

Training-induced Recovery of Visual Motion Perception after Extrastriate Cortical Damage in the Adult Cat

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Unilateral ibotenic acid lesions of the lateral suprasylvian (LS) cortex severely impair the ability of cats to integrate local motion signals (measured as direction range thresholds) and to extract motion signals from noise (measured as motion signal thresholds) in their contra-lesional visual hemifields. These deficits were found up to several months after the lesions and were limited to thresholds measured with random-dot stimuli, while contrast sensitivity for discriminating the direction of motion of sine-wave gratings remained unaffected. Our goal was to determine whether deficits of complex motion perception could recover and whether the recovery was spontaneous or required retraining. In each cat, a single location in the impaired visual hemifield was selected for visual retraining, which required the animals to discriminate motion direction using random-dot stimuli in which the range of dot directions was varied. Fifteen to 40 days of intensive retraining led to a gradual, complete recovery of motion integration. The recovery was stimulus specific since it did not transfer from direction range to motion signal thresholds, and it was largely restricted to the visual field locations retrained. Delaying the onset of retraining by several days to several months had no significant impact on the extent or rate of recovery. Once recovery was achieved, performance remained stable over a period of several months. These results suggest that recovery of complex visual motion perception after lesions of extrastriate visual cortex is an active process that requires extensive, stimulus- and retinotopically-specific visual retraining.

Introduction

The adult brain is in a state of constant flux or 'plasticity', both functionally and structurally (Kaas, 1995; Gilbert *et al.*, 1996). Spontaneous neural reorganization has been shown after cortical lesions in developing and adult mammals (Gilbert, 1993; Kaas, 1995; Florence *et al.*, 1998). In many instances, such reorganization appears to correlate with functional recovery or the development of compensatory behaviors (Elbert and Helm, 2001; Payne and Lomber, 2001). However, this apparently spontaneous functional recovery can still leave the subjects with significant long-term deficits. It is not known if such residual deficits are permanent or if something can be done to induce further recovery.

A growing literature demonstrates the importance of retraining for cortical reorganization and recovery of functions lost as a result of cerebral damage in adult humans and other animals. However, most of this information comes from work in motor (e.g. Nudo *et al.*, 1996; Hallett, 2001; see review by Taub *et al.*, 2002), somatosensory (e.g. Recanzone *et al.*, 1992b; Xerri *et al.*, 1996) or auditory (Recanzone *et al.*, 1993; Syka, 2002) systems. In the visual system, the extent to which recovery can occur after cortical lesions in adulthood is still controversial (Pambakian and Kennard, 1997), particularly with regard to lesions of primary or striate visual cortex (V1).

There is also conflicting evidence about whether visual retraining can produce visual recovery beyond the spontaneous improvements and compensatory mechanisms that develop after the cortical damage (Gassel and Williams, 1966; Sharpe *et al.*, 1979; Pambakian and Kennard, 1997; Tant *et al.*, 2002). Complete, unilateral V1 damage leads to a severe loss of conscious vision in the contra-lesional visual hemifield with sparing of unconscious vision referred to as 'blindsight' (for reviews, see Cowey and Stoerig, 1991; Rizzo, 1994). While several groups have found visual retraining useful in promoting some degree of visual recovery in human subjects with V1 lesions (e.g. Zihl, 1981; Kerkhoff *et al.*, 1992; Kasten and Sabel, 1995), some of these reports have been disputed (Bach-Y-Rita, 1983; Balliet *et al.*, 1985).

We chose to study lesions of the extrastriate, lateral suprasylvian (LS) visual cortex in cats. Damage to LS cortex, like lesions of areas MT and MST in primates, causes deficits in the processing of visual motion information (e.g. Newsome and Paré, 1988; Schiller and Lee, 1994; Rudolph and Pasternak, 1996, 1999; Lauwers *et al.*, 2000). Some of the above studies found various degrees of recovery of visual motion processing, but it is not clear to what extent this recovery was facilitated by post-lesion retraining (whether intentional or not) and to what extent it occurred spontaneously. The experiments described in this study aimed to distinguish spontaneous improvements from training-induced recovery following unilateral lesions of LS cortex in adult cats. By measuring the effects of post-lesion time, spatial specificity of retraining, and the nature of retraining stimuli on motion discrimination thresholds, we determined that the recovery of complex motion perception requires intensive visual retraining.

Materials and Methods

Subjects

Three normal, adult cats were used in this study. On weekdays, the cats were food restricted and received the majority of their daily food ration in the form of pureed beef rewards for correct answers given during behavioral testing. Following their testing session, the animals were supplemented with dry cat food, leaf lettuce and a vitamin pill to insure stable body weight and good physical health. On weekends or days when cats did not undergo behavioral testing, they were given an amount of dry cat food that assured maintenance of appropriate body weight. Water was continuously available in their home cage. All experiments were carried out according to NIH Guidelines for the Care and Use of Laboratory Animals (NIH publication no. 86-23, revised 1987) and following review by the University of Rochester's Committee on Animal Resources.

Visual Stimuli

All stimuli were computer-generated and displayed on a 19-inch monitor located 42 cm in front of the animals' eyes.

Gratings

Vertical sine-wave gratings (Fig. 1A), presented in a circular aperture, 6° in diameter, drifted either to the left or the right. Spatial frequency was 0.3 cycles/deg. and temporal frequency was 6 Hz, with a resulting drifting speed of 20°/s. The mean luminance of the display was 20 cd/m². Stimulus duration followed a 250 ms raised cosine temporal envelope. Contrast thresholds were measured by varying grating contrast, computed as $(L_{\min} - L_{\max}) / (L_{\min} + L_{\max}) \times 100$, where L_{\min} and L_{\max} refer to minimal and maximal luminance in the display. Contrast sensitivity was then calculated as the inverse of the contrast threshold.

Random-dot Stimuli

The random-dot stimuli were identical to those used previously (e.g. Rudolph and Pasternak, 1999). They consisted of dots repeatedly displaced in a direction chosen randomly from a uniform distribution of directions with a new set generated on each frame. The dots moved at a speed of 20°/s ($\Delta t = 13$ ms, $\Delta x = 0.26^\circ$) for cats B and C and at 27°/s ($\Delta t = 13$ ms, $\Delta x = 0.35^\circ$) for cat A. Dots were 0.03° in diameter and their luminance was set to ~3.5 log units above human detection threshold for a lifetime of 250 ms. Random-dot stimuli were presented in a circular aperture either 4° or 5° in diameter and dot density was maintained at 2.6 dots/deg.². The mean luminance of the display was 0.1 cd/m². Direction range thresholds were measured by varying the range of directions in which the dots were displaced (Fig. 1A). Motion signal thresholds were measured by varying the proportion of coherently (direction range = 0°) and randomly (direction range = 360°) moving dots in the display (Fig. 1A).

Behavioral Procedures

Control of Eye Position

Eye position was monitored with magnetic search coils (Rommel, 1984) using procedures that were identical to those previously described (Pasternak and Horn, 1991). Each cat was fitted with six to eight titanium orthopedic screws (Veterinary Orthopedic Implants Inc.) implanted into the skull and joined together by bone cement (Palacos Bone Cement) into which a brass rod was embedded. A sub-conjunctival search coil was implanted around one eye. During behavioral testing, the cats were placed inside a magnetic field generated by a set of 50 cm field coils. Their heads were immobilized using the implanted head-cap and signal from their eye coil was detected and calibrated using an eye coil phase detector (Riverbend Electronics). Eye position was calibrated prior to each daily testing session by rewarding the animal for positioning its gaze within an electronically defined, square window 1.5° in diameter, centered on the fixation spot. The animals were trained to maintain fixation within this window for 800–1000 ms. Fixation spots were positioned randomly at different locations on the display screen, within the central 10° of vision. About 20–30 trials were required to calibrate eye position, by making small adjustments to the signal offset and gain on the phase detector.

Direction Discrimination Task

The cats were trained to discriminate between left- and rightward motion in a two-alternative forced-choice paradigm (Fig. 1B). The animals initiated each trial by fixating a small spot for 800–1000 ms. Steady fixation within a 1.5° electronic window resulted in a tone signaling the onset of the trial and presentation of a stimulus during which the cats were required to maintain fixation. After the stimulus and the fixation spot were extinguished, two ‘response targets’, separated by 10°, were presented in the upper visual hemifield for stimuli shown in the lower field, and the lower visual hemifield for stimuli presented in the upper field. Correct responses consisted of a saccade to the right-most response target for rightward drifting stimulus, and a saccade to the leftmost response target for leftward drifting stimuli. Each correct response was rewarded with pureed beef. The sequence of presentation of rightward and leftward drifting stimuli was randomized. Incorrect responses resulted in a 3 s tone and no food reward. A break in fixation during stimulus presentation produced a brief, 1 s tone and the termination of the trial. To avoid positional biases, a correction procedure was used: after three incorrect saccades to the same response target, the trial was repeated until the animal made a correct response

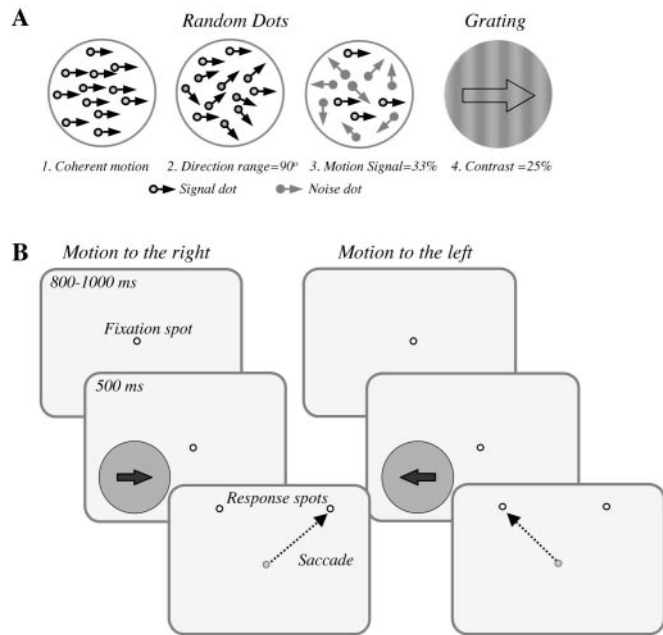


Figure 1. (A) Stimuli used to measure motion perception. (1) *Coherent motion* in random dot stimuli is degraded to measure complex motion thresholds (direction range and motion signal). (2) *Direction range* thresholds were measured by varying the range of dot directions in random-dot stimuli. (3) *Motion signal* thresholds were measured by varying the percentage of coherently moving dots in random-dot stimuli. (4) *Contrast* thresholds for direction were measured with sine-wave gratings in which luminance contrast was varied. (B) *Direction discrimination* task. After centering their eyes on a fixation spot for 800–1000 ms, the cats discriminated between leftward and rightward direction of motion of a stimulus presented for 500 ms at a selected location in the visual field. After the offset of the stimulus and the fixation spot, two response spots appeared side by side. The animals responded by making a saccade to one of the spots to indicate the direction of stimulus motion.

and this data was not used for analysis. Each daily testing session consisted of 200–300 trials separated by a 3 s inter-trial interval.

During initial training, the cats were rewarded for fixating a spot on the computer monitor. They were then trained to fixate the same spot placed in the middle of a moving, random-dot stimulus, while discriminating the direction of motion of the stimulus by making saccades to the correct response targets. After the animals reached the criterion level of performance of four consecutive sessions at $\geq 80\%$ correct, the location of the stimulus was progressively moved away from the fixation spot and motion thresholds were measured at different eccentricities.

Threshold Measurement

A staircase procedure was used to measure thresholds. During each session, a stimulus set was used that varied along a selected dimension (e.g. luminance contrast, direction range, percent motion signal), from the easiest to the most difficult. Three consecutive correct responses resulted in presentation of a less discriminable stimulus (i.e. reduced contrast, increased direction range or decreased motion signal) while a single incorrect response decreased the stimulus difficulty. Daily thresholds were estimated by fitting a Weibull function (Weibull, 1951) to the data and computing the stimulus value corresponding to 75% correct. Training continued until the thresholds stabilized at several visual field locations (defined as the time when the coefficient of variation <10% of the mean over at least five data points). Two to four threshold determinations were then made for each stimulus condition after performance reached stability. Once this mapping of baseline performance was completed, the cats received unilateral lesions of LS cortex.

Cortical Lesions

Cats were sedated with ketamine (15 mg/kg) and fully anesthetized with 3% isoflurane before being placed in a stereotaxic apparatus. A portion of the bone cement making up the animals' head cap was removed and a craniotomy was made from 5 mm posterior to 15 mm anterior to the inter-aural line, and from 8 to 17 mm lateral to the inter-aural line. The dura was cut and the brain was exposed. Cats received ~20–30 injections, each of 1 μ l of sterile ibotenic acid (10 mg/ml), into the right lateral suprasylvian (LS) cortex. All injections were made using a 10 μ l Hamilton syringe fitted with a 30 gauge, beveled needle. Injection sites were spaced at intervals of 1.7 mm, starting 3 mm posterior to the inter-aural line and ending ~14 mm anterior to the inter-aural line. Depending on antero-posterior location, between one and three injections were made at different depths in each penetration (~2 mm interval). The separation of the injections and the amount and dose injected were chosen to produce contiguous lesions (Huxlin and Pasternak, 2001). The animals' electrocardiogram, CO₂ and temperature were constantly monitored during the surgery and kept at physiological levels. After completing the injections, the dura and bone flap were pulled back into place. The muscles, subcutaneous tissues and skin were sutured around the head implant and the animals were then recovered under veterinary supervision.

Post-lesion Behavioral Procedures

Assessment of Visual Deficit

Post-lesion testing began 1–2 weeks after the lesion. Thresholds for direction range, motion signal and contrast were first measured at several locations in the hemifields ipsilateral to the lesion. Once it was established that post-operative thresholds in the unaffected hemifields were at pre-operative level, the animals were tested in the hemifields contralateral to the lesioned hemisphere. In cats B and C, performance for direction range was mapped throughout both upper and lower quadrants of the contralesional hemifield. For cat A this mapping was limited to minimize post-lesion delay in the onset of retraining. In this animal, direction range thresholds were only measured at two locations in the lower, contralesional quadrant: (-3° , -4°) and (-7° , -5°). For each cat, a single visual field location was selected as the site of visual retraining. At this location, cats were initially unable to discriminate the direction of coherently moving dots (direction range threshold = 0°) and thresholds were also abnormal at sites immediately surrounding this location. Motion signal and contrast thresholds were also measured at the chosen retraining location prior to the onset of retraining. All threshold measures were then repeated at corresponding locations in the ipsilesional (intact) hemifields to control for the animals' motivational and perceptual states.

Visual Retraining

Retraining consisted of daily sessions in which the cats discriminated between right- and leftward motion of random-dot stimuli in which the range of dot directions was varied between 0 and 355° in a staircase procedure. Retraining continued until the direction range thresholds reached control levels of performance, as determined at corresponding locations in the intact hemifields.

Once direction range thresholds had recovered at the retrained locations, we assessed whether this recovery had transferred to another measure of complex motion perception – motion signal thresholds – at the same visual field locations. Since motion signal thresholds were abnormal, we then assessed whether, like direction range thresholds, they could be recovered with further training on the motion signal task. Retraining continued until motion signal thresholds reached control levels, as determined from the animals' performance at corresponding locations in their intact hemifields.

Finally, we examined whether the recovery of direction range thresholds was limited to the retrained portion of the visual field by measuring these thresholds at several, iso-eccentric but non-overlapping sites, at increasing distances away from the retrained locations. Data were collected in one or two testing sessions at each site.

Histology and Lesion Reconstructions

At the end of the experiment, cats were sedated with an intra-muscular injection of 20 mg/kg Ketamine before undergoing euthanasia with an

overdose of sodium pentobarbital (100 mg/kg, intra-peritoneally). The cats were then perfused with 3% paraformaldehyde and 0.1% Glutaraldehyde in 0.1 M phosphate buffer (PB), pH 7.4. Once the brains were adequately cryoprotected, serial, frozen sections were cut at a thickness of 40 μ m. Alternate sections were reacted for cytochrome oxidase (CO), a marker of neuronal activity that can be used to precisely delineate brain regions where neurons have been killed, and for Nissl substance with cresyl violet. For the CO reaction, free-floating brain sections were incubated at 37°C for 3–4 h in a solution of 0.06% diaminobenzidine tetrahydrochloride (Sigma), 0.03% cytochrome C (Type III, Sigma) and 4.4% sucrose in 0.1 M PB. Once the sections reached the appropriate dark-brown coloring, they were rinsed and mounted onto subbed slides for analysis. The Nissl stain was used to verify the extent of the lesions, identify cortical layers and help distinguish borders between some cortical areas.

The cortical areas damaged by the ibotenic acid injections were reconstructed from Nissl and CO-stained sections. In sections stained with cresyl violet, the damaged portions of cortex were characterized by the absence of identifiable neurons, the presence of gliosis and vacuoles. In sections stained for CO, damaged cortex was identified by the lack of brown staining in the gray matter (Fig. 2). The damaged cortical areas were identified by matching stained coronal sections with the maps of Tusa and colleagues (Tusa *et al.*, 1978, 1979, 1981; Tusa and Palmer, 1980) and Palmer and colleagues (Palmer *et al.*, 1978).

Results

Lesion Extent

As shown in Figure 2, the brains of all three cats exhibited contiguous damage to LS cortex on both banks of the right LS sulcus. The approximate extent of damage to several, relevant visual cortical areas was determined by matching each brain section with physiologically determined maps (Palmer *et al.*, 1978; Tusa *et al.*, 1978, 1979, 1981; Tusa and Palmer, 1980). There were no islands of intact cortex along the entire extent of the ibotenic acid lesions, although the precise medio-lateral and antero-posterior extent of the lesions varied somewhat between the cats. Cat A had the largest, most complete lesion of LS cortex. Cat C exhibited the next largest cortical lesion, while cat B had the smallest lesion, predominantly because of sparing of infragranular cortical layers on the lateral bank of the LS sulcus (Fig. 2). In addition to the cortical areas on the banks of the LS sulcus, most or all of area 21a was also damaged in all cats, while areas 17, 18 and most of area 19 remained intact (Fig. 2).

Immediate Perceptual Effect of Unilateral LS Lesions

During the first 3–4 days after their lesion surgery, all cats exhibited a stereotyped, rotational behavior towards the side of the lesion, which decreased and disappeared by the fifth day post-lesion. Behavioral testing began 6–8 days after the lesions. Cat A became ill after his lesion surgery and the visual testing in this animal was not resumed until 15 days post-lesion.

Mapping of Direction Range Thresholds

Motion thresholds were first measured in the ipsilesional (intact) visual hemifields. Once it was established that direction range thresholds in the intact hemifields had not changed from pre-operative levels, mapping of the contralesional hemifields began. To minimize delay before the onset of visual retraining in cat A, the mapping was limited to two locations in the lower quadrant: (-3° , -4°) and (-7° , -5°). For cats B and C, direction range thresholds were measured at adjacent, non-overlapping locations throughout the contralesional visual hemifield. In these two cats, performance was mapped up to



Figure 2. Lesion reconstructions. Brain sections from cats A, B and C stained for cytochrome oxidase (gray shading). Visual cortical areas of interest are labeled on sections of the left hemisphere of cat A, with white lines separating different areas. Approximate antero-posterior location of each section is indicated in mm relative to the inter-aural line. Negative values are located posterior and positive values are located anterior to the inter-aural line. Note the areas of missing cortex around the LS sulcus in the right hemisphere of each cat's brain. The extent of the damage can best be appreciated from a comparison with the intact cortex on the banks of the left hemisphere's LS sulcus in each animal. PMLS, postero-medial lateral suprasylvian area; PLLS, postero-lateral suprasylvian area; AMLS, antero-medial suprasylvian area; ALLS, antero-lateral suprasylvian area; DLS, dorso-lateral suprasylvian area; VLS, ventro-lateral suprasylvian area. Scale bar = 20 mm.

an eccentricity of $\sim 22^\circ$, with no more than two, 200-trial training sessions at each location. The resulting maps of direction range thresholds are shown in Figure 3 and illustrate the contralesional nature of the deficit.

The severity of the deficit varied across the contralesional hemifield. Some areas of sparing were seen in all cats, especially within the central 5° of vision. Cat B exhibited the largest, contiguous area of sparing, centered just under the horizontal meridian and extending out to $\sim 20^\circ$ eccentricity. Nevertheless, the contralesional hemifields of all cats contained locations where the deficit was maximal (dark gray circles in Fig. 3). At these locations, cats could not reliably discriminate the direction of motion of stimuli, even with very limited direction range (thresholds of 0° to 150°). A single location of maximal deficit was chosen in all cats as the future site of visual retraining (arrowed dark gray circles in Figure 3). Corresponding locations in the intact hemifield (arrowed open circles in Fig. 3) were also selected for control measures. Over the first 3 days of testing, direction range thresholds at the chosen retraining locations were significantly lower than at

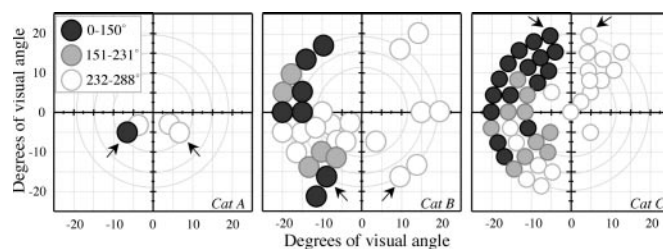


Figure 3. Mapping of direction range thresholds across the visual field following unilateral LS lesions. Circles (drawn to scale) indicate the size and position of the random-dot stimuli used to measure direction range thresholds post-lesion. Open circles, normal thresholds; light gray circles, moderate deficit (thresholds $> 150^\circ$); dark gray circles, severe deficit (thresholds $< 150^\circ$). Arrows point to visual field locations chosen for retraining (dark gray circles) and for control measures (open circles) in each cat. Note that only minimal mapping, necessary to identify a region of severe deficit, was carried out in cat A.

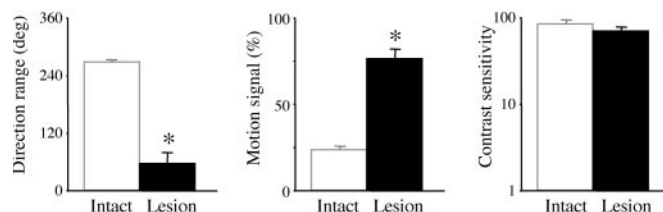


Figure 4. Average direction range, motion signal and contrast sensitivity thresholds measured before the onset of retraining in all three cats. Histograms plot thresholds (mean \pm SEM) obtained at the visual field locations chosen for retraining ('lesion') as well as at corresponding locations in the intact hemifield ('intact'), as arrowed in Figure 3. Note the large impairment in direction range ($*P < 0.01$, two-tailed Student's *t*-test) and motion signal thresholds ($*P < 0.01$, two-tailed Student's *t*-test), but not in contrast sensitivity for direction ($P = 0.32$, two-tailed Student's *t*-test).

corresponding, control locations in the intact hemifields (two-tailed Student's *t*-test, $P < 0.001$: Fig. 4).

Motion Signal Thresholds and Contrast Sensitivity for Direction

Before the onset of retraining on direction range thresholds, visual performance was further characterized at the future retraining location by measuring motion signal and contrast thresholds (Fig. 4). Motion signal thresholds, like direction range thresholds, were severely affected by LS lesions (two-tailed Student's *t*-test, $P < 0.01$). On the other hand, contrast sensitivity for discriminating the direction of gratings drifting at the same speed and in the same directions as the random-dot stimuli was not affected by the lesions in any of the cats (two-tailed Student's *t*-test, $P = 0.32$).

Recovery of Direction Range Thresholds

Retraining with Random-dot Stimuli

Once mapping was complete, daily retraining began either immediately (cats A and B) or following a delay of 158 days for cat C. At first, all cats were unable to reliably perform the task. Even when the dots moved coherently (0° range), they were unable to reach 75% correct levels. For these sessions, their thresholds were assigned a value of 0° . However, the cats' performance improved steadily with days of retraining. The time-course of this improvement is shown in Figure 5A. During the retraining period, direction range thresholds were also periodically measured at the corresponding, control locations

in the intact visual hemifields (gray lines and shaded areas in Fig. 5A; 'Intact' bars in Fig. 5B). The animals showed no behavioral difficulties in switching from one hemifield to another, and thresholds measured at control locations were consistently within the normal range (as determined from pre-lesion data). Recovery was considered complete when direction range thresholds returned to within the normal range, as defined by performance at equivalent locations in the intact hemifields (Fig. 5A). Cats B and C took ~15 days of daily training to reach near normal levels of performance. Cat A took considerably longer, requiring ~40 days to reach normal levels. Once direction range thresholds reached normal levels of performance, they remained at these levels for the remaining period of the experiment, which extended up to a maximum of 158 days post-lesion (corresponding to 50 days of retraining) in the case of cat A.

Delaying the Onset of Retraining

Although all three cats began visual testing 6–15 days after their lesion, additional time elapsed until their deficit was mapped in detail (for cats B and C) and retraining could begin. Retraining of cats B and C began at their chosen locations 24 and 42 days post-lesion, respectively. Retraining of cat A began 19 days post-lesion, since no detailed mapping of his visual field deficit was performed. Our results show that the length of the post-lesion delay in retraining did not affect performance – all cats showed very poor performance (0° range thresholds) at several visual field locations at the onset of retraining. Thus, no recovery of complex motion perception occurred at these locations until that time. It is noteworthy that in some cases, the delay in the onset of retraining was almost as long or longer than the number of days of retraining needed to achieve recovery. Indeed, although we first obtained direction range thresholds at the chosen, retraining location of cat C at 42 days post-lesion, this animal did not begin intensive (daily) retraining at this location until 158 days after his lesion. This cat was still able to achieve recovery of direction range thresholds at a rate (in terms of the number of days of retraining) that did not differ significantly from that seen in cats A and B, which began intensive retraining 19 and 24 days, respectively, after their lesion.

Spatial Localization of Training-induced Recovery

To assess whether recovery of direction range thresholds was spatially restricted to the retrained, visual field locations, direction range thresholds were measured at various distances from these retrained locations (Fig. 6A) within the contra-lesional hemifields. Identical measurements were performed at several control sites with matched eccentricities in the intact hemifields. Performance at contra-lesional visual field locations where complex motion perception was spared following LS lesions (open circles in Fig. 3) was not included in this analysis. As shown in Figure 6B, direction range thresholds in the contra-lesional hemifields of all three cats decreased gradually with increasing distance from the retrained locations. Thresholds measured in the affected quadrants opposite to those where retraining had been carried out were significantly below normal, suggesting that recovery had not spread extensively beyond the area occupied by the retraining stimulus. It was also noted that the decrease in performance with distance away from the retrained location was steeper for cat A, which

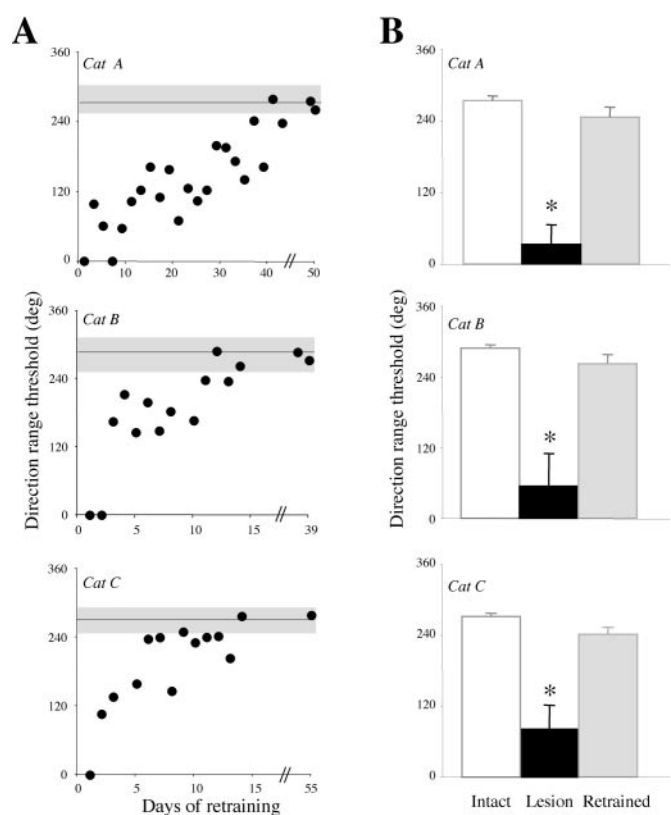


Figure 5. Training-induced recovery of direction range thresholds. (A) Black symbols show direction range thresholds for individual retraining sessions at the chosen locations in the contra-lesional hemifields. The last thresholds measured in the experiment are shown as the right-most black points on each graph. The mean and range of thresholds measured at corresponding locations in the intact, ipsilesional visual hemifields of the three cats are represented by the horizontal gray lines and shading. (B) Mean \pm SEM direction range thresholds measured in the intact (white bars) and the lesion hemifields before (black bars) and after (gray bars) retraining. Threshold performance in the impaired hemifield was averaged over the first 3 days of testing post-lesion ('Lesion') and over the last 3 days of retraining on direction range ('Retrained'). Note the initially severe deficits in direction range thresholds ($*P < 0.01$, two-tailed Student's *t*-test) relative to performance at the equivalent locations in the intact hemifield ('Intact' — cat A $n = 6$; cat B $n = 10$; cat C $n = 9$). The mean recovered direction range thresholds were not significantly different from thresholds at the intact locations ($P > 0.05$, two-tailed Student's *t*-test).

was retrained at $\sim 9^\circ$ eccentricity, compared with cats B and C, whose retrained locations were situated at $\sim 20^\circ$ eccentricity.

Stimulus Specificity of the Recovery

Once direction range thresholds had recovered at the original, retrained location, we assessed whether this recovery had transferred to the second type of random-dot stimulus described in Figure 1. Motion signal thresholds were thus examined in two of the cats at the retrained, visual field locations. Initial measurements (days 1 and 2 of retraining in Fig. 7A and 'Lesion' in the histograms in Fig. 7B) showed abnormally high motion signal thresholds at the retrained locations. We then determined if these deficits in motion signal threshold were permanent or would improve with additional training. With daily retraining using stimuli in which direction range was maintained at 0° and motion signal was varied, both animals showed relatively rapid improvements in motion signal

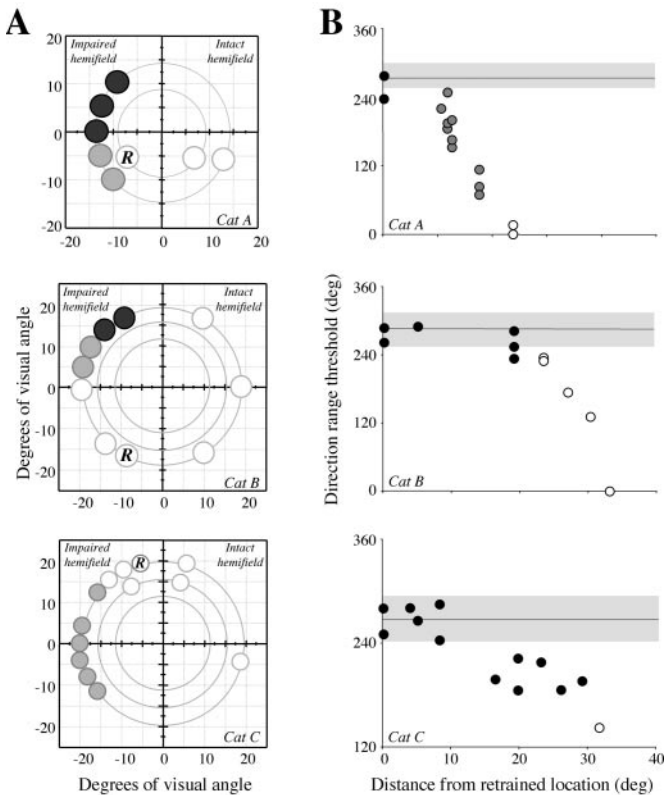


Figure 6. Spatial localization of functional recovery. (A) Visual field maps illustrating the location and size of visual stimuli presented at the retrained locations (R) and at adjacent, mostly iso-eccentric sites within the impaired and intact hemifields. Regions of the affected hemifields where thresholds were at normal levels during the initial post-lesion mapping (see Fig. 3 for locations) were not included in this analysis. Different performance levels are indicated using the same grayscale convention as in Figure 3. Open circles, normal thresholds; light gray circles, moderate deficit (thresholds > 150°); dark gray circles, severe deficit (thresholds < 150°). (B) Direction range thresholds measured at visual field locations shown in A, plotted as a function of linear distance from the retrained site (R) for each cat. Black symbols denote thresholds obtained in the impaired hemifields that represent significant improvements ($P < 0.05$, Student's t -test) over thresholds measured at the same locations soon after the lesion. Open symbols represent no improvement relative to original post-lesion measurements and gray symbols are used for cat A to indicate that the significance levels are unknown at those locations since no immediate post-lesion mapping was carried out in this animal following its lesion. Since performance in the intact hemifields did not vary significantly at the different test locations, these data were averaged for each cat (gray lines). The range of values obtained at these control locations is indicated by the extent of gray shading around each gray line.

thresholds, taking 5–9 days of additional training to reach normal levels (Fig. 7B).

Discussion

Our results show that unilateral lesions of the extrastriate, LS visual cortex of adult cats led to severe, contra-lesional deficits in the perception of complex visual motion. With extensive retraining, these deficits decreased and performance returned to near normal levels. Improvement was limited largely to the retrained visual field location and was specific to the motion stimulus used during retraining. The recovery was not significantly affected by delays in the onset of post-lesion retraining and appeared stable once it was achieved. These results suggest that deficit-specific visual retraining is an effective means of attaining functional recovery after permanent damage to extrastriate visual cortex in adulthood.

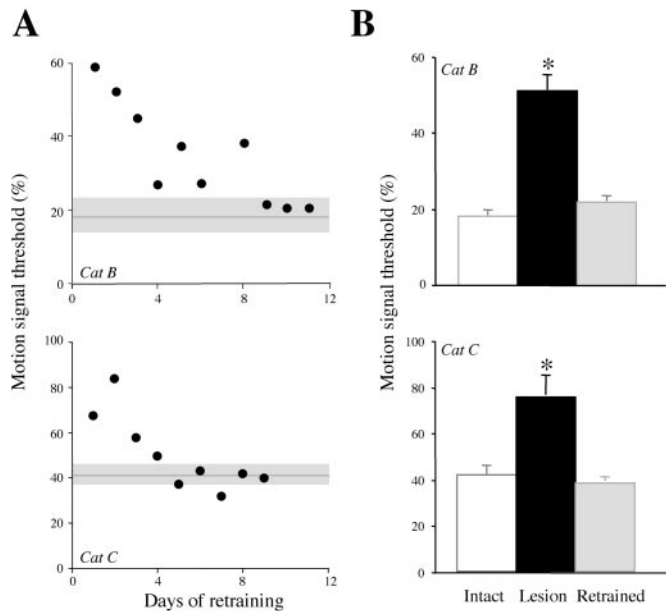


Figure 7. Training-induced recovery of motion signal thresholds in cats B and C. (A) Recovery of motion signal thresholds measured at the visual field locations where direction range thresholds had been retrained are indicated by black symbols. The mean and range of motion signal thresholds measured at equivalent locations in the intact hemifields are indicated by the gray lines and shaded areas in each graph. (B) Motion signal thresholds (mean \pm SEM) measured in the intact hemifields (white bars) and in the lesioned hemifields before (black bars) and after (gray bars) retraining on stimuli containing variable levels of motion signal. Following daily retraining, the deficits in motion signal thresholds ($*P < 0.01$, two-tailed Student's t -test) recovered to levels not significantly different from normal ($P > 0.05$, two-tailed Student's t -test).

Lesion Extent and Perceptual Deficit

Histological reconstruction of the lesions in all three cats revealed contiguous damage to cortex on both banks of the LS sulcus, although the precise amount of damage varied between the three animals. Cat B had the least complete lesion of LS cortex (see Fig. 2), which may explain why this cat exhibited sparing of complex motion perception at many locations in its contra-lesional visual field (see Fig. 3). Furthermore, this cat recovered relatively quickly, requiring less than 15 days to achieve normal direction range thresholds. In cat C, the lesion was slightly more extensive, with all components of LS cortex damaged to some extent and less visual sparing in the contra-lesional hemifield. This cat's recovery also required ~15 days of retraining. Cat A, whose damage to LS cortex was the most extensive, exhibited a profound deficit and the slowest recovery, requiring ~40 days to achieve normal thresholds. Overall, the extent of cortical damage was largely proportional to the amount of visual field exhibiting a deficit in complex motion perception and to the rate of recovery from that deficit.

The patchy sparing of motion thresholds after LS lesions could be explained by the complex retinotopic organization of LS cortical areas (Palmer *et al.*, 1978; Sherk and Mulligan, 1993). Sherk and Mulligan demonstrated that some regions of the visual field, such as the area centralis, the vertical and the horizontal meridians, are represented at multiple locations within LS cortex (Sherk and Mulligan, 1993). Indeed, all cats showed sparing of complex motion perception in the central 5–7° of vision, and along portions of the horizontal meridian, which could be due to survival of tissue in the most posterior

and/or anterior portions of LS cortex containing these representations (for example in cat B). It may be that unless all cortical sites processing information from a particular portion of the visual field are damaged, perception at that visual field location will be relatively spared.

Selective Impairment of Complex Motion Perception

At the start of post-lesion testing, cats could not reliably discriminate the direction of coherently moving dots. In contrast, at these same visual field locations, the direction of simple gratings could be discriminated at contrasts identical to those measured in the intact hemifields (see Fig. 4). A similar dissociation between direction discrimination of drifting gratings and random-dot stimuli was reported previously following bilateral LS lesions (Rudolph and Pasternak, 1996) and MT/MST lesions in monkeys (Pasternak and Merigan, 1994; Rudolph and Pasternak, 1999). The selective preservation of motion discrimination of simple gratings suggests that LS cortex may not be uniquely specialized for processing this type of motion signal. Indeed, in the cat, such discriminations have been shown to depend on earlier stages of visual cortical processing in areas 17 and 18 (Pasternak and Maunsell, 1992; Pasternak *et al.*, 1995, 1997).

Our results document the effect of LS lesions on two different measures of complex motion perception. One requires observers to extract global direction of motion from stimuli consisting of a large range of dot directions, while the other tests the ability to extract coherent motion in the presence of noise. Both tasks require neurons to pool and integrate local directional vectors (Williams and Sekuler, 1984; Watamaniuk *et al.*, 1989) as well as extract motion information in the presence of noise (Zohary *et al.*, 1996). The presence of effects of LS lesions on both direction range and motion signal thresholds suggests an important role for LS cortex in both motion integration and the extraction of motion information from noise. While the majority of postero-medial lateral suprasylvian (PMLS) neurons have been shown to respond to motion of noisy stimuli (Merabet *et al.*, 2000), it is not certain whether these cells are equipped to integrate local motion vectors. In fact, two previous studies failed to show that PMLS neurons are capable of integrating components of plaid stimuli (Gizzi *et al.*, 1990; Castelo-Branco *et al.*, 2000), unlike some neurons in areas V3 (Gegenfurtner *et al.*, 1997) and MT (Movshon *et al.*, 1985) of the monkey. It remains to be seen whether neurons in other portions of LS cortex damaged in our cats [such as the postero-lateral suprasylvian area (PLLS), antero-medial suprasylvian area (AMLS) and antero-lateral suprasylvian area (ALLS)] can perform integration of local directional vectors. One possibility is that deficits in motion integration after LS lesions are due to the loss of LS inputs to the anterior ectosylvian visual area (AEV; Symonds and Rosenquist, 1984a), a region shown to contain neurons capable of performing integration of local components of plaid patterns (Scannell *et al.*, 1996). In summary, the similarity in the deficits in motion perception produced by lesions of LS cortex (present study; Rudolph and Pasternak, 1996) and of areas MT/MST (Newsome and Paré, 1988; Pasternak and Merigan, 1994; Rudolph and Pasternak, 1999; Bisley and Pasternak, 2000) suggest that despite some differences in organization and response properties, these two regions may sub-serve similar functions in the two species.

Recovery of Complex Motion Perception

An important result of this study is that recovery of complex motion perception after LS lesions is not spontaneous but requires specific visual retraining. Prior to retraining, deficits measured a few days to several months after the lesion were not significantly different from each other, suggesting that intact visual cortical areas are not readily equipped to take over complex motion processing if LS cortex is destroyed. Recovery of motion thresholds started only after systematic, daily retraining began. Furthermore, improvements in threshold were largely specific to the visual field location retrained, decreasing with distance away from it. Interestingly, the spatial extent of the retraining effect appeared to depend on eccentricity. When retraining took place at 20° eccentricity, its effect disappeared at ~35° from the retrained location, while the effect of retraining at 9° eccentricity disappeared about 15° away. This difference in fall-off rates may be a consequence of differences in the receptive field sizes mediating the recovered function at the two retrained eccentricities. For example, receptive fields in area 18, which is known to contribute to motion perception (Pasternak and Maunsell, 1992; Pasternak *et al.*, 1997), and is normally interconnected with LS cortex (Symonds and Rosenquist, 1984a,b; Sherk, 1986; Shipp and Grant, 1991), increase ~2-fold between 9° and 20° of eccentricity (Tusa *et al.*, 1979; Dreher *et al.*, 1980, 1993).

The spatial specificity of improvements in performance observed in the present study further reinforces the notion that active retraining is necessary to elicit recovery of complex motion thresholds. Neither the passage of time nor passive visual experience was sufficient to induce functional recovery at sites removed from the retrained locations. Studies of cortical strokes (Xerri, 1998; Friel *et al.*, 2000; Taub *et al.*, 2002) and perceptual or motor skill learning in normal subjects (e.g. Karni and Sagi, 1991; Recanzone *et al.*, 1992a,b, 1993) also show that passive manipulations and environmental exposure are relatively ineffective at altering cortical structure and function compared with the demands of actively performing a task. Indeed, while the cats in this study were exposed to visual motion in their daily lives, this motion may not have sufficiently challenged peripheral portions of their visual fields that were affected by the lesion. We speculate that the 'forced-choice' and the 'controlled-fixation' aspects of the task used in our experiments were instrumental in stimulating recovery by requiring animals to actively discriminate the motion stimuli appearing in impaired portions of their visual fields. The lack of immediate transfer of recovery between direction range and motion signal thresholds further suggests that merely directing attention to a motion stimulus placed in the impaired visual hemifield is not sufficient to elicit recovery. It also implies that different mechanisms may govern processing of these stimulus types in retrained animals. Retraining on one stimulus type, in this case direction range, could modify a portion of the visual neural network, reinforcing a particular set of neural connections and rendering the network more efficient at performing vector averaging of local motion directions.

Comparisons with Human Studies

There are many similarities between the training-induced visual recovery reported here and observations in human patients with damage to motor cortex, which show that retraining can induce significant recovery of motor function

when introduced 7–14 days (Dromerick *et al.*, 2000) or 4 years after the stroke (Taub *et al.*, 1993). Studies of patients with damage to visual cortex show a similar pattern, with no better outcomes in those who started visual retraining shortly after their brain damage compared with several years after their lesion (Kasten and Sabel, 1995). These observations argue against the existence of a critical post-lesion period for initiation of effective retraining in adults. Several studies have also examined the deficits and occasional improvements in motion perception in patients with damage to temporo-parieto-occipital cortex (e.g. Zihl *et al.*, 1983; Baker *et al.*, 1991; Greenlee and Smith, 1997; Braun *et al.*, 1998; Vaina *et al.*, 2001), a region thought to include the human equivalents of the macaque monkey's areas MT/MST (e.g. Zeki *et al.*, 1991; Tootell *et al.*, 1995; Huk and Heeger, 2002) and thus, LS cortex. However, as in much of the monkey lesion work, these studies did not assess whether improvements were spontaneous or due to retraining/practice.

Finally, our visual retraining paradigm bears many similarities to constraint-induced movement therapy for humans and monkeys with strokes of motor cortex (Taub *et al.*, 2002). For example, Taub *et al.* (1993) studied patients with chronic symptoms of motor stroke whose unaffected arm was constrained for 90% of their waking time over 14 days. During this period, patients whose stroke-affected arm was extensively trained for 6 h per day, showed significant improvements in arm use, which were maintained for 2 years. Several critical features of this therapy were present in our retraining paradigm. Controlled fixation prevented the cats from using intact parts of their visual field. They were trained at the location of maximal deficit and the retraining was intensive, occurring daily, lasting 1 h per day, and consisting of 200–300 trials. Like the stroke patients of Taub *et al.* (1993), our cats showed training-specific improvement that lasted for many months.

Possible Neural Substrates of Training-induced Recovery

How does retraining affect the neural circuitry to elicit recovery? While an alteration in synaptic weights at existing cortical connections, such as a reduction in the weight of GABAergic inputs has been postulated to mediate rapid post-lesion changes in neuronal responsiveness (Merrill and Wall, 1972; Alloway and Burton, 1991; Garraghty *et al.*, 1991; Soper *et al.*, 1997; Chen *et al.*, 1998; Ziemann *et al.*, 1998), this phenomenon requires no post-lesion retraining (Eysel and Schweigart, 1999; Eysel *et al.*, 1999). The rapid time-course (Calford and Tweedale, 1988, 1991; Garraghty *et al.*, 1991; Faggin *et al.*, 1997) and spontaneity of alterations in synaptic weights suggest that they might represent a 'vegetative' response of the system to injury, rather than a critical substrate of the protracted, training-induced recovery observed in the present study. Alternatively, it has been suggested (Newsome and Paré, 1988; Yamasaki and Wurtz, 1991; Pasternak and Merigan, 1994) that intact visual cortical areas could take over functions lost as a result of the lesion. A number of cortical areas could be involved in the training-induced reorganization necessary for such a take-over. Given that cats were retrained to perform complex motion discriminations, it is more likely that visual cortical areas beyond area 17 are mediating the recovered function. Such regions could include areas 18, 19 and AEV, the latter being thought to play an important role in the processing of complex motion stimuli (Scannell *et al.*,

1996). A possible scenario is that reorganization of the connectivity of area 18, including the development or strengthening of new feedback inputs from higher-level visual areas, mediates the recovered ability to discriminate direction for complex motion stimuli. Our own preliminary work (Huxlin and Pasternak, 2001) shows that following LS lesions, the expression of the calcium-binding protein calbindin, an indicator of neural activity, was most severely affected in supragranular neurons of area 18, with no changes in the neurochemistry of areas 19 or AEV. Ongoing anatomical studies of the brains of retrained animals should provide better insights into the neural substrates of the observed functional recovery and allow us to formulate new hypotheses of how adult brain circuits can be altered and repaired by experience. It is hoped that such information will eventually lead to the development of therapeutic strategies using pharmacology and/or behavioral manipulations to promote sensory recovery following brain damage in adulthood.

Notes

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