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S. L. Pallas, P. Wenner, C. Gonzalez-Islas, M. Fagiolini, K. A. Razak, G. Kim, D. Sanes and B. Roerig

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## Visual Experience Is Necessary for Maintenance But Not Development of Receptive Fields in Superior Colliculus

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**Carrasco, M. M., K. A. Razak, and S. L. Pallas.** Visual experience is necessary for maintenance but not development of receptive fields in superior colliculus. *J Neurophysiol* 94: 1962–1970, 2005. First published May 25, 2005; doi:10.1152/jn.00166.2005. Sensory deprivation is thought to have an adverse effect on visual development and to prolong the critical period for plasticity. Once the animal reaches adulthood, however, synaptic connectivity is understood to be largely stable. We reported previously that *N*-methyl-D-aspartate (NMDA) receptor blockade in the superior colliculus of the Syrian hamster prevents refinement of receptive fields (RFs) in normal or compressed retinotopic projections, resulting in target neurons with enlarged RFs but normal stimulus tuning. Here we asked whether visually driven activity is necessary for refinement or maintenance of retinotopic maps or if spontaneous activity is sufficient. Animals were deprived of light either in adulthood only or from birth until the time of recording. We found that dark rearing from birth to 2 mo of age had no effect on the timing and extent of RF refinement as assessed with single unit extracellular recordings. Visual deprivation in adulthood also had no effect. Continuous dark rearing from birth into adulthood, however, resulted in a progressive loss of refinement, resulting in enlarged, asymmetric receptive fields and altered surround suppression in adulthood. Thus unlike in visual cortex, early visually driven activity is not necessary for refinement of receptive fields during development, but is required to maintain refined visual projections in adulthood. Because the map can refine normally in the dark, these results argue against a deprivation-induced delay in critical period closure, and suggest instead that early visual deprivation leaves target neurons more vulnerable to deprivation that continues after refinement.

### INTRODUCTION

Neural activity is thought to be essential for normal development in central visual structures such as the superior colliculus (SC), lateral geniculate nucleus (LGN), and visual cortex, but the specific contributions of spontaneous activity and visually driven activity remain under debate (Grubb et al. 2003; Huberman et al. 2003; McLaughlin et al. 2003b). Furthermore, little is known about how visual circuitry is maintained in adulthood or how early deprivation might influence later maintenance and plasticity. This study addresses the unique contribution of vision itself to the development, refinement, and maintenance of visual receptive fields (RFs) in SC.

It has been argued based on studies in visual cortex that visual deprivation stabilizes an early, diffuse stage of connectivity (Blakemore and Van Sluyters 1975; Chalupa 1995; Cynader 1983; Czepita et al. 1994; Daw 1995; Derrington 1984; Emerson et al. 1982), decreases GABAergic shaping of responses (Benevento et al. 1992, 1995; Morales et al. 2002),

and prolongs the critical period for plasticity (Lee and Nedivi 2002). Consistent with the diffuse terminal arbors, dark rearing throughout postnatal development can also result in enlarged cortical RFs, as defined electrophysiologically (Fagiolini et al. 1994). An alternative explanation for these results, however, is that the enlarged RFs in deprived animals result not from preservation of an early, unrefined state, but from a failure to maintain visual projections that were previously refined by spontaneous activity alone. Thus the extent to which spontaneous and visually driven activity contribute to the development and maintenance of stimulus specificity is unclear.

Examination of the factors contributing to the development and maintenance of response properties in a well-defined subcortical system such as the retinocollicular projection could help to resolve the separate roles of vision and spontaneous activity. In rodents, the SC plays a prominent role in visual perception. Moreover, unlike cortical ocular dominance column formation (Crowley and Katz 1999, 2000) or orientation tuning (Chapman et al. 1999; Crair et al. 1998; Fregnac and Imbert 1978), RF refinement in the visual midbrain is known to require retinal activity (see Udin and Fawcett 1988 for review), making it in some ways a better model system for studying the role of retinal activity in visual development.

There is substantial evidence suggesting that patterned, locally correlated retinal activity is required for development of subcortical retinotopic maps. In the SC, after activity-independent establishment of gross retinotopy, the retinocollicular projection progressively refines, as measured by a reduction in the size of single-unit RFs (Fortin et al. 1999; Huang and Pallas 2001) and a corresponding reduction in retinal axon arbor size and extent (Simon and O'Leary 1992; Yates et al. 2001). Blocking retinal activity with TTX prevents the normal refinement of retinal axon arbors in developing or regenerating retinotectal projections (Harris 1980; Meyer 1983; O'Leary et al. 1986; Schmidt and Buzzard 1993; Schmidt and Eisele 1985), as does synchronizing activity across the retina with strobe rearing (Chalupa and Rhoades 1978; Schmidt and Buzzard 1990; Schmidt and Eisele 1985). Blocking *N*-methyl-D-aspartate (NMDA) receptor-dependent activity from birth, which neither alters the level of activity nor blocks retinocollicular transmission, also prevents RF refinement (Huang and Pallas 2001), and knockout of the  $\beta 2$  acetylcholine receptor gene has the same effect (McLaughlin et al. 2003b). It has been reported in hamster SC that dark rearing has little effect (Chalupa and Rhoades 1978; Rhoades and Chalupa 1978b). Thus whether spontaneous activity is sufficient or whether

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vision is necessary for the developmental refinement and maintenance of retinocollicular projections in mammals remains unclear. We investigated this issue in this study.

We tested the hypothesis that refinement of RF size in the SC would be delayed or prevented in the absence of visual experience. We also studied whether vision would be necessary to maintain refined RFs, even if refinement was delayed by visual deprivation. Contrary to expectation, we found that the RFs in SC became fully refined in the dark, without any delay, yet they could not be maintained if animals remained in the dark as adults. These results are unexpected and important for understanding how early experience may influence the ability to recover from temporary vision loss late in life.

Some aspects of this study have been published previously in abstract form.

## METHODS

A total of 122 Syrian hamsters (*Mesocricetus auratus*) of different postnatal ages between P17 and P362 were used in this study. We chose Syrian hamsters as our model system because, although their visual system is much like that of rats and mice, they are born at an earlier stage of brain development, facilitating manipulations of early developmental events. All of the procedures used on animals met standards of humane care developed by the National Institutes of Health and the Society for Neuroscience and were approved by the Institutional Animal Care and Use Committee.

### Rearing conditions

Syrian hamsters were obtained from Charles River Laboratories (Wilmington, MA) or bred in-house. Normal hamsters were kept on a 14-h/10-h light/dark cycle. Dark-reared (DR) hamsters were maintained in a light-tight, dark room from before birth and exposed only to a dim red light for husbandry purposes (not visible to Syrian hamsters; Huhman and Albers 1994). These conditions were maintained until the recording session. All were acute preparations.

### Surgical procedures

Animals were prepared for terminal electrophysiological recordings as described previously (Huang and Pallas 2001; Pallas and Finlay 1989). Each animal was anesthetized with urethane (0.7 g/ml; 0.3 ml/100 g body weight in 4 IP aliquots at 20- to 30-min intervals), an anesthetic that has minimal effect on subcortical neurotransmission (Maggi and Meli 1986). After surgical exposure of the SC, visual cortex was aspirated bilaterally to visualize the SC. Removal of cortex has no effect on SC neuron RF properties in hamsters, except for a loss of direction tuning (Rhoades and Chalupa 1978a). The brain was kept covered with sterile saline solution, and the eye was protected by a custom-designed, plano contact lens throughout the experiment. In some of the youngest animals, an endotracheal tube was placed to facilitate respiration. The animal was placed in a stereotaxic device, and the conjunctivum was stabilized with 6-0 silk suture to prevent movement of the contralateral eye (Pallas and Finlay 1989). Anesthesia level was periodically monitored during experiments by checking withdrawal reflexes, and supplemental doses of urethane were given if needed.

### Electrophysiology

Teflon-coated tungsten electrodes (1–2 M $\Omega$ ; FHC, Bowdoinham, ME) were used for extracellular recording of single neurons within 200  $\mu$ m of the SC surface to ensure that all recorded units were contained in the stratum griseum superficiale (SGS, the retinorecipient layer) in the right SC. RF diameters of single neurons were plotted by

hand or with a computerized method. For the manual method used in the first group of experiments, single units were electrically isolated by shape and amplitude of action potentials in response to stimulation with a penlight. RF borders were plotted on a translucent dome fixed 30 cm from the eye, with the center of the dome aligned with the optic disk. A RF map was constructed by systematically recording along the rostrocaudal axis of the SC at 100- or 200- $\mu$ m intervals. Only neurons located in the rostral SC were considered for determining RF size (nasotemporal diameter), to be consistent with our previous studies and to provide a uniform population of cells across both experimental groups.

A computerized plotting method was used to gain greater resolution of RFs in some older animals. The data obtained by this method were analyzed separately because they necessarily yield different estimates of RF size. (The difference arises because the threshold for defining the RF edge is set differently and stimulus features are different, but the 2 methods are internally consistent; Pallas and Finlay 1989). Stimuli were generated and data were acquired as described previously (Huang and Pallas 2001). RF diameter of each neuron was determined by sweeping a spot of light (1° diam) from the top to the bottom of the computer monitor screen at successive nasotemporal locations. Successive sweeps started 2° lateral to the previous sweep, allowing a determination of the naso-temporal extent of the RF. The light spot was swept at 5°/s for neurons that preferred slowly moving stimuli or at 30°/s for neurons that preferred rapidly moving stimuli (Pallas and Finlay 1989). The estimated RF size did not change with the velocity of the stimulus used. Regardless of the method, we defined RF size as the naso-temporal diameter of the single unit RF. The zero position of the field was defined as the stimulus position that evoked the greatest response.

### Analysis of RF refinement

To determine when RFs were refined during postnatal development, we grouped normal and DR animals into 5-day age intervals and compared their RF diameters to those in the normal adult (>P80) using a Kruskal-Wallis one-way ANOVA on ranks and Dunn post hoc pairwise comparisons. Within age groups, comparisons between normal and DR animals were made using a Mann-Whitney rank sum test.

### Plotting of RF symmetry

We analyzed the symmetry of RFs by measuring the response level at progressive distances from the RF center. A ratio of the nasal location compared with the temporal location where response levels fell to 20% of maximum provided an estimate (asymmetry index) of how sharply the response declined on one side of the RF center (defined as 0) compared with the other. An asymmetry index exceeding 1 indicates that the decline in the response on the temporal side of the visual RF was sharper than on the nasal side and vice versa.

### Plotting RF substructure

To determine the extent of inhibition both within the RF and in the surround, two spots of light (1° diam each) were swept in parallel from the top to the bottom of the monitor. The second spot of light was swept at successive distances away from its previous location, whereas the first spot was always swept through the center of the RF. Each stimulus pair was repeated three to seven times. The response to the two spots of light was normalized to the response elicited by the center spot presented alone. This allowed us to determine the spatial extent and strength of inhibition of the response to the first spot as caused by the second spot.

## RESULTS

To determine the effect of visual deprivation on retinocollicular map topography and refinement of RFs, we recorded

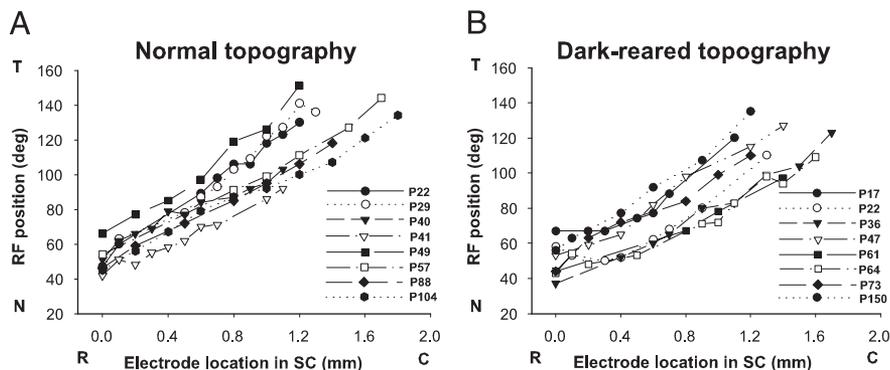


FIG. 1. Visual deprivation does not affect map topography. Maps of visual field location in the superior colliculus (SC) for (A) normal and (B) dark reared (DR) hamsters. Symbols correspond to the center of each receptive field (RF). Average values derived from linear regressions are comparable between normal ( $53.2 \pm 4.15^\circ/\text{mm}$ ,  $n = 77$  neurons) and DR ( $48.2 \pm 3.11^\circ/\text{mm}$ ,  $n = 57$  neurons) animals ( $P = 0.36$ ,  $t$ -test). N, nasal; T, temporal visual field; R, rostral; C, caudal edge of SC.

extracellularly from single units in the superficial layers of the SC. Included in the study were 404 units from 68 normal hamsters and 409 units from 46 DR hamsters. The ages of the animals ranged from P17 to P362. Eye opening in Syrian hamsters occurs between P12 and P14, and sexual maturity occurs between P60 and P90. We also recorded 115 units from eight hamsters whose dark rearing commenced at P60 and extended to adulthood.

#### Dark rearing has no effect on gross retinocollicular map topography

The retinocollicular projection in rats is roughly retinotopic before eye opening (Frost et al. 1979; Simon and O'Leary 1992; Yhip and Kirby 1990). Our recordings revealed that the same is true in hamsters; an orderly map of visual space was present in all normal animals at all ages (Fig. 1A). In the youngest normal animals examined (P22), an ordered retinotopic map was already present in the SC. We also found an orderly retinotopic map in animals dark reared from birth, at all ages (P17–P150; Fig. 1B). There were no differences in the rate of change or in the linearity of RF position along the rostro-caudal axis of the SC between the normal and DR groups [normal:  $53.2 \pm 4.15^\circ/\text{mm}$  (SE);  $n = 77$  neurons from 9 animals; DR:  $48.2 \pm 3.11^\circ/\text{mm}$ ,  $n = 57$  neurons from 8 animals;  $P > 0.3$ ,  $t$ -test;  $r \geq 0.90$  for all cases]. These results are consistent with previous findings that patterned sensory input is not necessary for the development of gross retinocollicular topography (Harris 1980; Thornton et al. 1996).

#### RF refinement is complete by 7 wk of age

We assessed the refinement of the retinocollicular projection by measuring RF size (nasotemporal diameter) of single units in the SC. We observed that in normal animals, RF diameter decreased with age (Fig. 2) and RF borders became more sharply defined. In the SC of animals  $<P40$ , visual responses were robust in the RF center but were less reliably elicited at the edges of the RF. As a result, measured variability in RF sizes was greater in young animals and became less variable with age. The extracellular recording methods used here cannot distinguish whether this variability might be caused by a rapid maturation of lateral inhibition or by a loss of weak excitatory inputs at the RF edges but both processes likely contribute (Shi et al. 1997; Simon and O'Leary 1992). In normal adults ( $>P80$ ), RF diameter averaged  $19.4 \pm 0.56^\circ$  ( $n = 32$  neurons). To quantify the time-course of refinement, we divided postnatal development into 5-day age intervals and compared the

mean RF size in these different age groups to that in normal adults (Fig. 2). By P46–P51 in normal animals, RFs had refined to their adult size (mean RF diameter  $21.3 \pm 0.84^\circ$ ,  $n = 21$  neurons). Before P46, RFs in normal animals were significantly larger than those measured in adults ( $P < 0.05$ , 1-way ANOVA on ranks). Within the group of normal adults, RF size did not vary significantly with increasing age beyond P46 ( $P > 0.15$ , ANOVA on ranks), showing that normal levels of visually driven activity are sufficient to maintain the refined map. The RFs in normal animals remained stable at least up to 12 mo of age, the oldest age examined.

#### Dark rearing has no effect on refinement of the retinocollicular projection

We reasoned that if visually driven activity is needed for the refinement process, RFs would fail to refine in DR animals and thus average RF size would be larger than normal. Alternatively, if the correlated “waves” of spontaneous retinal activity that are present from birth to eye opening (see Wong 1999 for review) or persistent spontaneous activity in the SC (Itaya et al. 1995) could compensate for a lack of visual input, refinement might be delayed or only partially completed rather than prevented altogether. In the DR animals, contrary to our expectation, we found that dark rearing neither prevented nor delayed the refinement process. RF diameters in the DR group, attained normal adult size by P46–P51 ( $21.8 \pm 1.08^\circ$ ,  $n = 33$ ; Fig. 2). RFs in DR animals remained

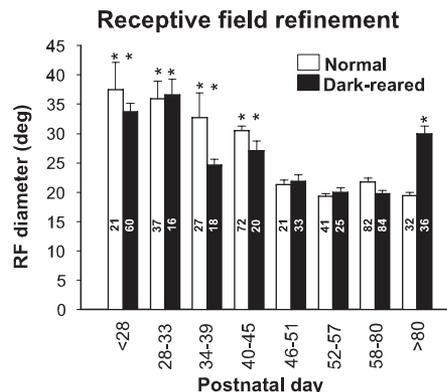


FIG. 2. Visual experience is necessary for maintenance but not refinement of RF size. Data from single unit recordings in DR animals were grouped into 5-day age intervals and compared with that from normal animals. There was no difference in RF size between normal and DR cases within any age group, with the exception of the  $>P80$  group. \*Statistical significance compared with normal adults ( $P < 0.05$ ). Numbers inside bars represent number of single units recorded.

stable in size between P46 and  $\sim$ P80 and were not significantly different in size from those in normal animals within the same age groups ( $P > 0.05$ , Mann-Whitney rank sum test) up to P80. These findings show that refinement follows the same time-course for both normal and DR animals. These results support the interpretation that visually driven activity is not necessary for the refinement of RF size in SC neurons and that visual deprivation does not alter the time-course of this process.

#### Dark rearing causes a failure to maintain RF size

After learning that RFs could refine in the dark, we hypothesized that continued dark rearing might result in a failure to maintain a refined retinotopic map. Indeed, in DR animals older than P80, RFs were enlarged significantly beyond normal size (Fig. 2), suggesting a failure to maintain RF refinement (DR  $>$  P80: mean RF diameter,  $29.9 \pm 1.28^\circ$ ;  $n = 36$ ;  $P < 0.001$  compared with normal adults at  $19.4 \pm 0.56^\circ$ ,  $n = 32$ ). To examine the transition from developmental refinement to subsequent maintenance, we looked more closely at RF size between P70 and adulthood, using a more precise computerized plotting method (Fig. 3). We compared four DR age groups (P70, P80, P89, and P125–P362) to the normal adults ( $\geq$ P75) using a Kruskal-Wallis one-way ANOVA on ranks and Dunn post hoc comparisons. We found that despite the chronic lack of visual experience, RFs of SC neurons in DR hamsters had normal adult RF diameters by P70. There was no significant difference in RF size of SC neurons between normal adults ( $\geq$ P75) and P70 DR animals (Fig. 3, A and B; normal adult:  $9.7 \pm 0.30^\circ$ ,  $n = 71$ ; P70 DR:  $9.6 \pm 0.42^\circ$ ,  $n = 14$ ;  $P > 0.05$ , 1-way ANOVA on ranks). However, consistent with the hand-plotted data in Fig. 2, we observed a progressive loss of refinement of the excitatory RF under prolonged dark rearing. DR animals  $\geq$ P80 had enlarged RFs compared with normal adult RFs (P80 DR:  $13.6 \pm 0.56^\circ$ ,  $n = 23$ ; P89 DR:  $14.1 \pm 1.16^\circ$ ,  $n = 14$ ; P125–P362 DR:  $15.6 \pm 0.55^\circ$ ,  $n = 66$ ,  $P < 0.05$ , 1-way ANOVA on ranks). A finer analysis of RF diameter in the normal adults confirmed that RFs are stable in size throughout adulthood in normal animals (Fig. 3C; life span for these animals is  $\sim$ 1 yr). Together these data show that a loss of refinement in the RFs occurs in the continued absence of light beyond early adulthood. It seems that the visual RFs in DR adults may continue to degrade further into adulthood. The P125–P362 DR animals had slightly larger RFs than the P80–P89 DR hamsters (P80–P89 DR:  $13.7 \pm 0.55^\circ$ ,  $n = 37$ ; P125–P362:  $15.6 \pm 0.55^\circ$ ,  $n = 66$ ;  $P < 0.02$ , rank sum test).

#### Dark exposure commencing after P60 does not affect RF size

To address the possibility that dark rearing can destabilize RFs regardless of when it occurs, we placed animals in the dark at P60, after the map would have reached its adult level of refinement in normal and DR animals but before the time when animals that had been dark reared from birth would exhibit enlarged RFs. In these animals, RF size remained stable regardless of the amount of time spent in the dark. This was true up to 198 days, the last time-point tested (Fig. 4; RF diameter: normal  $>$ P80:  $19.4 \pm 0.56^\circ$ ; P122–P139 DR at P60:  $19.4 \pm 0.38^\circ$ ; P177–P198 DR at P60:  $17.9 \pm 0.46^\circ$ ;  $P > 0.05$ , 1-way ANOVA on ranks; mean RF size of both age groups to-

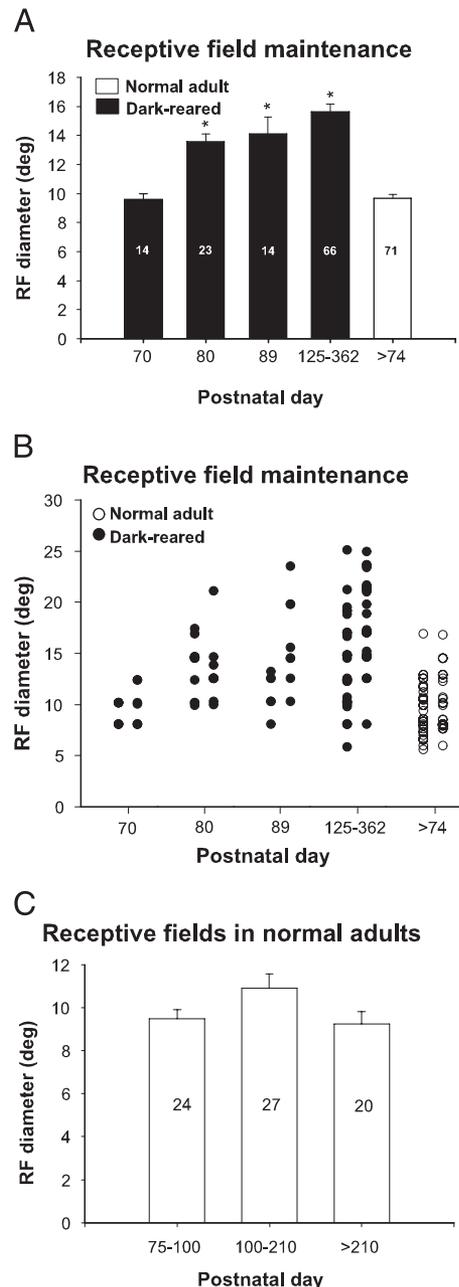


FIG. 3. Long-term dark rearing leads to a loss of RF refinement. A: data from normal animals with RFs plotted by a higher-resolution method showed that RF size at P70 in DR animals is similar to normal adult RF size ( $>$ P74). In animals dark reared for 80 days or more, RF diameters were significantly enlarged. B: data from A is plotted as a scatter plot (separated in 2 columns at each time-point for visibility) to show that the increase in mean RF size arises from a gradual shift in the distribution of RF sizes with age. C: data from normally reared adults show that RFs maintain their refined size from P75 throughout adulthood. Conventions as in Fig. 2.

gether =  $18.9 \pm 0.30^\circ$ ,  $n = 115$ ;  $P > 0.4$ ,  $t$ -test, compared with normal adult). These results indicate that early visual experience is sufficient to protect against the detrimental effects of visual deprivation later in life.

#### Dark rearing alters the symmetry of receptive fields in SC

To examine how this loss of refinement might occur, we looked at the fine structure of RFs in SC using the computer-

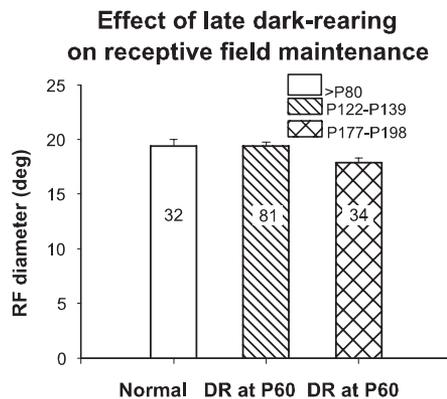


FIG. 4. Late dark rearing does not interfere with maintenance of RF size. Animals were dark reared beginning at P60 and tested for RF size in 2 groups: one at P122–P139 and one at P177–P198. No significant differences in RF size were found compared with normal adults.

ized plotting method. We found that prolonged dark rearing altered not only the size but also the shape of the excitatory RFs. Although neurons in the P70–P89 DR group had a symmetric RF structure as in normal animals (see representative examples in Fig. 5, *A* and *B*), DR animals older than P90 had asymmetric RFs that were expanded toward one side of the visual field (the nasal side in all cases so far examined; Fig. 5*C*). In addition, dark rearing resulted in some neurons having more than one spatial peak in responsiveness (Fig. 5*D*). This was never observed in normal adult animals, either in this study or our several previous studies of adult hamster SC. Calculating the ratio of nasal to temporal RF extent [defined as the asymmetry index (AI)] in neurons with a single response peak revealed that in the population of normal animals ( $n = 71$ ) and in the population of DR animals younger than P90 ( $n = 53$ ), the RFs were fairly symmetric (normal adults:  $AI = 1.14 \pm 0.054$ ,  $n = 71$ ; <P90 DR adults:  $AI = 1.12 \pm 0.05$ ,  $n = 53$ ; Fig. 5*E*). However, in older adult DR hamsters (P125–P362), RFs were on average less symmetric than normal (DR P125–P362:  $AI = 1.56 \pm 0.15$ ,  $n = 42$ ;  $P < 0.05$  compared with >P90 normal adults, 1-way ANOVA on ranks) and were always biased in the nasal, not temporal, direction. This change in symmetry could result from a loss of inhibition on one side of the RF, and thus we next examined the contribution of surround inhibition to the responsiveness of SC neurons in different parts of the RF in DR adults compared with normal adults.

#### Dark rearing alters the strength of the inhibitory surround

To assess the spatial arrangement and strength of inhibition within the RF in normal and DR adults before and after 3 mo of age, a second visual stimulus was placed at varying distances from the central stimulus as both were swept through the RF (Fig. 6). The center of the RF was defined as the location where the response to a single stimulus was highest. Response levels to the addition of the second stimulus at the other RF locations were normalized to the maximum response. This analysis revealed that inhibition was enhanced considerably beyond normal within the temporal part of the RF in 2- to 3-mo-old DR animals ( $n = 53$ ) but was reduced somewhat within the nasal part of the RF. In DR animals >3 mo, inhibition was significantly reduced compared with normal on

both sides of the RF, but the reduction was greater on the nasal side. These changes in the spatial arrangement of surround suppression, whether arising in SC or elsewhere, could account at least in part for the expanded and asymmetric receptive fields.

#### Dark rearing has no effect on responsiveness of SC neurons in adults

To address the possibility that differing levels of SC neuron responsiveness in normal compared with DR animals could bias RF measurements, we used a subset of the digitized recordings from the SC neurons in Fig. 3 to compare peak response levels in a subpopulation of the SC neurons from the adult DR and normal animals (Fig. 7). Levels of spontaneous activity were low in SC of normal animals under our recording

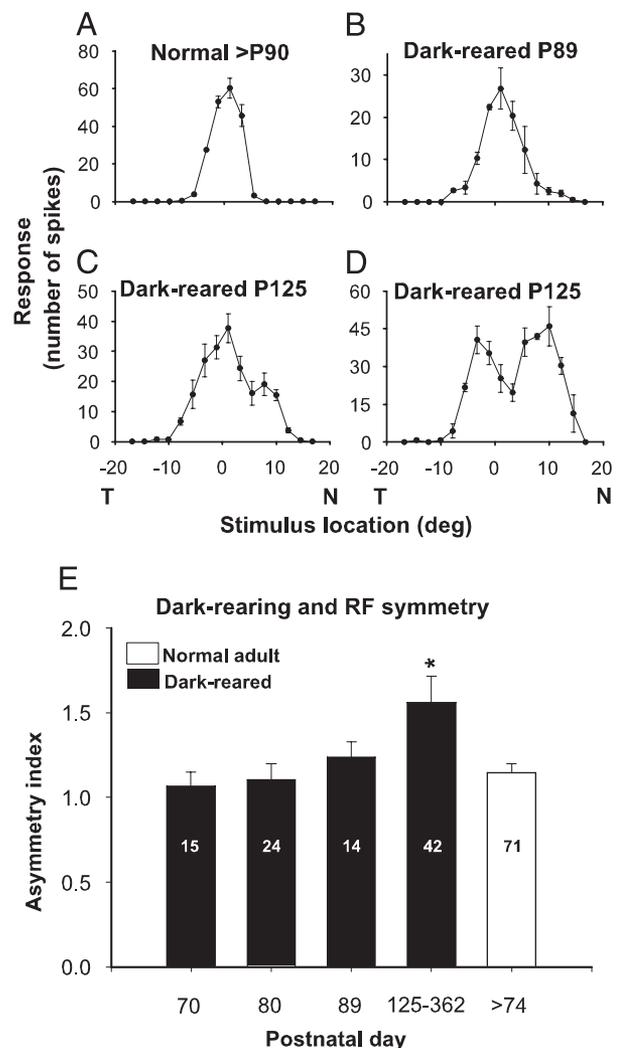


FIG. 5. Long-term dark rearing alters RF structure of SC neurons. *A–D*: representative examples of RF structure. *A*: RFs of normal SC neurons were symmetric in the nasotemporal dimension, with a single response peak. *B*: in DR animals <3 mo of age, RFs were symmetric. *C*: after 3 mo of dark rearing, asymmetric RFs extending further in the nasal than temporal direction were common. *D*: in some neurons from DR animals at this age, multiple response peaks were seen. *E*: data from the entire population. An asymmetry index (AI) >1 indicates an asymmetric RF expansion toward nasal visual field. Asymmetries were seen only in the older DR animals (>P89). Numbers inside bars are number of single units. N, nasal; T, temporal.

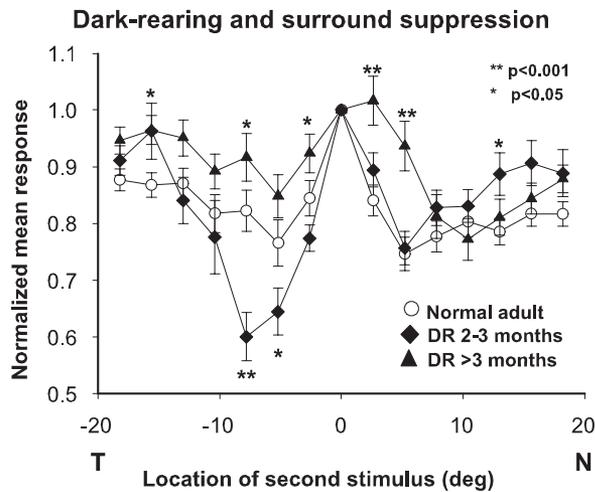


FIG. 6. Long-term dark rearing alters the spatial arrangement of surround inhibition. RF substructure was plotted using dual visual stimuli. One stimulus was swept through the RF center, and the other was swept at varying distances away along the  $x$ -axis, with nasal positive. In DR animals 2–3 mo of age ( $n = 30$ ), inhibition was stronger than normal in near temporal visual field but slightly reduced in strength at 1 nasal location and 1 far temporal location (\*). In DR animals >3 mo old ( $n = 52$ ), inhibition was significantly reduced compared with normal animals in several locations but highly significantly reduced in the nasal locations. Visual experience seems necessary to maintain balance between excitation and inhibition in the RF.

conditions, and this was also the case for DR animals. We found no significant difference in peak response levels between the normal and DR animals (response in spikes/s: normal:  $15.8 \pm 0.85$ ; DR:  $16.6 \pm 1.21$ ;  $P > 0.25$   $t$ -test), indicating that the enlarged RFs in the older DR animals were not an artifact of a general increase in responsiveness, and thus further supporting the hypothesis that dark rearing results in a failure to maintain refined RFs in the retinocollicular pathway of Syrian hamsters.

## DISCUSSION

The hypothesis tested in these experiments was suggested by results from sensory deprivation experiments in visual cortex. Those results led us to expect that visual experience would be necessary for refinement, but not maintenance, of visual RFs in SC neurons. We found the opposite. Animals dark reared from birth to adulthood, thus experiencing spontaneous activity but no visual stimulation (see Feller 2002 and Wong 1999 for reviews), refined their RFs to the same extent, over the same period of time as in normal animals, with maximum refinement attained by 2 mo of age. This seems appropriate for a fossorial rodent like the hamster that does not exit the burrow until later in development. Prolonged dark rearing into adulthood, however, led to a failure to maintain RF size commencing long after refinement was complete. Light deprivation in adulthood had no effect. These results show that spontaneous activity is sufficient and that visual experience is not necessary for developmental refinement of the retinocollicular projection. Furthermore, they suggest that visual experience during development is necessary for long-term stabilization of synapses such that projections can be maintained in a refined state throughout adulthood.

## Visual experience is not necessary for establishing gross retinotopy in SC

Using physiological methods, this study showed that gross retinotopy in SC is present by the third postnatal week in hamsters and possibly earlier. Furthermore, our recordings in this study and in a previous one (Huang and Pallas 2001) never discovered any mistargeted projections, suggesting that retinal axon targeting is quite specific from the outset. This result is consistent with previous findings in lower vertebrates (see Udin and Fawcett 1988 for review) and birds (see Mey and Thanos 1992 for review) and supports previous anatomical evidence that initial topography is determined independently of visually driven activity (McLaughlin et al. 2003b). The preponderance of evidence to date thus argues strongly that formation of gross retinotopy is directed entirely by activity-independent molecular guidance cues (Mann et al. 2004; McLaughlin et al. 2003a).

## Refinement of the retinocollicular projection occurs independently of visual experience

After establishment of gross retinotopy in SC, RFs are refined through retinal ganglion cell death and elimination of retinal axon collaterals. In normal hamsters, we found that complete refinement of SC RFs did not occur until P50 or later. This is surprising given previous reports of refinement by P30 or earlier (Binns and Salt 1997; Simon and O'Leary 1992) and considering that hamsters are sexually mature by  $\sim$ P60. This may be explained by the finding that the number of synapses in SC is not stable until P80 (Warton and McCart 1989). Syrian hamsters are altricial rather than precocial, and it is unlikely that development of their visual system occurs more slowly than in other rodents commonly employed in studies of the visual system (Clancy et al. 2001). This raises the possibility that a similarly protracted refinement period occurs in other rodents but has not been noted because of differences in the timing of experiments. Regardless, this suggests that remodeling of synaptic connectivity can occur quite late in rodents, as it does in humans (Giedd et al. 1999).

Previous studies employing activity blockade through intraocular TTX (O'Leary et al. 1986; Thompson and Holt 1989) have shown that retinal activity in some form is necessary for

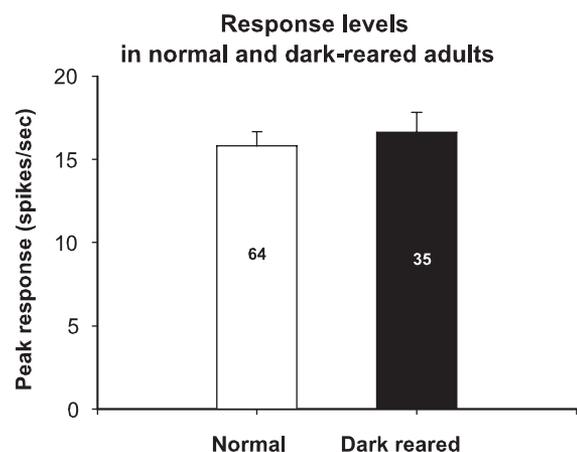


FIG. 7. Dark rearing does not alter responsiveness to visual stimulation. Number of spikes per second to a visual stimulus in the center of RF was measured and was not significantly different between normal and DR adults.

complete RF refinement. Systemic knockout of the  $\beta 2$  subunit of the nicotinic acetylcholine receptor (nAChR) results in unrefined retinotopic maps in LGN and SC (Grubb et al. 2003; McLaughlin et al. 2003b), consistent with the idea that the early cholinergic waves of correlated retinal activity (Feller 2002; Wong 1999) are necessary to achieve a mature pattern of connections. A side effect of  $\beta 2$  nAChR gene knockout, however, is compensatory change in glutamatergic waves (Feller 2002), complicating the interpretation. Blockade of NMDA receptors in SC, either throughout postnatal development, as shown physiologically (Huang and Pallas 2001), or in the first 2 postnatal wk when spontaneous waves are present and eyes are not open, as shown anatomically (Simon et al. 1992), also disrupts map refinement. These experiments suggest that both cholinergic and glutamatergic spontaneous retinal activity are important to retinocollicular development, although their separate contributions remain to be elucidated.

Before this study, little was known about the specific role of visually driven activity in RF refinement. An early physiological study in hamsters found that dark rearing had little effect on SC response properties or on visual behavior (Chalupa and Rhoades 1978). In a study on rats, it was suggested that dark rearing causes a delay in RF refinement in SC (Binns and Salt 1997). Refinement was assessed in that study by measuring the size of the visual stimulus that evoked the best response. Cells in the SC are tuned to stimulus size, however, and prefer stimuli much smaller than the RF (Razak et al. 2003; Stein and Dixon 1979). Thus the apparent delay in refinement may have reflected an increase in the time taken for development of stimulus size tuning in DR animals. In this study, we measured RF size directly to avoid this potential confound.

The conclusion that retinocollicular projection refinement occurs normally in the dark has important implications for understanding visual system development. Our finding that lack of visual experience did not prevent, delay, or prolong the development of a refined visual projection supports the conclusion that spontaneous activity is sufficient to refine the retinocollicular projection. This activity could arise from cholinergic or glutamatergic retinal input, from other inputs to the SC, or from the SC itself (Itaya et al. 1995). Our results contrast with previous studies in visual cortex, in which dark rearing prevented refinement of RFs, reduced acuity, increased RF size, and caused a delay in both the onset and the close of the critical period for ocular dominance plasticity (Cynader 1983; Daw 1995; Mower and Christen 1985; Sherman and Spear 1982; Swindale 1988). Some reports suggest that the critical period for ocular dominance plasticity in visual cortex never closes in DR animals and that acuity never reaches normal values (Fagiolini et al. 1994). It has been suggested that a similar delay may also occur in SC (Binns and Salt 1998; Fosse et al. 1989; Shi et al. 1997). Indeed, our earlier work showed that chronic postnatal NMDA receptor blockade results in enlarged RFs (Huang and Pallas 2001). Only adults were examined, however, and it is conceivable that RF enlargement occurred secondarily to initial refinement, or that postnatal NMDA receptor blockade resulted in RF enlargement through blocking detection of spontaneous retinal activity and not by interfering with detection of coincidence in visually driven activity.

### *Visual experience is necessary for maintenance of refined retinocollicular projections*

Despite the resistance of the refinement process to visual deprivation, we found that refined RFs could not be maintained in adulthood in the continued absence of light. It is surprising that deprivation led to a failure to maintain the refined projection already present in our adult DR animals. Late light deprivation had no such detrimental effect. The loss in refinement did not result from an increase in spontaneous activity or a differential increase in overall response levels in DR compared with normal animals, although this occurs in visual cortex (Benevento et al. 1992).

The signal leading to the loss of refinement in adult RFs could come directly from a reduction in overall activity independent of its source. In all vertebrate species studied to date, waves of correlated spontaneous activity in the retina cease when the eyes open (Feller 2002; Wong 1999). DR mice do not present abnormal characteristics or a different time-course of loss of spontaneous retinal waves compared with normally reared animals (Demas et al. 2003). Thus correlated activity levels would drop at  $\sim P14$  and not be replaced by visually driven activity in the DR animals. Spontaneous activity levels after eye opening are quite low in SC (Huang and Pallas 2001) and thus may not be able to compensate for the lack of visual experience. We conclude from these results that spontaneous activity is not sufficient and visual experience is necessary for maintenance of refined retinotopy into late adulthood. Because the loss of refinement occurs well into adulthood, after the projection has been fully refined in the dark, we argue that it does not result from a delay in closure of a critical period as seen in visual cortex. Rather, retinocollicular synapses formed in the dark are apparently less stable over the long term. This finding is inconsistent with a period of retinotopic map plasticity that irreversibly closes in adulthood. The mechanism responsible for map maintenance may be independent of the mechanism underlying initial map refinement (Frenkel and Bear 2004; Sawtell et al. 2003) and may not be subject to a critical period.

### *Possible mechanisms underlying the failure to maintain refined RFs*

What could be responsible for the latent instability in retinocollicular synapses in adulthood? If light exposure is required for maturation of NMDA receptors (Philpot et al. 2001; Yoshii et al. 2003), the failure to maintain refined RFs may result from a late deprivation-induced loss of NMDA receptor (NR)2A-containing receptors at the postsynaptic density (PSD). This could affect the time-course of NMDA receptor-dependent long-term potentiation (LTP) and long-term depression (LTD) (van Zundert et al. 2004). This scenario predicts that response levels in the center of the RF would decline, however, which does not occur.

An alternative explanation was pursued in the context of this study. The delayed enlargement of RFs in adult DR hamsters could result from a decrease in number or strength of inhibitory inputs. We found that visual responses were biased toward the nasal side of the RF in  $>3$ -mo-old DR animals but not in normal adults or  $<3$ -mo-old DR animals. In many SC neurons surround suppression is greater on the nasal side of the RF

(K.A.R. and S.L.P., unpublished data). A uniform loss of lateral inhibition would therefore result in a nasal expansion of the RFs in those neurons, biasing the population statistics. The results from our tests of surround suppression (see Fig. 6) show that lateral inhibition is undergoing dynamic changes in adult DR animals. Sensory deprivation leads to a shift in the balance between excitation and inhibition in visual cortex (Kilman et al. 2002; Morales et al. 2002) that can also occur in adulthood (Hendry et al. 1994), consistent with this suggestion. A failure in the maturation of inhibitory synapses could occur through failure to anchor mature GABA receptors (Kneussel et al. 1999), as shown for activity-dependent NMDA receptor anchoring (Philpot et al. 2001; Yoshii et al. 2003), along with a delay in the maturation of GABA receptor composition. This would be an interesting avenue for further study.

In summary, our results suggest that a reinterpretation of some earlier studies of visual system plasticity may be warranted. If animals that are deprived of light during development are not examined until well into adulthood, it may seem that projections have never refined, when instead they have refined and subsequently deteriorated. Because visual defects at birth are often not corrected until many months or years have passed, it is important to understand when intervention would be of most benefit, underscoring the clinical relevance of our findings. In conclusion, our results point out the relevance of early sensory experience to the maintenance of visual RF properties and suggest that disuse of sensory organs during the early postnatal period could have severe consequences much later in life than might be expected.

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