

The development of direction selectivity in ferret visual cortex requires early visual experience

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Development of the selective response properties that define columns in sensory cortex is thought to begin early in cortical maturation, without the need for experience. We investigated the development of direction selectivity in ferret visual cortex using optical imaging and electrophysiological techniques and found an exception to this view. Unlike orientation selectivity and ocular dominance, direction selectivity was not detected at eye opening. Direction selectivity emerged several days later and strengthened to adult levels over the following 2 weeks. Visual experience was essential for this process, as shown by the absence of direction selectivity in dark-reared ferrets. The impairment persisted in dark-reared ferrets that were given experience after this period, despite the recovery of response amplitude, preference and bandwidth for stimulus orientation, spatial and temporal frequency, and contrast. Visual experience in early postnatal life plays a necessary and unique role in the development of cortical direction selectivity.

The development of response properties in the primary visual cortex (V1) is thought to involve two distinct phases: an experience-independent phase in which the basic neural circuits that underlie neuronal selectivities become established and organized into cortical maps, and a subsequent phase of plasticity in which initial circuits are elaborated and refined by visual experience^{1–7}. The conclusion that visual experience has little impact on the establishment of cortical response properties rests on two well-documented observations: (i) ocular dominance and orientation preference are present and arrayed in a columnar fashion before the onset of visual experience^{1–9}, and (ii) total visual deprivation has little impact on the formation of either property^{5,10}. However, comparable evidence regarding the establishment of other columnar properties is lacking, leaving open the question of whether this conception of sensory cortical development provides an adequate framework for understanding the role of sensory experience in postnatal brain maturation.

In this study, we used intrinsic signal optical imaging methods and electrophysiological recordings to test the necessity of visual experience for the development of cortical direction selectivity in juvenile ferrets. Like orientation selectivity, direction selectivity is first expressed at the level of cortical circuits and, like both ocular dominance and orientation preference, neurons that are tuned for the same direction of motion are clustered into columns, with the columnar array organized into a map of direction preference¹¹. However, much less is known about the emergence of this response property. Direction-selective units have been recorded in newborn macaques¹² and very young kittens¹, but the prevalence of sharply tuned neurons in visually naïve animals is low^{13,14}, and it is unknown whether these neurons are organized into a map of direction preference at the onset of visual experience. Furthermore,

altered forms of experience during development (for example, dark rearing^{10,13–15} and strobe rearing^{16–19}) affect the prevalence and magnitude of direction-selective responses, but it is unclear whether these changes are due to a disruption of the establishment of direction selectivity or to plasticity in a subsequent phase of consolidation.

Our results showed that direction selectivity first emerged after eye opening and then rapidly achieved mature levels of tuning over the following 2 weeks. Thus, the development of direction selectivity lagged behind the establishment of ocular dominance and orientation preference, both of which were present and organized into functional maps at the time of eye opening in these same individuals. Experiments on ferrets reared in absolute darkness showed that visual experience during this formative period was essential for the development of direction selectivity. Furthermore, later experience did not substitute for early experience: direction selectivity remained severely impaired in ferrets that were dark reared until about 3 weeks after eye opening and then provided with experience for another 3 weeks during the peak of the critical period for ocular dominance plasticity^{20,21}. This dependency on early experience clearly distinguished direction selectivity from orientation selectivity, spatial and temporal frequency tuning, and contrast sensitivity, all of which were affected by early deprivation but showed complete recovery with later experience. Direction selectivity was only present in those ferrets that experienced the visual environment in an early formative period after eye opening.

RESULTS

Direction selectivity emerges after eye opening

To investigate the initial emergence of direction selectivity, we used optical imaging techniques to determine when direction selectivity is

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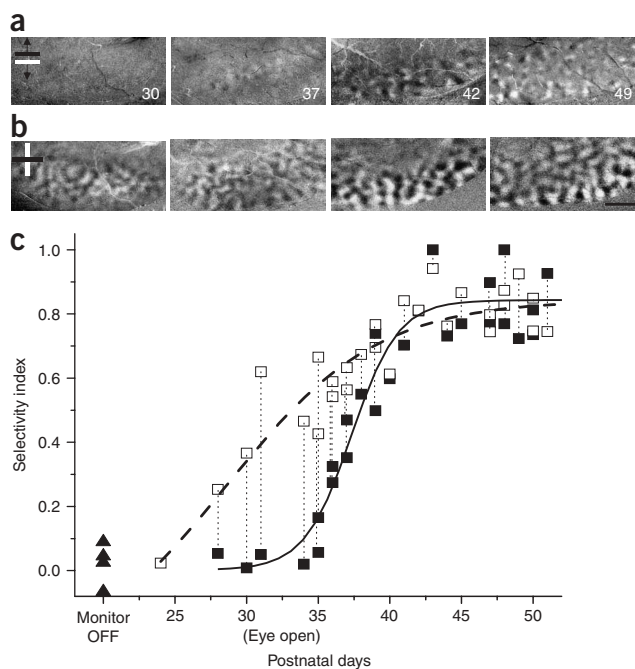


Figure 1 Development of direction and orientation selectivity. **(a)** Difference images showing differential responses to upward and downward motion; numbers indicate age in postnatal days (scaled to ± 0.0010 difference of $\Delta R/R$). **(b)** Difference images showing differential responses to horizontal and vertical orientations from the same ferrets. Scale bar, 2 mm (scaled to ± 0.0015 difference of $\Delta R/R$). **(c)** Indices of direction (filled squares) and orientation (open squares) selectivity normalized to maximum value. Square symbols, individual cases (vertical lines connect data from the same ferret); triangles, baseline values recorded with the monitor off. Direction and orientation selectivity indices were fit by Boltzmann functions ($R^2 = 0.77$ for direction selectivity; $R^2 = 0.90$ for orientation selectivity).

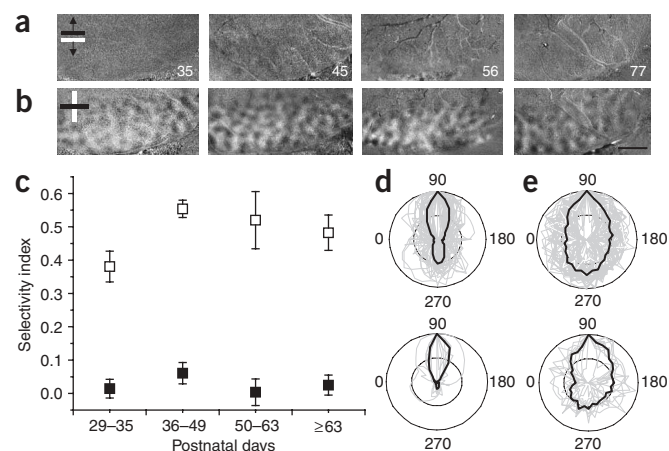
the magnitude of direction selectivity and the distribution of columnar direction-selective signals increased rapidly, such that direction selectivity achieved functional maturity at roughly the same time as orientation selectivity (**Fig. 1c**). In sum, these intrinsic signal imaging observations in normal juvenile ferrets showed that direction-selective signals emerged after eye opening and after the establishment of ocular dominance and orientation selectivity.

Dark-reared ferrets lack direction selectivity

The emergence of direction-selective responses after eye opening raises the possibility that visual experience is essential for this process. To test this possibility, we examined ferrets that were completely deprived of visual experience by absolute dark rearing from postnatal day 17 (before the time of cortical responsiveness to visual stimuli²) until sedation for terminal optical imaging and electrophysiological experiments. No direction-selective signals were detected in any dark-reared ferret, regardless of age (postnatal days 30–77) (**Fig. 2**). The fact that this deficit was seen in older ferrets, including those examined near the end of the critical period for ocular dominance plasticity^{20,21}, indicates that the absence of direction-selective signals in younger juveniles cannot be summarily attributed to a delay in visual cortical development^{26,27}. As these same dark-reared ferrets also showed robust orientation selectivity (**Fig. 2b**), the visual cortex did not simply become unresponsive. Indeed, single-condition images, which report cortical responsiveness, showed columnar activation to each unidirectional stimulus tested (**Supplementary Fig. 2** online); however, individual cortical columns responded equally well to opposite directions of motion, and no selectivity signal was obtained in direction difference images. Furthermore, this impairment was not the result of using visual stimuli that lack the spatial and temporal frequencies and contrasts appropriate for eliciting direction-selective responses in dark-reared ferrets. Direction selectivity was not detected with a broad range

evident in the population response. In the youngest ferrets examined (postnatal days 28–34), there was little or no differential response to opposite directions of motion, despite the presence of columnar patterns of orientation-selective and eye-specific activity (**Fig. 1a,b** left panels, and **Supplementary Fig. 1** online). This was observed with both high-contrast, rectangular wave gratings used in previous studies^{5,11} and sine wave gratings that varied over four octaves of spatial and temporal frequency and contrast. As direction selectivity is sensitive to contrast²² and strongest at higher temporal frequencies in young kittens^{23–25}, it was important to use a broad range of stimulus parameters. In doing so, the same result was obtained, ruling out the possibility that we failed to provide an adequate stimulus to detect direction-selective responses in immature ferrets. In ferrets a few days older (postnatal days 35–37), direction-selective signals could be detected, but they were weak and often localized to restricted portions of visual cortex (**Fig. 1a** second from left), even as orientation selectivity signals became stronger across V1 and V2 (**Fig. 1b** second from left). When assessed quantitatively across a large sample of juveniles ($n = 45$), cortical activity patterns produced by subtracting responses to opposite directions of motion did not differ from nonstimulated background signals until after eye opening (postnatal days 28–33) and did not achieve 50% of mean adult levels until postnatal day 37 (± 1 d), about 10 d after the comparable 50% mean adult orientation selectivity index was achieved (postnatal day 28 ± 2 ; **Fig. 1c**). Despite this delay,

Figure 2 Impaired development of direction selectivity in dark-reared ferrets. **(a)** Difference images showing differential responses to upward and downward motion; numbers indicate age in postnatal days (scaled to ± 0.0010 difference of $\Delta R/R$). **(b)** Difference images showing differential responses to horizontal and vertical orientations from the same ferrets. Scale bar, 2 mm (scaled to ± 0.0015 difference of $\Delta R/R$). **(c)** Indices of direction (filled squares) and orientation (open squares) selectivity normalized to maximum value (symbols represent mean \pm s.d.). **(d,e)** Direction selectivity of multiunit recordings from layer 2/3 of V1 in normal **(d)** and dark-reared **(e)** ferrets. Upper plots, all sites; lower plots, the ten most directionally selective sites. Gray lines, individual sites; black lines, median tuning functions normalized to a preferred direction of 90° and maximal response.



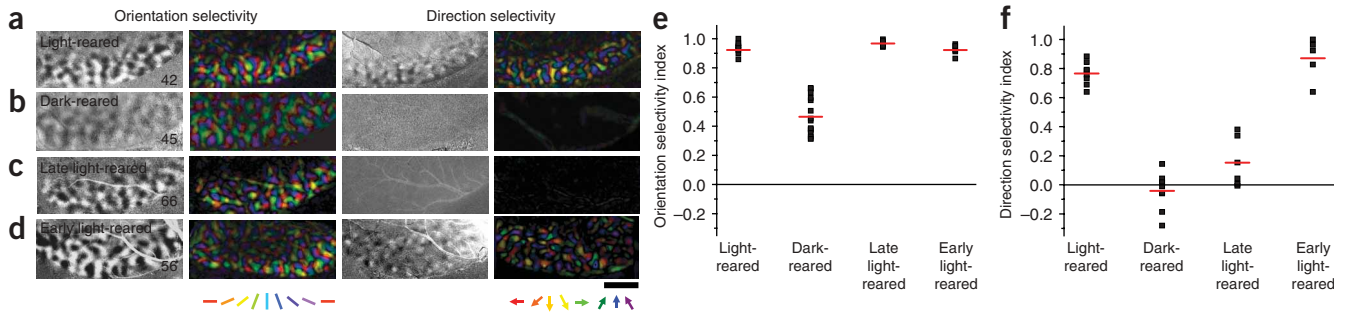


Figure 3 Early visual experience promotes the development of direction selectivity. (a–d) Difference images and polar-magnitude maps of orientation selectivity (left) and direction selectivity (right) from representative ferrets. Numbers indicate age. Scale bar, 2 mm (orientation images scaled to ± 0.0015 difference of $\Delta R/R$; direction images scaled to ± 0.0010 difference of $\Delta R/R$). (a) Normal, light-reared ferret. (b) Dark-reared ferret. (c) Dark-reared ferret with late vision (from postnatal day 45). (d) Dark-reared ferret with early vision (from postnatal day 35). (e, f) Quantification of orientation (e) and direction selectivity (f).

of sine wave gratings, even with those combinations of frequencies and contrasts that yielded maximal orientation-selective responses and robust maps of ocular dominance (Fig. 2b,c and Supplementary Figs. 1 and 2).

These optical imaging results were confirmed with the analysis of direction-selective responses in extracellular recordings from normal and dark-reared ferrets (Fig. 2d,e). On average, multiunit recordings from supragranular layers of V1 in normal ferrets showed nearly three times the response for motion in the preferred direction compared to the opposite direction (preferred/opposite \pm s.d. = 2.90 ± 0.40). In contrast, comparable sites from dark-reared ferrets showed only weak directional biases (preferred/opposite \pm s.d. = 1.32 ± 0.04 ; Supplementary Table 1 online), with none of the recording sites in the dark-reared group (Fig. 2e) approaching the sharpest tuning recorded in normal ferrets (Fig. 2d). Similar results were observed when single units were analyzed (Supplementary Fig. 3 online). Thus, it is unlikely that limitations in the spatial resolution and/or sensitivity of optical imaging methods^{28,29} can explain the absence of direction selectivity in dark-reared ferrets. Similarly, the imaging results cannot be attributed to an intermixing of well-tuned neurons that prefer opposite directions of motion.

Direction selectivity requires early visual experience

The results from dark-reared ferrets indicate that visual experience is necessary for the development of direction selectivity; however, they do not address the question of when visual experience is required. Given the set of widespread developmental changes in ferret visual system structure and function that ensue at or shortly after eye opening^{5,9,30–32}, it is possible that vision must occur in this restricted period of time for cortical direction selectivity to develop. Alternatively, it is possible that vision remains efficacious throughout the period when thalamocortical circuits are normally subject to experience-dependent plasticity^{20,21} and perhaps longer, should dark rearing delay the time course of cortical development^{26,27}. To determine if this is so, we asked whether the effects of early dark rearing might be ameliorated by later exposure to lighted environments. Thus, we dark-reared groups of ferrets from postnatal day 17 until postnatal days 45–50 and then continued rearing with a standard 12-h, light-dark cycle for another 2–3 weeks before assessing orientation selectivity and direction selectivity (Fig. 3). The results showed that the direction selectivity of these ferrets remained profoundly impaired (Fig. 3c,f). This strongly implicates visual experience in the first 2–3 weeks after eye opening as a crucial factor in the development of direction selectivity. To confirm that this is the decisive period when vision may exert its formative influence, we dark-reared another group of ferrets until postnatal day 35 and then exposed them

to lighted environments for 2 or 3 weeks. In contrast to all other dark-reared ferrets in this report, each of these ferrets showed well-tuned direction-selective responses and the formation of a complete map of direction preference (Fig. 3d). The average index of direction selectivity obtained from this cohort was significantly greater than that from both the dark-reared and late vision groups (Tukey HSD, $P < 0.01$) but the same as that measured in ferrets reared normally (Fig. 3f).

Unique role for early experience in direction selectivity

The severe impairments of direction selectivity in ferrets deprived of early visual experience clearly distinguished this property from orientation selectivity and ocular dominance, both of which were present in dark-reared ferrets. However, dark rearing had a broader impact on cortical response properties, in addition to its abrogation of direction selectivity (Fig. 2). Consistent with a previous report⁵, dark rearing prevented the full maturation of orientation selectivity (Fig. 3b,e). In addition, dark rearing induced shifts in the tuning of the population response to spatial and temporal frequency and contrast (Fig. 4). Compared to age-matched ferrets reared normally, dark-reared ferrets responded best to lower spatial frequency over a narrow bandwidth of temporal frequencies, and only at high contrasts (see Supplementary Table 2 online). Furthermore, the amplitude of the cortical response was reduced by at least one-third of normal in the dark-reared group, even when these stimulus parameters were optimized to yield the maximal response (Fig. 4).

However, with the sole exception of direction selectivity, each of these dark rearing-induced deviations from normal response parameters was completely rectified in ferrets that were provided with late visual experience (Fig. 4, Supplementary Fig. 4 online and Supplementary Table 2). Direction selectivity was, therefore, unique among visual cortical response properties in its dependence on visual experience in the first 2–3 weeks after eye opening. Furthermore, these observations indicate that the failure of direction-selective responses to develop in the late vision group cannot be attributed to long-lasting alterations in other receptive field properties and response preferences, including temporal frequency tuning and contrast sensitivity, two properties that modulate the expression of direction selectivity in normal animals^{22,33}.

DISCUSSION

Functional maps of columnar properties are among the most striking features of sensory cortical areas in the mammalian brain, and they have long served as model systems for understanding the interactions between endogenous mechanisms of brain development and sensory

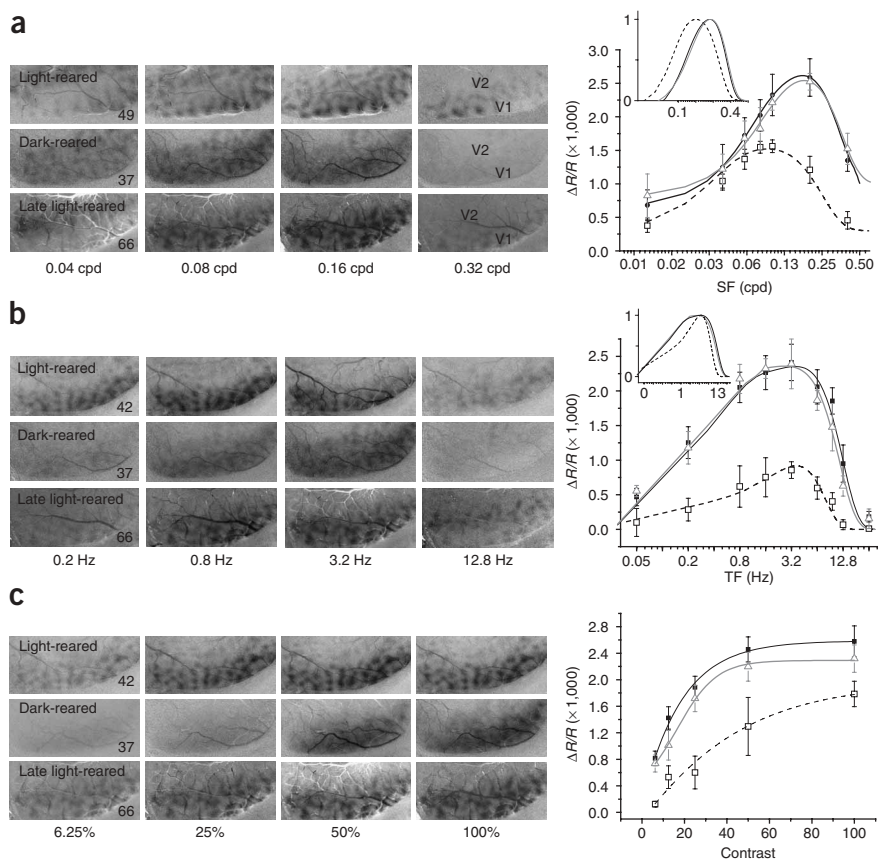


Figure 4 Effects of varying spatial and temporal frequency and contrast. **(a)** Spatial frequency. **(b)** Temporal frequency. **(c)** Contrast sensitivity. Each panel shows single-condition images from a normal, light-reared ferret (top row), a dark-reared ferret (middle row) and a dark-reared ferret with late vision from postnatal day 45 (bottom row). Numbers indicate age; images scaled to 0.003 $\Delta R/R$ with positive values indicating increased light absorbance; scale bar, 2 mm. On right, graphs of quantitative assessments of the difference images in each panel (normal, black; dark-reared, dashed; late light-reared, gray).

experience. Studies of the development of ocular dominance and orientation selectivity in the visual cortex have led to the view that there are two phases of sensory cortical development: an initial phase in which columnar properties are established and organized into maps by molecular cues and endogenous patterns of neural activity, and a later phase defined by the experience-dependent mutability of functional maps and the plasticity of underlying neuronal response properties^{4,6,7,34}. Our studies of direction selectivity are difficult to reconcile with this view of sensory cortical development; they demonstrate a role for experience in the emergence and maturation of a columnar response property during a brief, early period of cortical development.

For normal ferrets, this experience dependency manifests as a developmental lag in the formation of the map of direction preference until after the onset of patterned visual experience and after the organization of columnar structure in the maps of ocular dominance and orientation preference^{5,9,35,36}. This developmental sequence provides an explanation for why continuity in the mapping of orientation preference (full-cycle representation with point singularities) takes precedence over continuity in the direction map (half-cycle representation with linear fractures)^{11,37}. This also accounts for the nested geometrical relation between the maps of direction and orientation preference^{11,37–39}. Neurons that respond to the same axis of motion are first organized into orientation columns that subsequently differentiate into paired subregions that prefer opposite directions of motion.

dependent mechanisms could bring about the convergence of inputs whose receptive field locations and response latencies establish the appropriate space-time gradient, if the proper inputs are coactive in a narrow time window before a neuron's spike⁴³. Although conditions for this instruction might be met by endogenous neural activity^{44,45} and could account for the presence of a small percentage of direction-selective units in visually naïve animals^{1,12–14}, the present results indicate that such activity is insufficient to construct the circuits that underlie the map of direction preference. Rather, our findings suggest a requirement for space-time correlations in neural activity engendered by early visual experience.

But why should this formative influence of experience be constrained to a brief period immediately after eye opening? Notably, in ferrets at least, this is when exuberant retinogeniculate inputs are pruned and LGN neurons acquire their circular receptive fields and narrow distribution of response latencies³⁰. We suggest that the instruction necessary for the development of direction selectivity must ensue when LGN neurons are relatively immature, so that their subsequent maturation may be optimized to meet the space-time requirements of postsynaptic cortical targets. This could occur by means of retrograde signals generated at the cortical level by visually evoked patterns of neural activity that supervise the refinement of geniculate receptive fields and sharpen the timing of information flow through the thalamic relay. Recent studies of hippocampal cultures⁴⁶ and the developing

Consistent with the delayed development of direction selectivity in the ferret, anatomical and single-unit studies of nonhuman primates show adult-like distributions of ocular dominance columns³ and orientation-selective units⁸ in the first week of postnatal life, but more immature distributions of direction selectivity, characterized by a large fraction of non-directionally selective neurons¹². Recent studies using visually evoked potentials in human infants suggest a similar postnatal lag in the development of direction selectivity⁴⁰. Despite substantial phylogenetic and ontogenetic differences in eye and brain maturation at birth, the relative immaturity of direction-selective responses immediately following the onset of visual experience could signify a common developmental mechanism. If so, early, patterned visual experience should be considered critical for the proper emergence and maturation of cortical direction selectivity.

The unique dependence of direction selectivity on visual experience may reflect the requirements for constructing circuitry that detects the temporal order of stimulus presentation. At the first stage of cortical processing, thalamic inputs from the lateral geniculate nucleus (LGN) and intracortical inputs to direction-selective simple cells are arranged in a fashion that instantiates a spatial gradient of timing signals: response latencies progressively decrease for sequential positions along the preferred direction, producing a net summation of excitatory inputs for this direction of motion that is absent for motion in the opposite direction^{18,19,24,25,41,42}. Activity-

retinotectal system⁴⁷ suggest molecular mechanisms that could mediate such retrograde synaptic modification in neural systems, and it is conceivable that similar mechanisms operate in the mammalian visual pathway to fulfill the stringent demands of response selectivity in the visual cortex. In the absence of the appropriate instructive signals, the spatiotemporal properties of LGN neurons would be shaped by intrinsic activity in the visual pathway that, although competent to instantiate orientation selectivity⁵, evidently fails to establish an effective space-time gradient in cortical simple cells for direction selectivity. Indeed, recent studies of geniculate receptive fields in dark-reared ferrets⁴⁸ show severe spatial and temporal abnormalities that, evidently, cannot be rectified to satisfy the requirements of cortical direction selectivity. Thus, the early impact of experience attenuates with the tuning and consolidation of the spatiotemporal properties of LGN neurons, maturational processes that abate before the end of the critical period for the experience-dependent modification of thalamocortical arbors and intrinsic cortical circuits that underlie other cortical response properties^{49,50}.

METHODS

All experimental procedures were approved by the Duke University Institutional Animal Care and Use Committee and were performed in compliance with guidelines published by the US National Institutes of Health.

Rearing conditions. Normal sable ferrets (*Mustela putorius furo*) of both sexes ($n = 45$) were reared in a 12-h light-dark cycle. Other ferrets ($n = 26$) were subjected to continual dark rearing beginning on postnatal day 14 to 17. During this time, the kits were nursed by their jill through the age of weaning (near postnatal day 30), with water and soft diet provided *ad libitum*; no adverse effects were observed, as assessed by body weight measurements and daily observation of motoric activity (using night vision goggles equipped with an infrared light source; American Eagle). On postnatal day 35 ($n = 6$) or 2 weeks later (between days 45 and 50, $n = 5$), dark-reared ferrets were placed in a 12-h light-dark cycle for another 2–3 weeks until terminal experiments.

Surgical procedures. Briefly, ferrets were sedated with ketamine and xylazine, anesthetized with a mixture of N₂O and O₂ (2:1) and 3–4% halothane. We then performed a tracheotomy (for artificial ventilation) and femoral vein cannulation (for delivery of medications and fluids). After posterior craniotomy and dura reflection, a chamber made of agar and a coverslip was mounted over the brain. Ferrets were paralyzed with intravenous rocuronium bromide (0.3 mg kg⁻¹ h⁻¹) and maintained on 1–2% halothane at 38 °C with expired CO₂ near 4%.

Optical imaging and visual stimuli. Optical imaging of intrinsic signals was performed with an enhanced video acquisition system or an Imager 3001 (both systems by Optical Imaging). Stimuli were full-field, high contrast rectangular wave gratings or sine wave gratings, with direction of motion (0°, 45°, 90°, 135°, 180°, 225°, 270° or 315°) perpendicular to grating orientation; each experiment entailed 20–40 repetitions of each stimulus set. Difference images of direction or orientation selectivity were generated by subtracting images obtained from a pair of opposite directions of motion or a pair of orthogonal orientations, respectively. To assess orientation and direction selectivity, selectivity indices (OSI and DSI, respectively) were computed for each orientation and direction difference image and average OSI and DSI values were computed across images for each case. This was done by clipping the floating point distribution (at ± 3 s.d. from the median), calculating the s.d. of the distribution of gray levels within V1 and V2 (ref. 5), and subtracting from this value the average blank OSI or DSI obtained in an identical manner from a set of control optical imaging experiments ($n = 4$) with the monitor powered off. Some values of DSI from visually naive ferrets were slightly negative, indicating that the differential signal obtained with this method was less than the mean obtained from the blank experiments (Fig. 3f). To assess cortical responsiveness, the response to a blank screen was subtracted from the response to a grating stimulus, and the differential reflectance, expressed as a fraction of total reflectance ($\Delta R/R$), was measured from 32-bit single-condition images. With the exception of applying

low- and high-pass spatial filters to the images that were used to compute the angle maps of orientation and direction preference in Figure 3, all other images shown were not filtered. All quantitative analyses of cortical response and population tuning in Figure 4 were performed on raw, 32-bit images. One-way analyses of variance followed by *post-hoc* Tukey tests were used to assess the significance of selectivity indices and population tuning parameters.

Electrophysiology. Single- and multi-unit activity was recorded extracellularly from V1 with tungsten microelectrodes (impedance = 8–14 M Ω). Action potentials were recorded from the supragranular layers (<400 μ m) and discriminated using Spike2 software (Cambridge Electronic Design). Direction tuning curves were obtained by panning grating or line stimuli in one of 16 directions (at 22.5° intervals); action potentials were counted for the entire stimulus duration (1–2 s), and offline spike sorting and tuning analysis were done using custom Spike2 software. An index of direction selectivity (DSI) was calculated as follows: $1 - (\text{response to opposite direction}/\text{response to preferred direction})$. Unpaired *t*-tests were used to assess statistical significance.

Note: Supplementary information is available on the Nature Neuroscience website.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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