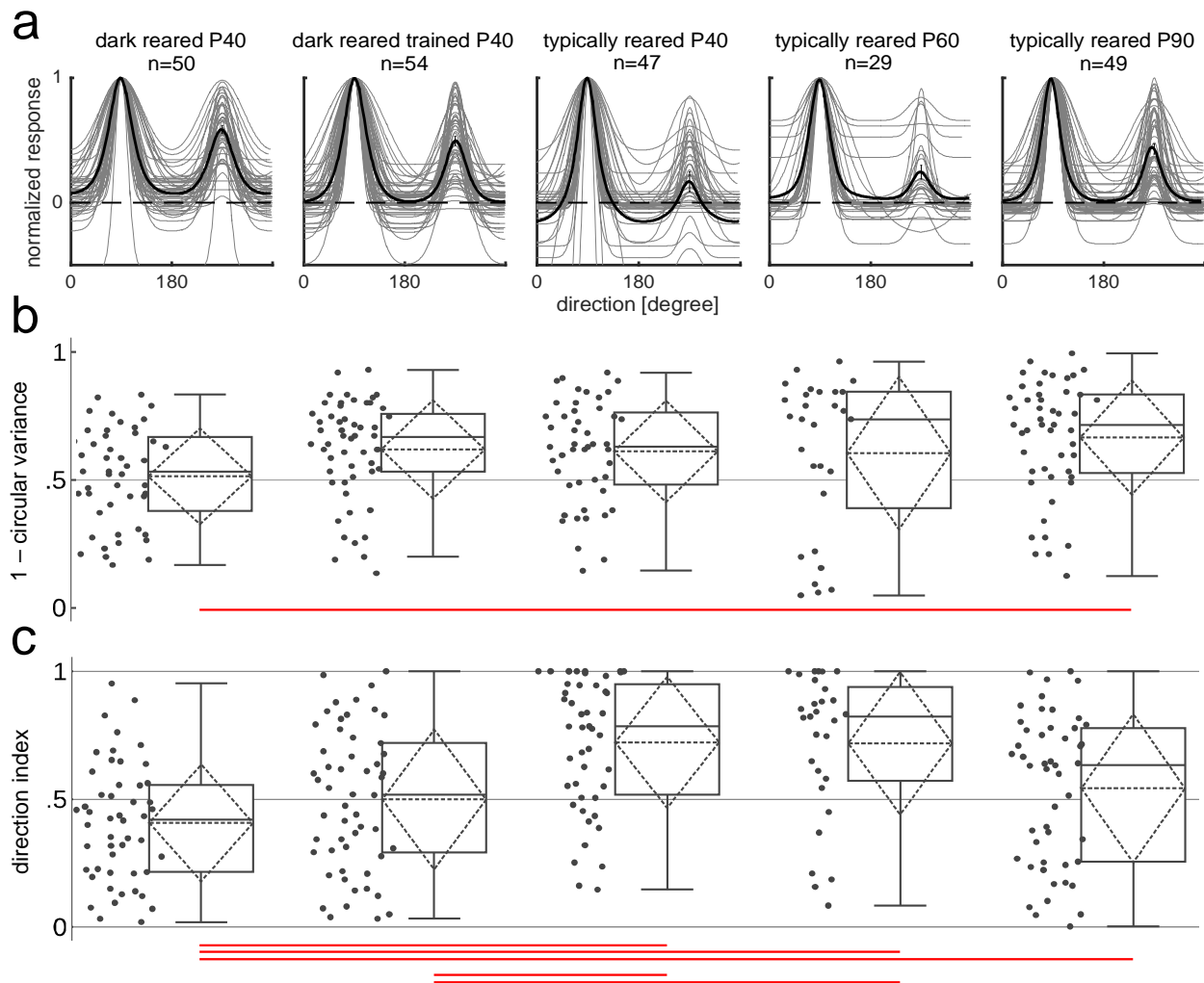


Figure 7. Effects of experimental condition on the development of orientation and direction tuning. a) Normalized direction tuning curves for the 5 experimental conditions; b) orientation selectivity quantified as 1-circular variance; c) direction selectivity quantified as direction index. Dashed lines are at 0.5 DI and 1- circular variance; red lines indicate pairwise differences significant at $p < 0.05$ (Kruskal-Wallis test, Bonferroni correction). As expected from previous studies, both orientation selectivity and direction selectivity exhibit increases with experience. Unexpectedly, direction selectivity reached a peak at P40/P60 and reduced slightly at P90, consistent with the idea that direction selectivity does not develop in a monotonic manner.

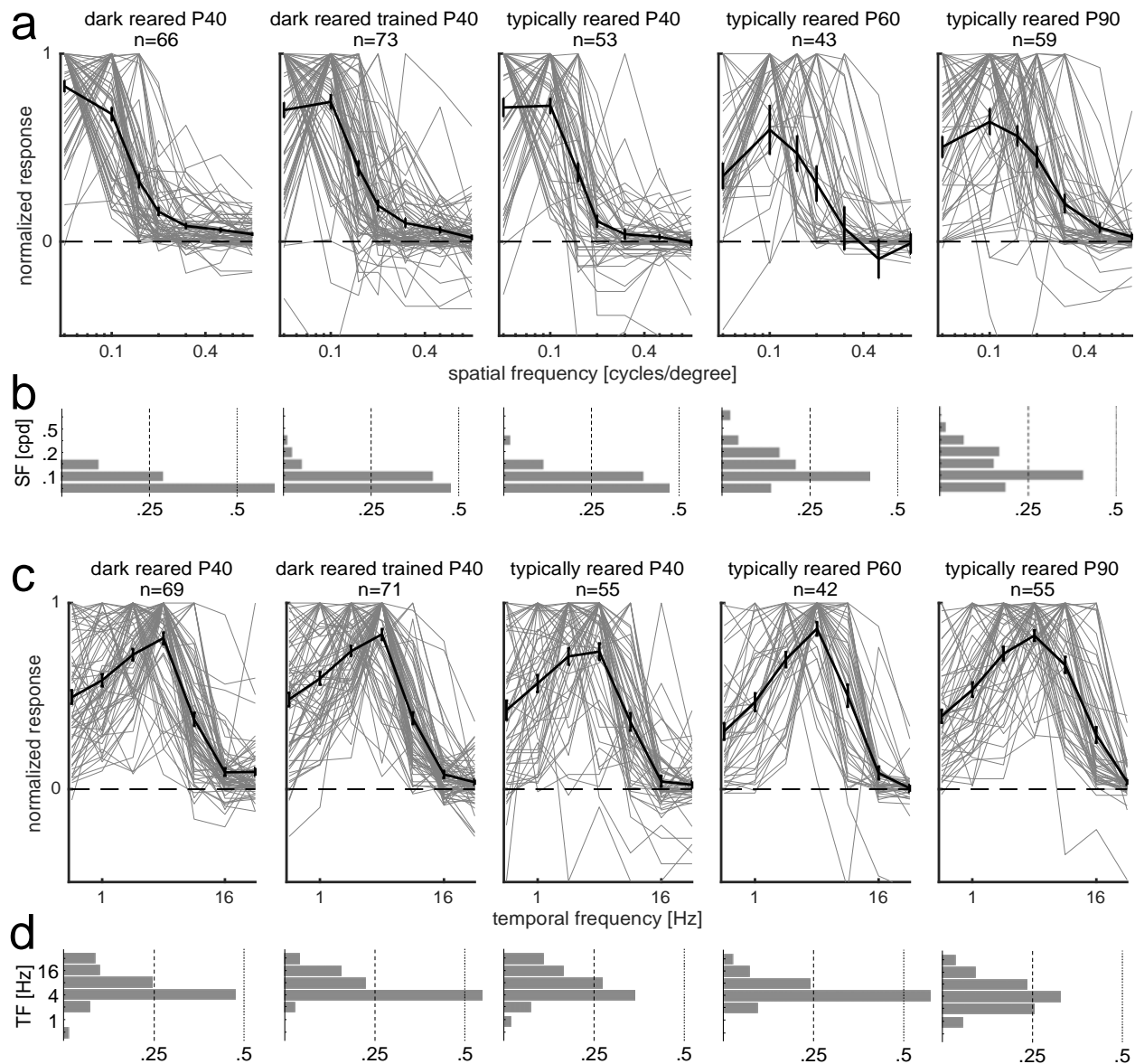


Figure 8. Effects of experimental condition on the development of spatial and temporal frequency preference. a) Normalized spatial frequency tuning curves for the 5 experimental conditions; b) normalized spatial frequency histogram; ticks on the y axis denote 0.05, 0.1, 0.15, 0.2, 0.3, 0.5, and 0.8 cycles per degree (cpd) (bottom to top). c) Normalized temporal frequency tuning curves for the 5 experimental conditions; d) normalized temporal frequency histogram; ticks on the y axis denote 0.5, 1, 2, 4, 8, 16, and 32 Hz (bottom to top). As expected from previous studies, and consistent with decreases in receptive field size that are reported in **Figure 6**, spatial frequency preferences exhibited slight increases with age, indicating that the spatial resolution of visual processing increases with age.

Temporal frequency preferences were relatively constant over the ages and rearing conditions studied here.

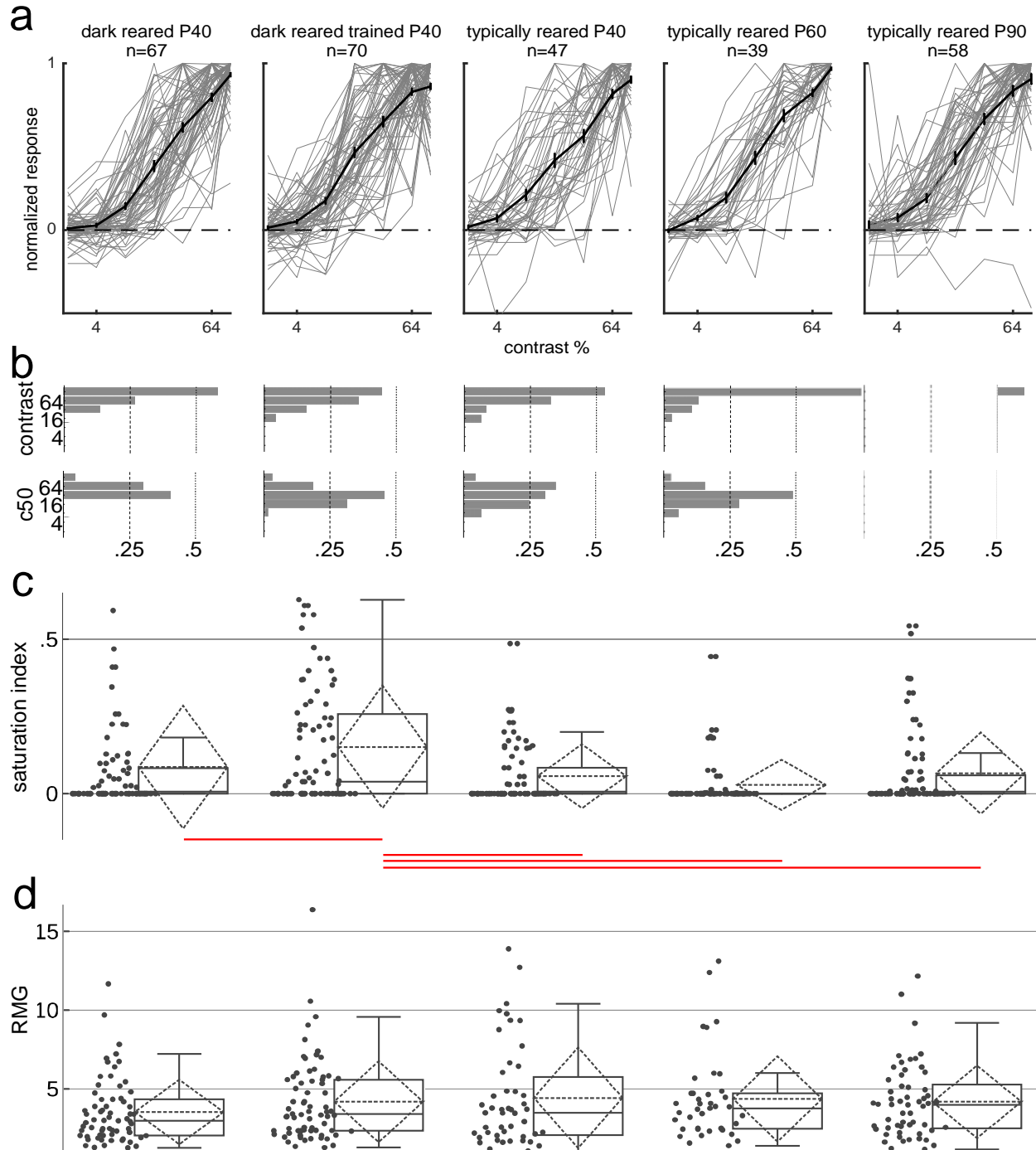


Figure 9. Effects of experimental condition on the development of contrast preference. a) Normalized contrast tuning curves for the 5 experimental conditions; b) contrast at peak (top), and half-peak response (bottom); c) saturation index of contrast response curve; d) linearity in response to contrast quantified by relative maximum gain, lower values indicate more linearity. Red lines indicate pairwise differences significant at $p < 0.05$. Contrast responses were relatively constant over the developmental ages and rearing conditions studied here, with some slight variation in saturation index.

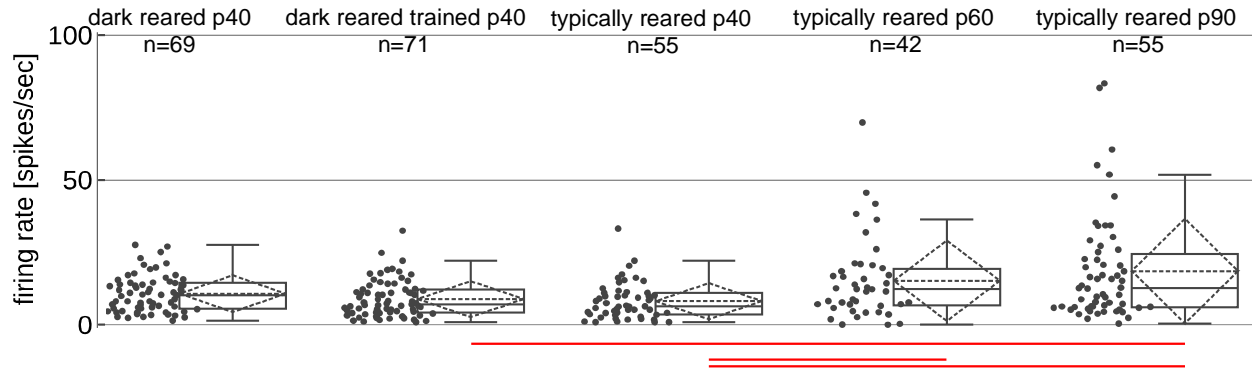


Figure 10. Firing rate across experimental conditions. Red lines indicate pairwise differences (Kruskal Wallis test, Bonferroni corrected) significant at $p < 0.05$. The oldest animals exhibited substantially higher firing rates than younger animals.