

Disinhibition of the Superior Colliculus Restores Orienting to Visual Stimuli in the Hemianopic Field of the Cat

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ABSTRACT

Following unilateral removal of all known visual cortical areas, a cat is rendered hemianopic in the contralateral visual field. Visual orientation can be restored to the blind hemifield by transection of the commissure of the superior colliculus or by destruction of the superior colliculus (SC) or the substantia nigra pars reticulata (SNpr) contralateral to the cortical lesion. It is hypothesized that a mechanism mediating recovery is disinhibition of the SC ipsilateral to the cortical lesion. The ipsilateral nigrotectal projection exerts a robust inhibitory tone onto cells in the SC. However, ibotenic acid destruction of SNpr neurons, which should decrease inhibition onto the SC, does not result in recovery. The failure of ipsilateral SNpr lesions to produce recovery puts into question the validity of SC disinhibition as a mechanism of recovery. We directly tested the disinhibition hypothesis by reversibly disinhibiting the SC ipsilateral to a visual cortical lesion with a gamma-aminobutyric acid (GABA)_A antagonist, bicuculline methiodide. In accordance with the hypothesis, transient disinhibition of the SC restored visual orienting for several hours in three of eight animals. Recovery was not a volume or pH effect and was distinct from the release of irrepressible motor effects (i.e., approach and avoidance behaviors) seen within the first hour after injection. Thus, in the absence of all visual cortical areas unilaterally, disinhibition of the SC can transiently restore the ability of the cat to orient to visual stimuli in the previously "blind" hemifield. *J. Comp. Neurol.* 387:568-587, 1997. © 1997 Wiley-Liss, Inc.

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Sprague (1966a) demonstrated that the hemianopic cat can recover visuomotor function. An animal with no visual cortical areas unilaterally can regain responsiveness to visual stimuli in the previously blind hemifield subsequent to transection of the commissure of the superior colliculus (CSC) or after destruction of the superior colliculus (SC) or the substantia nigra pars reticulata (SNpr) contralateral to the cortical lesion (Sprague, 1966a; Wallace et al., 1989, 1990).

Recovery is not mediated by spared cortical areas. Neither the intact contralateral hemisphere nor frontal areas spared in the damaged hemisphere are necessary for recovery (Sherman, 1974, 1977; Sprague and Chambers, unpublished observations). The subcortical area implicated in recovery is the SC. Ibotenic acid destruction of the SC ipsilateral to a visual cortical lesion reinstates hemianopia in the recovered animal (Wallace et al., 1989).

Several hypotheses have been proposed to explain recovery. The underlying premise common to all hypotheses is that the mechanism of recovery is disinhibition of the SC ipsilateral to a visual cortical lesion. The loss of excitatory corticotectal afferents depresses neuronal activity in the

ipsilateral SC (Anderson, 1970; Goodale, 1973; Saraiva et al., 1978; Nagata et al., 1980; Hardy and Stein, 1988). It is hypothesized that transection of the CSC or destruction of the SC or SNpr contralateral to a cortical lesion produces recovery via the removal of inhibitory afferents to the SC, i.e., via disinhibition (Sprague, 1966a; Wallace et al., 1989, 1990).

Recent work has questioned the validity of the disinhibition hypothesis. Unlike the contralateral nigrotectal projection, the ipsilateral nigrotectal projection is robust (Hopkins and Niessen, 1976; Rinvik et al., 1976; Edwards et al., 1979; Beckstead et al., 1981; Gerfen et al., 1982; Beckstead and Frankfurter, 1983; May and Hall, 1986; Harting et al., 1988; Appell and Behan, 1990; Wallace et al., 1990). The

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ipsilateral pathway is known to be inhibitory (Vincent et al., 1978; Chevalier et al., 1981; DiChiara et al., 1982; Kilpatrick et al., 1982; Araki et al., 1984; Karabelas and Moschovakis, 1985; Behan et al., 1987; Ficalora and Mize, 1989), to modulate the responsiveness of cells in the deeper laminae of the SC (McHaffie et al., 1993), and to modulate visual orienting behavior (Boussaoud and Joseph, 1985; Joseph and Boussaoud, 1985; Hikosaka and Wurtz, 1989). However, ibotenic acid destruction of the SNpr ipsilateral to a visual cortical lesion, which should disinhibit the SC, does not result in recovery (Ciaramitaro et al., 1997).

The present study directly tested the hypothesis that disinhibition of the SC ipsilateral to a visual cortical lesion is a mechanism mediating recovery. The SC has one of the highest concentrations of gamma-aminobutyric acid (GABA) in the central nervous system (for review see, Mize, 1992), and the source of GABA is both intrinsic and extrinsic. GABA has been shown to modulate visual orienting (Hikosaka and Wurtz, 1985a,b; Boussaoud and Joseph, 1985).

The SC consists of three primary subdivisions—the superficial, intermediate, and deep layers (for review, see Huerta and Harting, 1984). A subset of cells in the intermediate and deep layers of the SC discharges in response to a visual stimulus and before an eye movement that brings the visual axis onto the locus of points in space defining the visual receptive field of the cell (e.g., Schiller and Koerner, 1971; Schiller and Stryker, 1972; Wurtz and Goldberg, 1972; Sparks, 1975; Mohler and Wurtz, 1976; Sparks et al., 1976; Peck et al., 1980; Grantyn and Berthoz, 1985). Some of these cells fail to discharge before spontaneous or reflex saccades that are not triggered by visual stimuli. Thus, there are neurons in the intermediate and deep layers of the SC that are well suited for triggering orienting movements to visual stimuli (for review, see Wurtz and Albano, 1980).

Given the role of the SC and GABA in visual orienting, we hypothesized that disinhibition (via a GABA antagonist) of neurons in the intermediate and/or deep layers of the SC may lead to recovery. We tested this hypothesis by applying bicuculline methiodide, a GABA_A antagonist, directly into the intermediate and/or deep layers of the SC ipsilateral to a cortical lesion. In three of eight animals studied, this intervention transiently restored visual orienting into the previously hemianopic field. Preliminary results have been reported previously in abstract form (Ciaramitaro et al., 1994, 1995).

MATERIALS AND METHODS

General

Nine adult male cats (4.2–5.2 kg) were used in the study. Animals were maintained on a 12-hour light/dark cycle in individual housing with ad libitum access to food and water except before surgery or behavioral testing. Animals were tested for normal neurological function and binocular visual fields (see below) and were excluded from the study if responses were abnormal. All procedures conformed to federal regulations and guidelines for animal welfare and were approved by the Institutional Animal Care and Use Committee.

Cannula assembly. Single cannula assemblies were fabricated using commercially available, 22-gauge, stainless steel guide cannulae and appropriately sized dummy cannulae and injection needles (Plastics One, Roanoke,

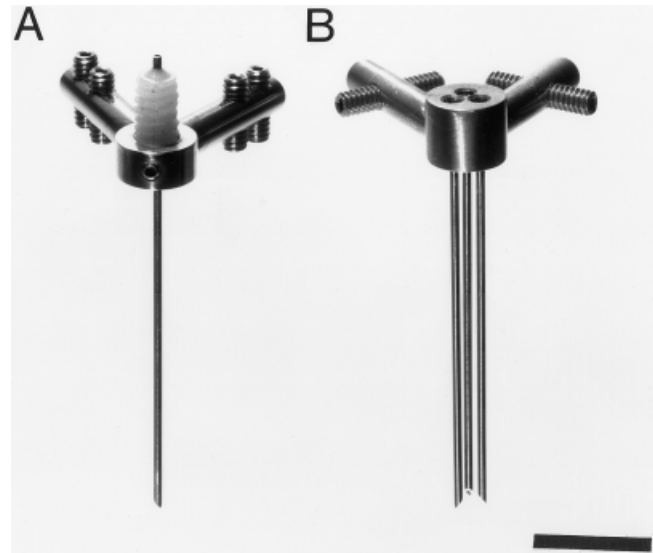


Fig. 1. Cannula Assembly. Pictures of the guide cannulae are shown to depict the various parts of the assembly and the scale. (A) The single commercially available guide cannula (Plastics One, Roanoke, VA) and our specially designed holder. (B) The specially designed triple guide cannula assembly. For both the single and triple guide cannula assembly, the cannulae protrude 30 mm below the metal collar. Scale bar = 10 mm.

VA). The guide cannulae were bevelled, and a stainless steel ring with a V-shaped protrusion was built that could fit onto the Teflon threading of the guide cannulae to improve the stability of the assembly (Fig. 1).

Triple cannula assemblies were specially designed such that three 22-gauge guide cannulae were positioned in a triangular array, 1.8–2.0 mm apart, center to center. As in the single cannula assembly, the guide cannulae were bevelled and had an added structural element for increased stability (Fig. 1). Dummy cannulae and injection needles were specially constructed and appropriately sized to fit the assembly.

Surgical procedures

General. Animals were deprived of food 12–24 hours before surgery. Surgical procedures were performed using standard aseptic technique and barbiturate or gas anesthesia. Barbiturate anesthesia was induced with an intramuscular injection of a mixture of ketamine HCl (15–20 mg/kg) and atropine sulfate (0.025 mg/kg). A loading dose of pentobarbital (20–50 mg) was delivered through a cannula in the femoral or cephalic vein. Procaine penicillin (200,000 units) was then given intramuscularly, and the trachea was intubated. Supplemental anesthesia, a 1:1 mixture of pentobarbital diluted in sterile saline, was provided as necessary. For gas anesthesia, cats were preoperatively given an intramuscular injection of ketamine HCl (15–20 mg/kg) and induced with intravenous thiopental (10–18 mg/kg). Procaine penicillin (200,000 units) was then given intramuscularly, and the trachea was intubated. Anesthesia was maintained with 2–4% isoflurane.

Once the animal was anesthetized, the head was positioned in a standard cat stereotaxic frame and prepared for sterile surgery. All animals received a unilateral visual cortical lesion, and a single or triple cannula assembly was

implanted ipsilateral to the cortical lesion approximately 2 mm above the SC.

Visual cortical lesions. A midline incision was made, and the temporalis and scalp muscles were dissected from their points of attachment and retracted. A unilateral craniotomy was then performed to expose the cortical areas to be removed. The dura was cut and reflected, and the following visual cortical areas were removed by suction aspiration: 5, 7, 17, 18, 19, 20a, 20b, 21a, 21b, dorsal lateral suprasylvian area (DLS), ventral lateral suprasylvian area (VLS), posterior suprasylvian area (PS), posterior medial lateral suprasylvian area (PMLS), posterior lateral lateral suprasylvian area (PLLS), anteromedial lateral suprasylvian area (AMLS), anterolateral lateral suprasylvian area (ALLS), and splenial visual area (SVA; Rosenquist, 1985). Varying amounts of damage were sustained by the ectosylvian visual area (EVA).

SC cannula placement. Following the cortical lesion, parts of the lateral, posterolateral, and posterior cingulate gyrus; retrosplenial cortex; and hippocampus were gently suctioned to expose the surface of the underlying SC. The cannula assembly was then lowered to the appropriate medial/lateral and anterior/posterior position as determined stereotaxically, based on the atlas of Reinoso-Suarez (1961). The vertical placement was guided visually (i.e., the cannula was lowered to the surface of the SC and then was raised to lie 2 mm above the surface).

The cannula was kept patent via an indwelling dummy cannula, which extended the length of the cannula without protrusion. Exposed areas of the brain were covered with gelfoam, and the cannula assembly was fixed in place with dental cement (Teldyne, Elk Grove Village, IL) that was anchored to skull screws (stainless steel mounting screws 0–80 thread, 3/32", Plastics One). Excess skin around the dental cement mound was removed, and the remaining skin was surgically stapled anteriorly and posteriorly. Animals were closely monitored for the 48 hours subsequent to surgery and allowed to recover for 2–4 weeks before postoperative testing.

Injection procedures

Preparation of solutions. (–) Bicuculline methiodide (Sigma, St. Louis, MO) was dissolved in 0.9% sterile saline, and the pH was adjusted to 6.0. Saline (0.9%; pH 6.0) served as a vehicle control. Solutions were stored at 5°C.

Preparation of injectors. Injections were made into the SC via a 28-gauge injection needle that fit the guide cannula, protruding various distances from the tip. For the single cannula assembly, an injector was prepared by modifying a commercially available injection needle (Plastics One). For the triple cannula assembly, an injector was specially constructed. All injection needles were beveled to a 1-mm tip, and a Delrin cap was affixed to the injection needle so that it could be screwed securely onto the guide cannula. For the single cannula assembly, the cap was connected directly to the injection needle. For the triple cannula assembly, the cap was not connected directly to the injection needle, thus minimizing coring of tissue when the injector was screwed onto the guide cannula. To allow for delivery of solutions, PE20 polyethylene tubing was permanently affixed to the upper end of the injection needle (Fisher Scientific, Pittsburgh, PA).

General. Using a sterile technique, the injection needle and connecting tubing were loaded with solution and attached to a 5- μ l Hamilton syringe filled with the same

solution. Excess solution was pushed through the delivery system before the injection to ensure that the delivery system was patent and to check for air bubbles. While the animal was mildly restrained, the injection needle was lowered into the guide cannula and screwed in place. Volumes of 0.25–4.0 μ l of various concentrations of solution were injected manually over the course of 1 minute. The injection needle was left in place for an additional minute before it was unscrewed and removed from the guide cannula. At the end of the injection, the dummy cannula was put back in place. Once the appropriate volume had been delivered and the injection needle removed, excess solution was again pushed through the system to ensure that the system had been functional during the injection into the SC. Injections were intended to be 1.5–2 mm beneath the surface of the SC. Given that the cannula had been visually placed a set distance above the SC, injection needles were cut to an appropriate length.

Behavioral procedures

General. In preparation for behavioral procedures, animals were handled regularly and adapted to the mild restraint required for testing. Animals were deprived of food for 24–48 hours and then shaped to run in a visual perimetry paradigm (see below). Visual field status was assessed in food-deprived animals preoperatively, postoperatively, and at several time points after each injection.

Visual perimetry testing. Binocular visual fields were assessed by using the visual perimetry paradigm adapted from Wallace et al. (1989). Briefly, a food-deprived animal was positioned on a table marked into 12 15-degree sectors, ranging over a visual angle of 90° to the left and 90° to the right of straight ahead. The animal was trained to fixate a central stimulus and indicate detection of a novel peripheral stimulus by orienting to the stimulus. An experimenter restrained the animal while the animal fixated a central visual stimulus (a food reward held in a pair of forceps by a second experimenter) approximately 40 cm from the cat's nose. While the animal fixated, a second stimulus was introduced at one of the peripheral 15° sector lines, either from above or below, and the cat was given 1–2 seconds to orient to this novel stimulus. Once the animal detected and oriented toward the stimulus, the animal was released and given a food reward at the peripheral stimulus. This was the test trial. Such behavior on a test trial was considered a positive result. If the animal failed to detect the stimulus, the animal was released and given a food reward at the fixation stimulus. Such behavior on a test trial was considered a negative result. Because the animal was rewarded regardless of its response, there was little or no incentive to develop scanning strategies into the "blind" hemifield to maximize reward. A trial was aborted if the animal broke fixation before the presentation of the novel stimulus or if the animal did not initiate fixation. The experimenter at the central fixation position, presenting the stimuli, determined whether the animal had broken fixation due to extraneous factors and whether the animal responded to the stimuli presented.

A control trial was presented every fourth trial. On a control trial, the animal maintained fixation while a visual stimulus was presented outside the visual field (i.e., 120° to the left or right of central fixation). Control trials measured the prevalence of spontaneous scanning behavior into the right or left visual field. If the animal broke fixation during the 1- to 2-second interval during which

the stimulus was presented, the behavior was counted as a scan. The data were normalized to account for the direction of spontaneous scanning behavior according to the method described in detail elsewhere (Wallace et al., 1989; Sherman, 1974, 1977). In brief, the percentage of scans on control trials in the left hemifield was subtracted from the percentage of positive test trials in the left hemifield and similarly for test and control trials in the right hemifield.

To assess preoperative and postoperative behavior, food-deprived animals were usually tested in a visual perimetry paradigm (described above) on a weekly basis. Testing did not resume subsequent to surgical procedures until transient behavioral motor biases had resolved. Testing continued until the animal completed a total of 180 test trials and 60 control trials.

To assess preinjection and postinjection behavior, food-deprived animals were tested in the visual perimetry paradigm up to 1 hour before injection, usually 1 hour after the injection, and at various subsequent time points, usually 1- to 2-hour intervals, covering a 24-hour postinjection period. The testing regimen varied, depending on the motivation of the animal and the presence of any overt motor biases that precluded testing. Whenever possible, testing consisted of a session presenting a visual stimulus randomly at each of the 13 possible locations 3 times. Thus, the animal was tested on a maximum of 39 test trials and 13 control trials for each session, with an average total of 9–10 sessions in a 24-hour period.

At the end of each session of visual perimetry testing, the ability of the animal to orient to auditory and somatosensory stimuli in the left and right hemifield was also assessed. Animals were presented with one or two auditory stimuli in each hemifield, generated by tapping a forceps, for roughly a 1- to 2-second period, out of the line of sight. One or two somatosensory targets were also presented, while the animal was not looking, on each side of the body and consisted of touching the hindlimbs and/or forelimbs with a forceps for 1–2 seconds. At a minimum, a 24-hour period intervened between injections. Usually, a 48-hour to 12-day period intervened between injections.

At least one of the two experimenters testing the animal was unaware of the substance being injected. Furthermore, postinjection behavior and visual perimetry testing were videotaped, and many sessions were independently scored by observers unaware of the substance injected or of the animal's history.

Neurological examination. A neurological examination was performed on all animals preoperatively and postoperatively, according to the methods described in Wallace et al. (1989). In brief, the examination consisted of the following: (1) tests for visuomotor capacities, including localization of stationary stimuli, visual placing, blink-to-threat, open field following, eye movements, pupillary symmetry and responsiveness, open field visually guided behavior, and relative neglect of either hemifield to the presentation of two simultaneous stimuli; (2) tests for the presence and symmetry of palpebral, pineal, buccal, and vibrissal responses to light touch; (3) tests for somatomotor and auditory-motor capacities; and (4) tests of spontaneous motor activity for detection of possible asymmetries in locomotion or posture.

Histological and anatomical reconstruction

Tissue preparation. After the completion of all behavioral testing, animals received an overdose of pentobarbi-

tal and were perfused through the heart with physiological saline, followed by 10% formalin. The brain was then blocked in the standard stereotaxic frontal plane, removed from the skull, postfixed, and processed for embedding in celloidin. The tissue was cut into 48- μ m thick sections. Every tenth section was stained for Nissl substance with cresyl violet, and adjacent sections were stained for fibers using the Heidenhain-Mahon myelin technique.

Tissue analysis

Cortical lesions. Serial coronal sections stained for Nissl or myelin were reconstructed to determine the extent of the cortical lesion. The extent of damage was determined relative to the intact hemisphere, taking into account asymmetries in the plane of cut. The damaged area was then charted onto a drawing of the intact hemisphere. The completeness of cell loss in the dorsal lateral geniculate nucleus was also examined to assure that lesions to areas 17 and 18 were complete.

SC injection site. Repeated injections of bicuculline methiodide into the SC resulted in an area of reactive gliosis and neuronal cell loss. To determine the general location of the injection site, the gliotic area was outlined by visualization of Nissl- and adjacent Mahon-stained sections under high-power magnification on a compound microscope. Sections were charted via an x-y plotter that was electrically coupled to the microscope stage. These data were imported to a computer graphics system (MDPlot, Minnesota Datametrics, St. Paul, MN). Sections were then reconstructed, and nuclei, fibers, and other anatomical landmarks were depicted by projecting the section onto the reconstructed drawing.

To allow for comparisons across animals, all data were replotted onto a standard dorsal view of the SC. The anterior/posterior and medial/lateral extent of the SC was determined based on the atlases of Reinoso-Suarez (1961) and Berman (1968), and the resulting map was positioned to correspond to the topography of retinal projections to the SC based on the map of Feldon et al. (1970). The sensory map of the SC was used, given that in the monkey it has been shown that the motor map of the SC varies depending on whether the animal's head is free to move (Freedman et al., 1996). The central locus of reactive gliosis for each animal was then charted onto the dorsal view of the SC. We assumed that the center of gliosis and the center of the injection site were the same. Furthermore, we assumed that the center reflected the site most affected by the injection.

The central locus of damage was determined from the section with the largest area of damage. The anterior/posterior location of the center of the injection was taken from the section with the greatest extent of damage. From this same section, the medial/lateral location of the center of the injection was also determined (i.e., the center of the medial/lateral spread of the gliosis). It was assumed that the solution injected spread symmetrically from the center of the injection site and thus that the region of gliosis would be distributed uniformly around the central focus of the injection. The vertical dimension of the gliotic area was not represented in this standard atlas.

RESULTS

A total of eight animals (cases 1–8) sustained a unilateral cortical lesion and were implanted with one or more chronic indwelling cannulae above the ipsilateral SC. One

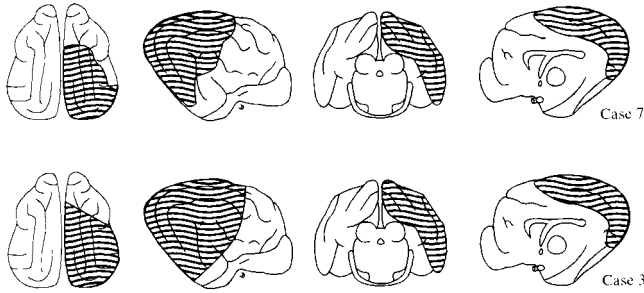


Fig. 2. Cortical Reconstructions. The extent of the cortical lesion (shaded areas) shown for two cases in (from left to right) coronal, lateral sagittal, dorsal, and medial sagittal views. Case 7 depicts the case with the smallest extent of cortical damage, and case 3 depicts the case with the largest extent of cortical damage.

additional control animal without a visual cortical lesion (case 9) was stereotaxically implanted with a cannula above the SC.

Histological analysis

The primary aim of the anatomical reconstructions was to determine the extent of damage to the cortex and to the SC. It was important to ensure that cortical lesions were complete so that any recoveries seen could be more directly attributed to midbrain mechanisms. SC injections were intended to be in the intermediate and/or deep layers of the SC where neurons are known to be involved in sensorimotor integration (Meredith and Stein, 1986; Meredith et al., 1987; for review, see Peck et al., 1993). The location of the SC lesion, as assessed by anatomical reconstruction, was used to determine the general location of the injection.

Occipito-parieto-temporal cortical lesions. Anatomical reconstruction of the cortical damage revealed that no visual cortical areas were spared, except possibly for portions of EVA. Cortical destruction included the medial and lateral banks of the lateral gyrus, posterolateral gyrus, suprasylvian gyrus, and the anterior and posterior ectosylvian gyrus. Figure 2 shows the smallest (case 7) and the largest (case 3) extent of cortical damage. The dorsal lateral geniculate nucleus was completely atrophied in all cases, thus confirming that destruction of area 17 was complete (Sprague, 1966b).

Cannula placement. Reconstruction of the gliotic region confirmed that the intermediate and/or deep layers of the SC were the sites of injection. In the majority of cases, damage also extended into the superficial layers of the SC. This more superficial damage most likely reflects destruction of the tissue sustained following repeated penetration with the injection needle, rather than damage resulting from the solution itself. The photomicrographs in Figure 3 show the damage caused by the injections for cases 2 and 5. Figure 4 shows a summary of the reconstructions of all eight cases. The three animals that recovered are depicted in the top row, and the five animals that failed to recover are depicted below.

In cases 1–7, animals were implanted with a single cannula above the SC. Injections were centered in the intermediate and/or deep layers of the SC over a range of anterior/posterior and medial/lateral locations (Fig. 4). Figure 5A shows the central focus of the damaged area for each animal transferred onto a standard dorsal view of the

SC. The central focus of damage represents the center of the injection site. The centers of the injection sites across animals cover a collicular area of roughly 3 mm along the anterior/posterior axis and 2 mm along the medial/lateral axis of the SC. The majority of injections are in the anterior aspect of the SC, with one injection site located posteriorly (case 3).

In case 8, the animal was implanted with a triple cannula assembly above the SC. Injections were in the intermediate and/or deep layers of the SC (Fig. 4). Figure 5B shows the central focus of the damaged area for each of the three injection sites, 8a–c, transferred onto a standard dorsal view of the SC. The centers of the injections cover a collicular area of roughly 1.5 mm along the anterior/posterior axis and 2 mm along the medial/lateral axis. Injection 8a is the most medial and anterior site, 8c is the most lateral and caudal site, and 8b is located between these two areas.

Thus, based on areas of reactive gliosis and neuronal cell loss in the SC, injections were in the appropriate layers of the SC and the central focus of the injections varied over a range of anterior/posterior and medial/lateral locations both across animals and within a single animal. The present data fail to assess the actual physical spread of the drug from the center of the injection site. More importantly, the pharmacological spread of the drug (i.e., the locus of neurons effectively disinhibited by the drug) remains unknown.

Behavioral analysis

The primary aim of the behavioral work was to determine performance on visual perimetry testing following disinhibition of the SC ipsilateral to the cortical lesion. The release of other behaviors following SC disinhibition was also assessed because such behaviors could confound the recovery effect and because previous work in the rat has demonstrated the importance of the SC in both approach and avoidance behaviors (for review, see Dean et al., 1989; Dean and Redgrave, 1992).

Before surgery, all animals had normal results on neurological examination and had normal binocular visual fields extending at least 90° left and right of midline. Orienting behaviors to visual, auditory, and somatosensory stimuli were normal.

Postoperative visual fields and behavior. Following recovery from anesthesia, all animals sustaining unilateral occipito-parieto-temporal lesions displayed a marked turning and circling tendency ipsilateral to the side of the lesion. This motor bias resolved within 2–4 weeks, at which point behavioral testing began. All animals presented with a complete and enduring homonymous hemianopia as assessed by visual perimetry testing and neurological examination. Cats could not orient to stationary or moving stimuli, follow moving stimuli, or visually place or blink to threat in the hemianopic field. Animals were able to fixate normally and were able to make eye or head movements into the contralateral visual field.

Some impairments were also noted in orienting to auditory or somatosensory stimuli. In three of eight animals, responses to auditory stimuli in the hemifield contralateral to the cortical lesion were absent. Responses to somatosensory stimuli presented to the hindlimb contralateral to the cortical lesion were absent in four of eight animals. These impairments often resolved. By the conclusion of behavioral testing, auditory responses returned in

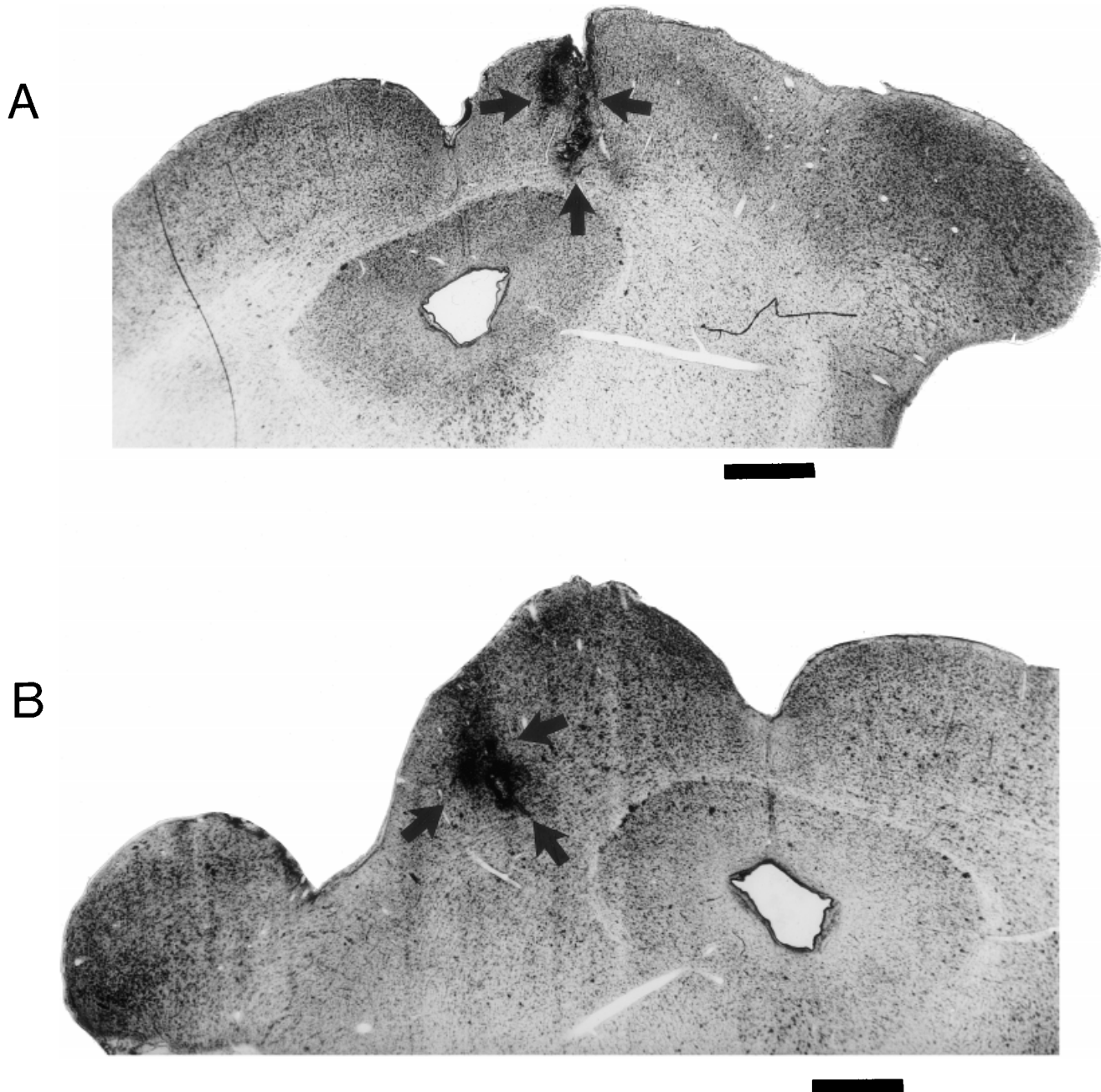


Fig. 3. Histology. Photomicrographs of the area of reactive gliosis and neuronal cell death (i.e., the lesion site) resulting from repeated injections. (A) Low-power view of a Nissl-stained section from case 2.

The arrows point to the lesion in the right SC. (B) Low-power view of a Nissl-stained section from case 5. The arrows point to the lesion in the left SC. Scale bars = 1 mm.

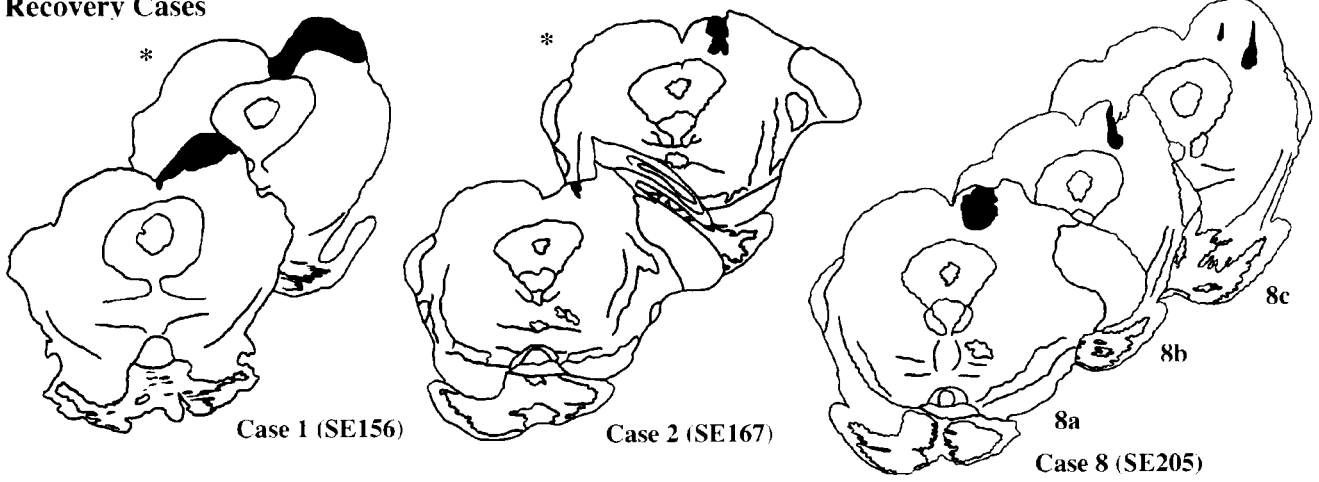
one of three animals and somatosensory responses resolved in three of four animals with a previous impairment (Table 1).

Visual fields and behavior were again assessed on completion of all injections (i.e., 4–10 injections per animal carried out over a period of 3.7–19.9 weeks). After repeated pharmacological intervention with a GABA_A antagonist, behavioral measures showed no permanent change from hemianopia (i.e., animals still presented with a complete homonymous hemianopia).

Postinjection visual fields and behavior. All animals presented with a complete and enduring homonymous hemianopia in the visual field contralateral to the cortical lesion before each injection. No asymmetries were noted in spontaneous behaviors such as posture or locomotion.

Recovery of visual orienting (1–26 hours after injection). The visual orienting response was transiently restored in the previously blind hemifield in three of eight animals (cases 1, 2, and 8) subsequent to the injection of bicuculline

Recovery Cases



Non-Recovery Cases

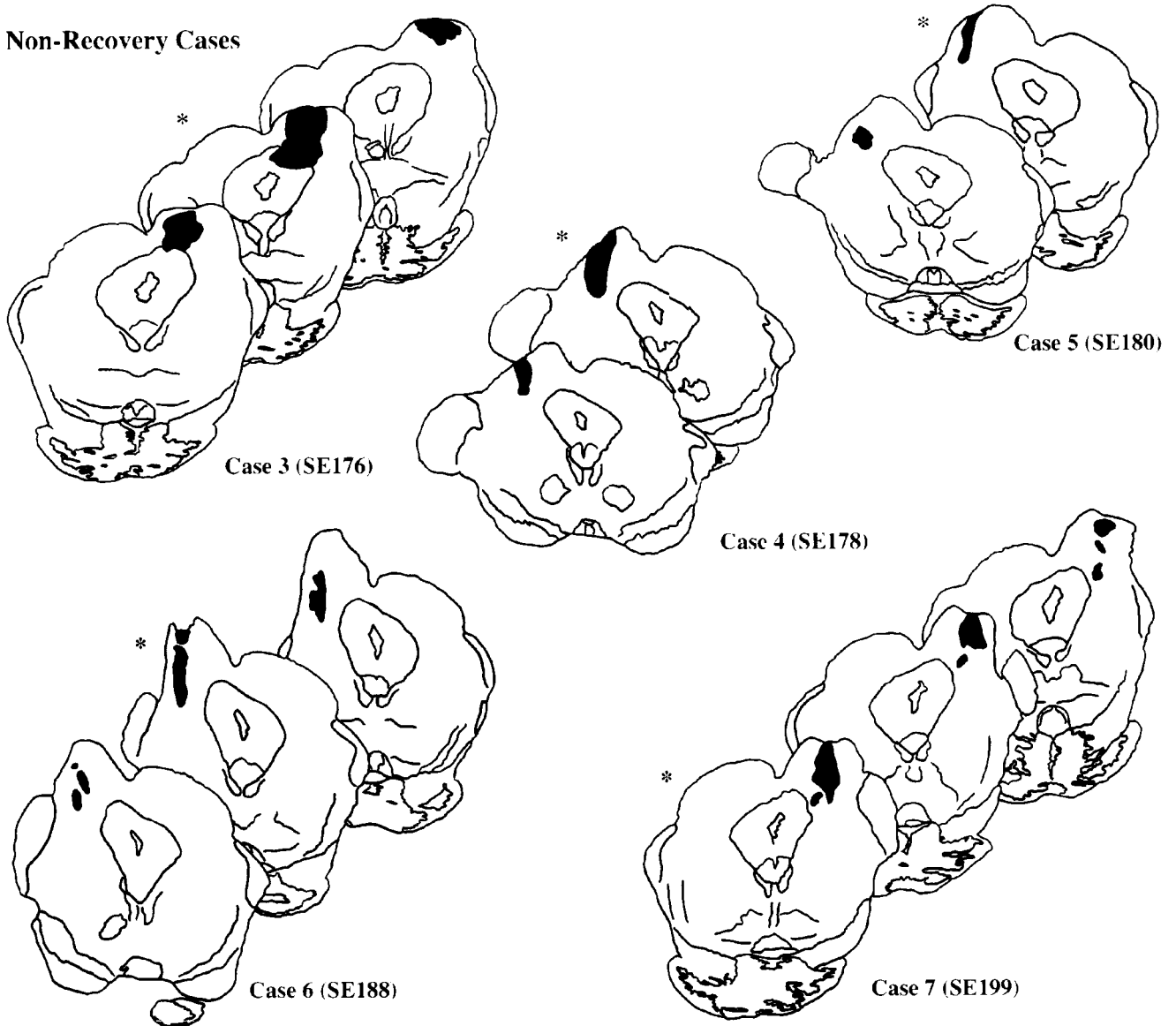


Figure 4

methiodide in the SC. The performance of the three animals that recovered on the visual perimetry task is depicted as a function of time and the volume and concentration of the drug injected in Figures 6 and 7. All three animals were unresponsive to visual stimuli in the hemianopic field before injection, with 0% correct responsiveness in the hemianopic field. Within 1.5–3 hours after injection, responsiveness to visual stimuli in the “hemianopic” field was robust with an average maximal percent correct ranging from 85–100% across the three animals. Recovery was transient, with animals returning to preinjection hemianopic conditions within 24 hours.

In all cases, the visual hemifield either recovered entirely or not at all. The central portion of the hemifield, 0–45° from midline, was restored first, followed by the more peripheral portion, 45–90° from midline (Figs. 6, 7). In Figures 6 and 7, the recovery is divided into three stages: the start of recovery, the maximal effect, and the beginning of the loss of recovery. The following criteria were used to categorize data: the start of recovery was defined as $\geq 33\%$ correct responsiveness to visual stimuli in the “hemianopic” field, and the beginning of the loss of recovery was defined as $\leq 33\%$ correct responsiveness into the “hemianopic” field. Using this subdivision of the data, a trend is seen such that at the beginning of recovery a greater responsiveness is seen on average for stimuli in the central portion of the hemifield. This trend is presented more clearly as a graph (Fig. 8).

The recovery of visual orienting after bicuculline methiodide injection is not a volume or pH effect. Injections of comparable volume and pH of a vehicle control fail to elicit a recovery (Table 3 and Figs. 6, 7). Most importantly, the recovery does not simply reflect a nonspecific and irrepressible release of orienting behavior (i.e., a purely motor disinhibition not triggered by a visual stimulus). Such scanning behavior is accounted for on control trials and if excessive would negate any recovery effect on test trials.

A summary of scanning behavior over the course of the experimental paradigm is depicted for all cases in Table 2. At the end of all injections, cases 1 and 2 showed some increase in scanning behavior into the hemifield contralateral to the cortical lesion (Table 2). Only case 1 developed a truly noticeable increase in scanning that persisted over the course of several weeks and required retraining the animal (data not shown). This animal received the largest volume injection of bicuculline methiodide. It is possible that the injection was not causally related to the increase in scanning, because a small percentage of animals sustain-

Fig. 4. Reconstructions of the SC. Drawings of coronal sections through the midbrain demonstrating the extent of neuronal cell loss and reactive gliosis (black regions) resulting from injections into the SC. From left to right, the coronal sections progress from more rostral to more caudal for each animal. Cases 1, 2, and 8 depict the animals with injection sites that were effective in eliciting recovery. Cases 1 and 2 depict the damage resulting from a single cannula placed above the SC. (Note: Case 1 was processed by frozen sectioning rather than celloidin embedding; thus, its reconstruction is less precise.) Case 8, sections a–c, represents the area of SC damage resulting from each cannula in the triple cannula assembly. Location 8a was the only effective injection site in eliciting recovery. Cases 3–7 depict the animals with injection sites that were ineffective in eliciting recovery. Asterisks indicate the section for each case with the greatest extent of damage from which the anterior/posterior and medial/lateral coordinates were determined for the representation of the central focus of the damaged area illustrated in Figure 5.

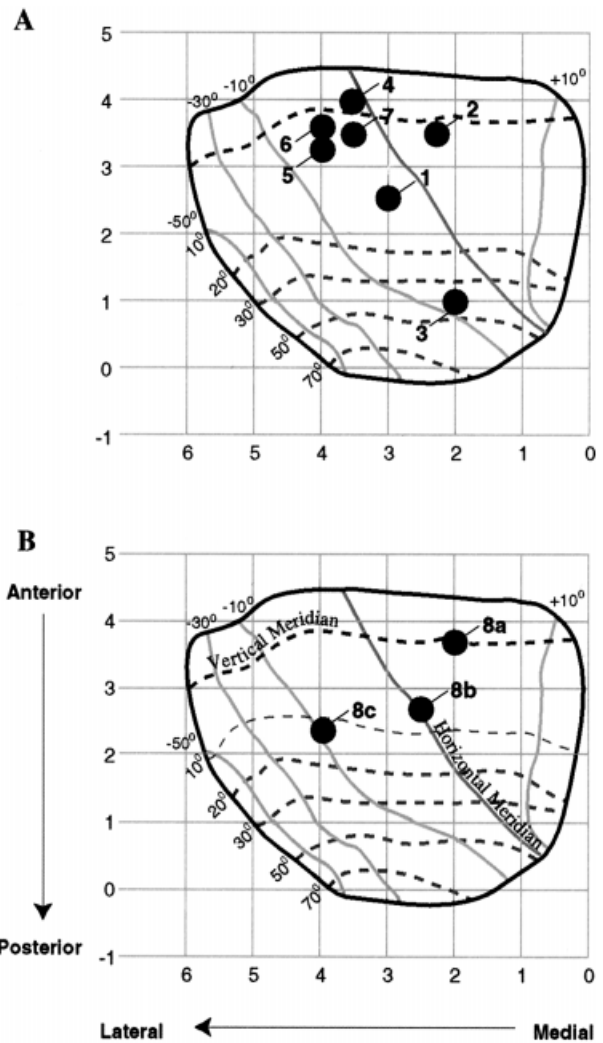


Fig. 5. Summary of the Central Focus of Injection Sites in the SC. A transformation of the central focus of the damaged area depicted in Figure 4 onto a two-dimensional representation of the dorsal view of the SC based on the sensory map of Feldon et al. (1970). The anterior/posterior and medial/lateral coordinates of the central focus were determined for each case from the section in Figure 4 with an asterisk. Dashed lines depict the vertical meridian and the various eccentricities of azimuth from +10 to +70°. Solid lines depict the horizontal meridian and the various eccentricities of elevation from +10 to -50°. Filled circles depict the central focus of the damaged area for each animal, indicating the center of the injection site. The anterior/posterior and medial/lateral units are in millimeters. (A) The central focus of damage is shown for each animal with a single cannula above the SC, cases 1–7. (Note: It was difficult to determine the exact anterior/posterior and medial/lateral location of damage in case 1 due to the more extensive degradation of this tissue.) (B) The central focus of damage is shown for an animal with three cannulae above the SC, case 8.

ing unilateral visual cortical lesions spontaneously develop scanning behavior (Rosenquist et al., unpublished observations).

Of the eight animals injected, the most notable increase in scanning behavior during the several hours after injection was seen for the three cases that recovered (cases 1, 2, and 8; Table 2 and Figs. 6, 7). However, for two of three cases (cases 1 and 8), the same increase in scanning was

TABLE 1. Orienting to Auditory and Somatosensory Stimuli¹

Case no.	Auditory			Somatosensory		
	Pre-operative	Post-operative	End of injection	Pre-operative	Post-operative	End of injection
1	ok L ok R	ok L ok R	*	ok L ok R	ok L ok R	*
2	ok L ok R	ok L ok R	ok L ok R	ok L ok R	ok L ok R	ok L ok R
3	ok L ok R	ok L ok R	ok L ok R	ok L ok R	ok L ok R	R > L
4	ok L ok R	ok L OR	ok L OR	ok L ok R	L > R	ok L ok R
5	ok L ok R	ok L OR	ok L OR	ok L ok R	L > R	L > R
6	ok L ok R	ok L ok R	L > R	ok L ok R	L > R	ok L ok R
7	ok L ok R	ok L ok R	ok L ok R	ok L ok R	R > L	ok L ok R
8	ok L ok R	OR ok R	ok L ok R	ok L ok R	ok L ok R	ok L ok R

¹The preoperative columns present data reflecting orienting to either somatosensory or auditory stimuli to the left (L) and right (R) of midline before any surgical intervention. The postoperative columns present data reflecting orienting following the cortical lesion and cannula implant. The end of injection columns present data reflecting orienting at the end of all injections.

*, denotes that no data were obtained at this time point. Bolded notations indicate orienting asymmetries between the L and R sides.

seen in both hemifields and thus did not preferentially bias responsiveness into the hemianopic field. Furthermore, the increase in scanning was not typical during the first few injections that resulted in recovery. Rather, the maximal increase in scanning developed subsequent to multiple injections, by which time the animal usually failed to recover. As can be seen in Table 2, the percent of scanning behavior during the period of maximal recovery in these three cases is substantially less than the maximal percent of scanning behavior seen following any particular injection (i.e., a range of 0–15% compared with a range of 17–38%, respectively). Finally, all data were normalized to account for spontaneous scanning behavior. Despite increases in spontaneous scanning, the recovery of visual orienting remains robust.

In summary, the following statements can be made. (1) Direct disinhibition of the SC ipsilateral to a visual cortical lesion via pharmacological injection of the GABA_A antagonist bicuculline methiodide is sometimes sufficient to restore visual orienting responses in the previously blind hemifield of the cortically blind cat. (2) The restoration of visual orienting is not a volume or pH effect, given that injections of the vehicle control at comparable volumes and pH are ineffective. (3) The recovery is transient, and animals return to preinjection conditions of a complete hemianopia within 24 hours after injection. (4) Either the animal recovers the entire hemifield or fails to recover at all. (5) When an animal starts to recover, there is a tendency for the central aspect of the visual hemifield to recover first, followed by the more peripheral aspect. (6) Animals that recovered preferentially show an increase in scanning behavior into the hemianopic field within the 25-hour period subsequent to injection. However, the maximal increase in scanning is not evident during the period of maximal recovery.

Immediate postinjection behaviors (up to 1 hour after injection). Other behaviors released after SC disinhibition were also assessed because such behaviors could confound the recovery effect. Depending on the volume and concentration of the injection, various short-term behaviors precluded visual perimetry testing for up to 1 hour after injection. Starting several minutes after injection, most cats showed two primary response types: approach behaviors and avoidance or defensive behaviors (Table 3). The frequency of both approach and avoidance behaviors diminished over the course of 1 hour.

The approach responses included deviation of the eyes, head, and/or body into the visual field contralateral to the

injection site. Intermittent movements of the eyes and head often appeared, with the quick phase contralateral to the injection site. Animals usually exhibited tight circling toward the side contralateral to the injection site, varying from continuous circling to intermittent, ballistic circling. These orienting-like behaviors released in the approach response were not directed to any specific sensory stimulus, and animals failed to respond to visual or auditory stimuli that were presented during this period.

The avoidance or defensive responses consisted of hissing, growling, and movement away from an imaginary, feared stimulus in the contralateral visual field as manifested by backward circling and pawing behavior. Backward circling was manifest as a movement away from the visual field contralateral to the injection site, and pawing behavior included swiping movements of the forelimb contralateral to the injection site. The eyes, head, and/or body were also deviated toward the field contralateral to the injection site. Thus, for both approach and avoidance behaviors, the animal was biased toward the visual field contralateral to the injection site. Approach and avoidance behaviors were quantified for the first 30 minutes after injection (see Table 3 for a description).

The relation of behavioral outcome (i.e., approach and avoidance behaviors) relative to the central locus of the injection site is depicted across animals (Fig. 9A) and in the case of a single animal with multiple cannulae (Fig. 9B). As can be seen in Figure 9, both approach and avoidance behaviors can be elicited from the same injection site.

The immediate postinjection effects were replicated in one animal with intact cortices (case 9; SE168) after injection of bicuculline methiodide into one SC (Table 3). Thus, the immediate postinjection effects are unlikely to be related to the absence of visual cortical areas. Furthermore, the immediate postinjection effects are not volume or pH effects, because injections of the vehicle control (saline) at comparable volumes and pH failed to elicit any of these behaviors.

A dependency of behavioral outcome on drug volume or concentration can be seen for the immediate postinjection effects (Table 4). Increasing the concentration of the bicuculline methiodide without increasing the volume resulted in an increase in avoidance behavior. Thus, for case 6, injection 2 (0.5 mg/ml) elicited no defensive response, whereas injection 1 (1 mg/ml) elicited a severe defensive response. For case 8a, injection 2 (0.5 mg/ml) was ineffective, yet injection 4 (1 mg/ml) was effective in eliciting a defensive response. Similarly, increasing the volume of bicuculline methiodide without altering the concentration increased the severity of the avoidance response (compare cases 2, 3, and 8).

In summary, the following statements can be made. (1) Disinhibition of the SC ipsilateral to a visual cortical lesion via injection of bicuculline methiodide produces immediate postinjection effects, irrepressible approach and avoidance behaviors. (2) The immediate postinjection effects are graded (i.e., the severity of the response is dependent on the volume and concentration of bicuculline methiodide injected). (3) These immediate effects are not a volume or pH effect and are not simply an abnormal response related to disinhibition of the SC in the absence of visual cortical areas. (4) The immediate postinjection effects are transient, typically diminishing over the course of 1 hour. (5) Both the approach and avoidance behaviors can be elicited from the same injection site.

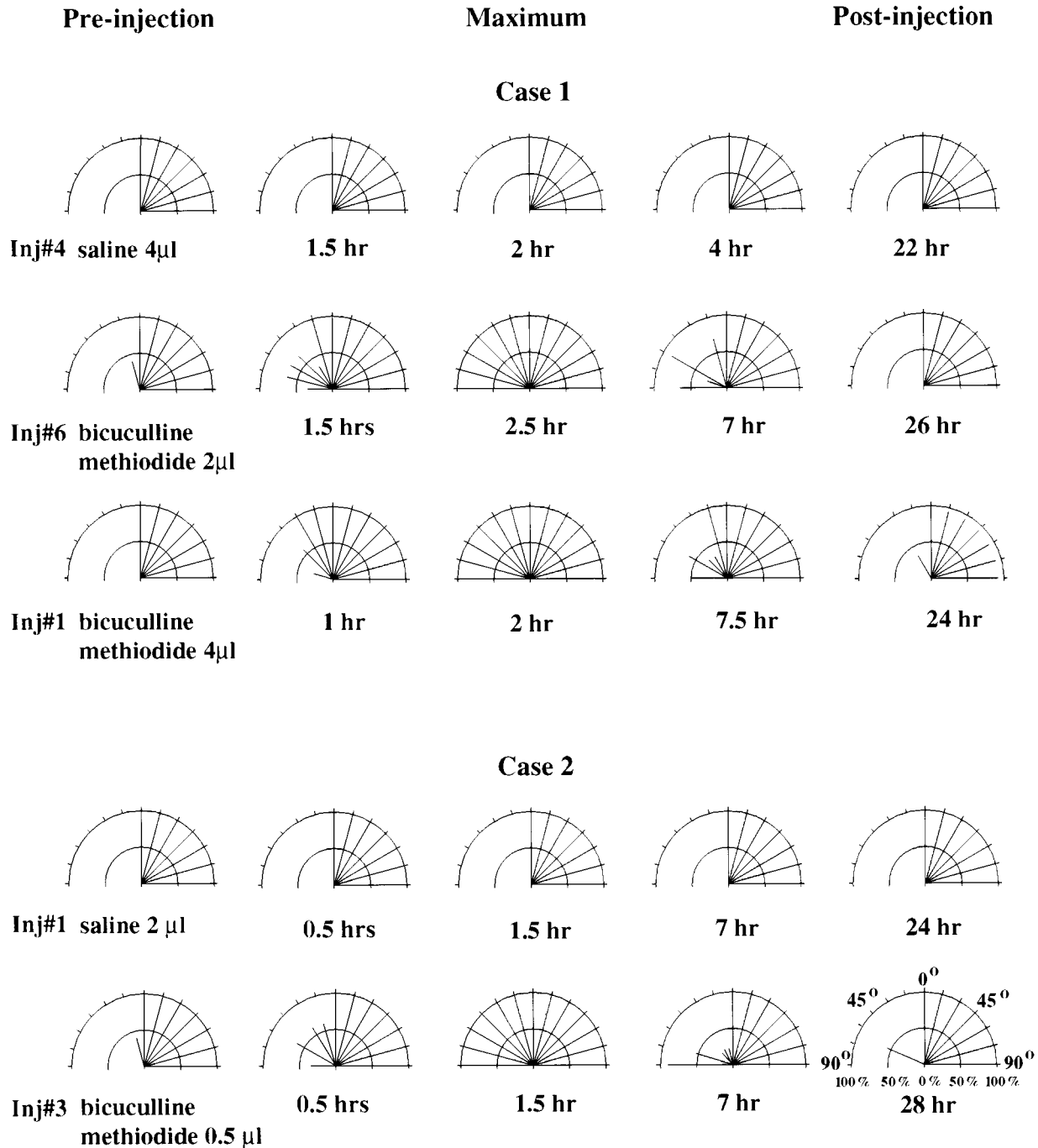


Fig. 6. Pharmacologically Induced Recovery as a Function of Time. Visual perimetry data are shown for two animals (cases 1 and 2) that recovered visual orienting into the previously "hemianopic" field. Percent correct responsiveness for visual stimuli is shown as a function of time and concentration or volume of solution injected. Data are normalized to account for spontaneous scanning behavior on control trials when no visual stimuli were present. The recovery effect is demarcated into three stages—the start of recovery, the maximal effect, and the beginning of the return to hemianopia. The following criteria were used to categorize data along these dimensions. (1) The

start of recovery was defined as greater than or equal to an average of 33% correct responsiveness to visual stimuli in the "hemianopic" field. (2) The beginning of the return to hemianopia was defined as less than or equal to an average of 33% correct responsiveness into the "hemianopic" field. For both cases, injections of bicuculline methiodide led to a recovery of visual orienting into the previously hemianopic visual field. Recovery progressed until, at the period of maximal drug effectiveness, the entire visual hemifield was restored. Injections of saline had no effect on visual orienting over the same time course.

Dissociation between short-term behaviors and recovery of visual orienting. There is a dissociation (Kendall correlation coefficient, -0.22) between the restoration of

visual orienting responses and the immediate postinjection effects. The release of approach or avoidance behaviors is not significantly correlated with, that is, does not

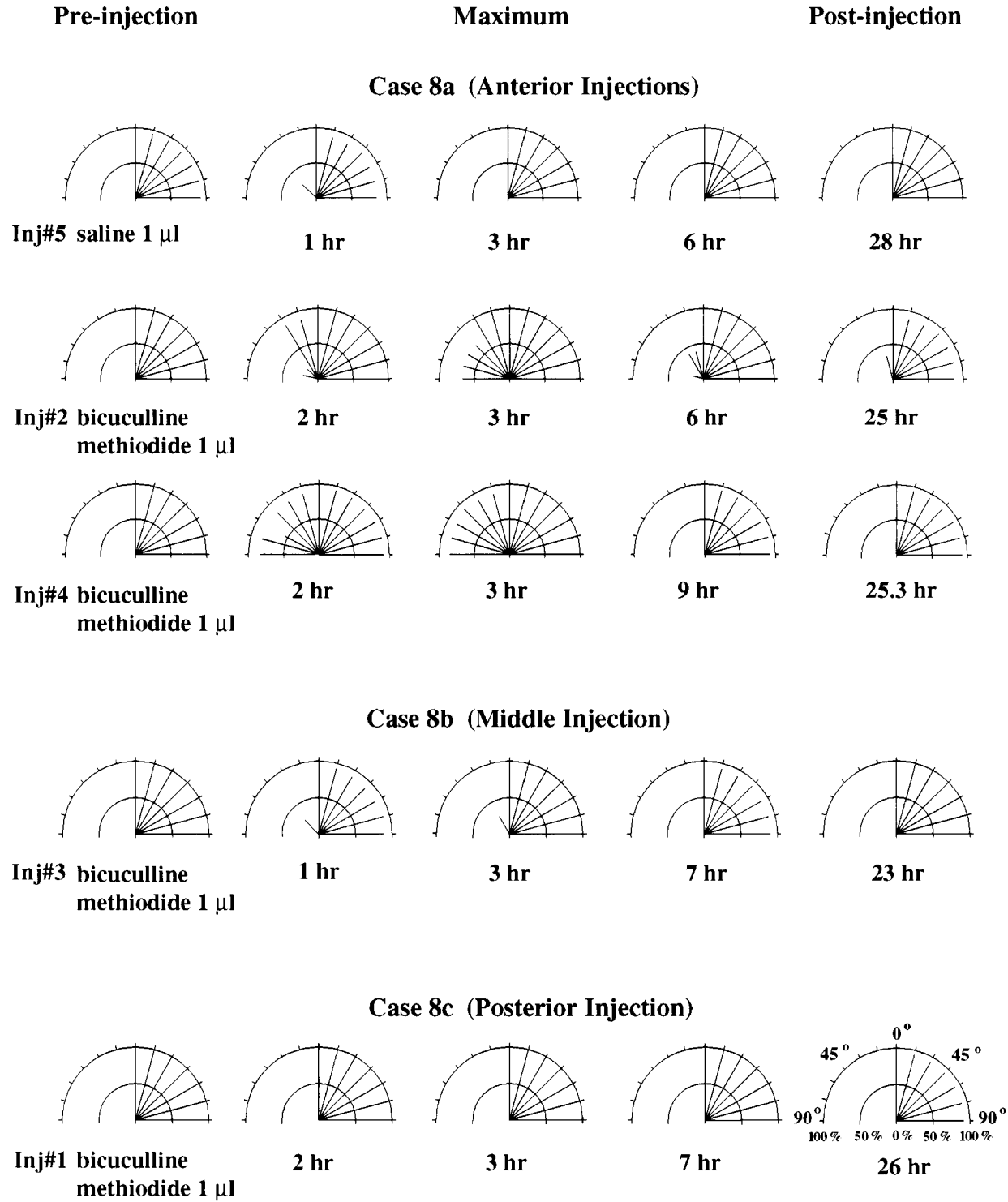


Fig. 7. Pharmacologically Induced Recovery as a Function of Time: A Case Study. Visual perimetry data are shown for a single animal with three cannulae above the SC (case 8, a-c). Percent correct responsiveness for visual stimuli is shown as a function of time and concentration or volume of solution injected. The recovery effect is demarcated into three stages—the start of recovery, the maximal effect, and the beginning of the return to hemianopia, as defined in Figure 4. For an effective injection site, the recovery of visual orienting

progressed until, at the period of maximal drug effectiveness, the entire visual hemifield was restored. Only one of the three injection sites (8a) was effective in producing a recovery. Injections of bicuculline methiodide at sites 8b and 8c had no effect on visual orienting behavior into the previously hemianopic field. Injections of saline at any of the three sites had no effect on visual orienting over a comparable time period.

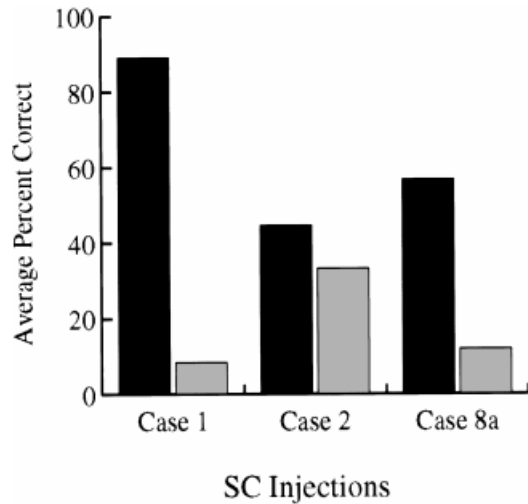


Fig. 8. Recovery of the Central Versus Peripheral Portions of the Hemifield. Visual perimetry data for the period marking the beginning of recovery (criterion: an average of $\geq 33\%$ correct responsiveness to stimuli in the previously "hemianopic" field) are shown for the three cases that recovered subsequent to bicuculline methiodide injection in the SC. The graph reflects a subset of the data summarized in Figures 4 and 5. Average percent correct responsiveness is collapsed across the central hemifield, visual stimuli presented 0–45° from midline (black bars), and the peripheral hemifield, visual stimuli presented from 45–90° from midline (shaded bars). Data reflect injection 1 for case 1, injection 2 for case 2, and injection 2 for case 8a.

predict, the recovery of visual orienting into the blind hemifield.

Animals were injected multiple times at the same site on different days. Injections were numbered sequentially. Dependent on the order of the injection and on differences in the concentration and volume of the injection, the same animal injected at the same location showed diverse effects. Thus, recovery was possible without the prior immediate postinjection effects. Cases 1, 2, and 8 recovered with no previous defensive reaction after injections 6, 3, and 2, respectively (Tables 3, 4). Conversely, five of eight animals never recovered although they exhibited immediate postinjection effects as severe as those seen in animals that did recover (Table 4). Furthermore, subsequent to multiple injections, there was at times a loss of drug efficacy in eliciting recovery with no loss in eliciting immediate postinjection behaviors. Thus, the same volume and concentration of bicuculline methiodide no longer produced recovery although it continued to elicit immediate postinjection effects (Table 4, case 8a, injection 4 vs. 10).

The most striking evidence in support of the dissociation between the immediate postinjection effects and recovery is a single animal implanted with three cannulae over the SC (Table 3). The maximum distance between injection sites was only 2 mm along the medial/lateral axis and 1.5 mm along the anterior/posterior axis. However, whereas two of three injection sites were effective in eliciting both approach and avoidance behaviors (case 8a and 8c), only one of these sites (case 8a) was effective in eliciting recovery (Fig. 9). Similarly, in animals with single cannulae, although most injection sites were effective in eliciting either approach or avoidance behaviors, very few sites were effective in eliciting a recovery of visual orienting.

In summary, the following statements can be made. (1) The immediate postinjection release of approach and avoidance behaviors is distinct from the recovery of visual orienting. (2) The presence or absence of immediate postinjection effects is not predictive of recovery. (3) Nearly all injection sites are effective in eliciting approach and avoidance behaviors, whereas fewer sites appear to be effective in restoring visual orienting.

DISCUSSION

The present study tested the hypothesis that disinhibition of the SC can mediate recovery of visual function in the blind hemifield of the cat. Injection of bicuculline methiodide, a GABA_A antagonist, into the SC ipsilateral to a visual cortical lesion transiently restored orienting to visual stimuli in the contralateral, previously hemianopic field in three of eight cats. Recovery was not a volume or pH effect given that comparable volumes and pH of vehicle control injections failed to elicit recovery (Table 2; Figs. 6, 7).

Immediate behaviors resulting from disinhibition of the SC

The recovery effect was not a confound of other behaviors resulting from disinhibition of the SC. Previous work has demonstrated the release of irrepressible saccades into the contralateral field following injections of GABA antagonists into the SC of the intact monkey (Hikosaka and Wurtz, 1985a) and rat (Dean et al., 1988a). In the present study, disinhibition of the SC ipsilateral to a visual cortical lesion would be expected to release spontaneous orienting movements (i.e., scanning) into the contralateral, hemianopic visual field. Such a result could confound the recovery of visual orienting. However, the recovery effect is distinct from immediate postinjection effects (i.e., the release of approach and avoidance behaviors seen within the first hour after injection) due to the following factors. (1) Visual perimetry testing began only after nonspecific orienting movements had subsided. (2) The animal's performance (percent correct on visual perimetry testing) was normalized to account for spontaneous scanning. Thus, despite the maximal increase in scanning behavior seen preferentially in the three animals that recovered, the recovery effect was still robust. (3) The maximal increase in scanning was not seen during the period of maximal recovery. (4) The occurrence of immediate postinjection effects was not predictive of recovery. Not all animals exhibiting immediate effects recovered visual orienting in the previously blind hemifield and conversely not all animals recovering exhibited immediate effects. (5) Although immediate postinjection behaviors could be elicited from nearly all injection sites tested, few of these sites were effective in eliciting a recovery.

Work done in the rat and gerbil suggests that the release of approach versus avoidance behaviors is site specific (for review, see Dean et al., 1989; Dean and Redgrave, 1992). Stimulation (Kilpatrick et al., 1982; Ellard and Goodale, 1986; Sahibzada et al. 1986; Dean et al., 1988a,b). Lesion studies in the rat and gerbil (Dean et al., 1986, 1988c; Ellard and Goodale, 1988) have demonstrated that distinct descending tectal pathways mediate approach versus avoidance behaviors. In the present study, both approach and avoidance behaviors were elicited from the same injection site. However, injections were fairly large, and these re-

TABLE 2. Percent Scanning in Left and Right Visual Hemifields as Assessed on Control Trials¹

Case no.	Lesion	Preoperative		Postoperative		Postinjection					
						Within 25 hours		At maximal recovery		At end of all injections	
1	R Ctx	0%R	0%L	3%R	0%L	17%R	17%L	0%R	0%L	*	
2	R Ctx	0%R	0%L	0%R	0%L	0%R	38%L	0%R	15%L	0%R	28%L
3	R Ctx	0%R	0%L	0%R	0%L	8%R	8%L			2%R	0%L
4	L Ctx	0%R	0%L	0%R	2%L	8%R	8%L			2%R	2%L
5	L Ctx	0%R	0%L	0%R	0%L	15%R	8%L			0%R	0%L
6	L Ctx	2%R	0%L	5%R	0%L	0%R	15%L			0%R	6%L
7	R Ctx	0%R	0%L	0%R	0%L	0%R	8%L			0%R	0%L
8	R Ctx	0%R	3%L	0%R	0%L	23%R	23%L	0%R	15%L	12%R	0%L

¹Destruction of the left visual cortex is indicated by L Ctx; destruction of the right visual cortex is indicated by R Ctx. The portions of the table in bold reflect the hemifield in which a scanning bias would influence the recovery effect. Thus, in an animal with a right cortical lesion, increased scanning into the left hemifield would be an increase into the previously blind hemifield (i.e., the hemifield where one expects a recovery of visual orienting behavior). The preoperative and postoperative columns represent the maximum percent scanning on blank trials over a total sum of 60 blank trials. Animals were tested over the course of several days. The postinjection section consists of three columns. The within 25 hours column reflects the maximum percent scanning behavior seen within the 25-hour period after injection on blank trials over a total of 13 blank trials. The maximum percent scanning in the left and right hemifields does not reflect the same time period subsequent to injection. The at maximal recovery column reflects the percent scanning behavior on blank trials at the postinjection period when the animal showed the largest percent correct responsiveness into the previously blind hemifield. The at end of all injections column shows the maximum percent scanning behavior on blank trials over a total sum of 60 blank trials. Animals were tested over the course of several days.

*, denotes that no data were obtained at this time point.

TABLE 3. Summary of Behavioral Results¹

Case no.	Injection no.	Drug	Concentration (µg/µl)	Volume (µl)	Approach		Avoidance				Vision
					Circling	Circling	Hissing	Pawing	Composite		
1	4	SAL	1	4	*	*	*	*	*	*	0%
	6	BM	1	2	0	0	0	0	0	0	100%
2	1	SAL	1	2	0	0	0	-8	-8	-8	0%
	2	BM	1	2	133	17	208	439	664	664	79%
3	1	SAL	1	2	-12	0	0	0	0	0	0%
	4	BM	1	0.75	70	215	0	0	215	215	0%
4	1	BM	1	1	16	0	0	0	0	0	0%
	4	SAL	1	2	*	*	*	*	*	*	*
5	2	BM	1	1	-29	0	0	1128	1128	1128	0%
	5	SAL	1	2	0	0	0	0	0	0	0%
6	1	BM	1	1	35	34	45	601	680	680	0%
	9	SAL	1	1	36	0	0	0	0	0	0%
7	4	BM	1	1	92	0	0	0	0	0	0%
	9	SAL	1	1	1	0	0	0	0	0	0%
8c	1	BM	0.5	1	16	0	0	0	0	0	0%
8b	3	BM	1	1	0	0	0	0	0	0	0%
8a	4	BM	1	1	39	72	48	0	120	120	85%
	5	SAL	1	1	0	0	0	0	0	0	0%
9	3	BM	1	1	0	124	319	398	839	839	*

¹The immediate postinjection effects are measured for the first 30 minutes after injection and include approach behavior as manifest by circling behavior toward the side contralateral to the injection and avoidance behaviors reflecting the sum of three components—hissing, pawing, and circling behavior away from some feared stimulus (i.e., backward circling). Circling and pawing behavior are represented as the overall preference for the side contralateral to the injection site (i.e., the difference between the contralateral and ipsilateral preference). Circling was measured as a continuous variable meeting the criterion of the animal completing one revolution without changing direction. Approach behavior reflects the overall preference for circling toward the contralateral side, whereas avoidance behavior reflects the overall preference for circling away from the contralateral side (i.e., backward circling). Pawing was measured as a continuous variable meeting the criterion of a swiping movement close to or above the head. This behavior was very stereotyped and distinct from grooming movements. The criterion for hissing, also a continuous variable, was an opening of the mouth followed by a hissing noise. For visual behavior, data from visual perimetry testing are shown. The data show the percent correct responsiveness, collapsed across the entire hemifield, for visual stimuli in the previously hemianopic field at the time of maximal effectiveness of the drug, x-y hours after injection. All data are normalized to account for spontaneous scanning behavior in the absence of visual stimuli on control trials.

*, denotes that no data were obtained that could be quantified. SAL, saline; BM, bicuculline methiodide.

sults do not necessarily demonstrate that approach and avoidance behaviors could not be site-specific effects in the cat as well.

Thus far, disinhibition of the SC has been demonstrated to result in both approach and avoidance behavior only in the rat and gerbil. However, across species, SC architecture displays a similar segregation in the distribution of afferents and efferents as well as discontinuities in the distribution of various neurotransmitters and enzymes (e.g., Huerta and Harting, 1984; Stein, 1984; Illing and Graybiel, 1985, 1986; Karabelas and Moschovakis, 1985; Dean et al., 1988c; Harting and Van Lieshout, 1991). Such a mosaic-like organization is well suited to establishing specialized domains of function within the SC. Despite the similarities in SC organization, it has been argued that the involvement of the colliculus in various behaviors may vary across species depending on the role of the forebrain in decision processing, the prevalence of predators, and the development of foveal vision (Dean et al., 1989; Dean and Redgrave, 1992). Our results indicate that in the cat, as in

the rat and gerbil, the SC is involved not only in approach behaviors but also in avoidance behaviors, suggesting that general SC function may remain constant across species.

The recovery mechanism

Disinhibition. In the present study, it was assumed that the mechanism by which the GABA_A antagonist leads to recovery is one of disinhibition. Although there is no direct physiological evidence in this study to confirm that SC cells were disinhibited (i.e., depolarized), other studies using similar volumes and concentrations of bicuculline methiodide have demonstrated depolarization and have reported similar immediate postinjection effects (Chevalier et al., 1981; Hikosaka and Wurtz, 1985a; Buee et al., 1986; Crossman et al., 1988; Yoshida et al., 1991; Dean and Redgrave, 1992; Matsumura et al., 1995).

If bicuculline methiodide disinhibited SC neurons in all eight animals studied, it is unclear why only three of eight animals recovered. The variability in the data could reflect

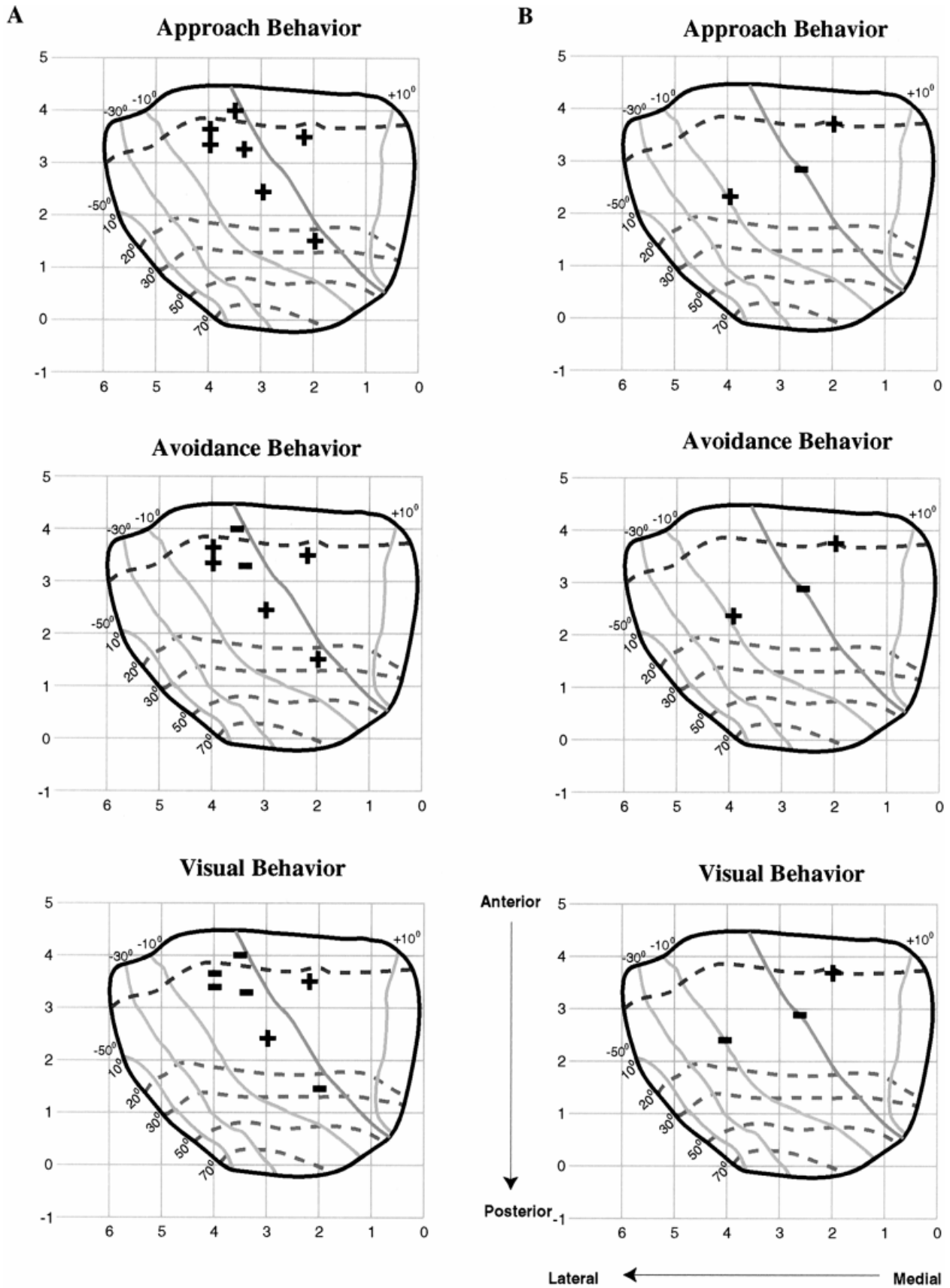


Fig. 9. Behavioral Outcome Relative to the Location of SC Disinhibition. A summary of the localization of the central focus of the injection in the SC relative to behavioral outcome. Approach behavior, avoidance behavior, and visual orienting into the blind hemifield are shown. Plus signs reflect the presence of a particular behavior; minus

signs reflect the absence of that behavior for the most effective injection of bicuculline methiodide. (A) Summary of data for animals with a single cannula above the SC (cases 1-7). (B) Summary of data for one animal with three injection sites in the SC (case 8). Conventions as in Figure 5.

TABLE 4. Summary of Effects of Volume and Concentration on Behavioral Results¹

Case no.	Injection no.	Concentration (µg/µl)	Volume (µl)	Approach	Avoidance	Vision
2	2	1	2	133	664	100%
	3	1	0.5	52	0	100%
3	2	1	0.25	60	20	0%
	3	1	0.5	152	72	0%
	4	1	0.75	70	215	0%
5	1	1	0.5	49	17	0%
	2	1	1	29	1128	0%
6	1	1	1	35	680	0%
	2	0.5	1	7	0	0%
	8	1	1	38	326	0%
7	2	0.5	1	0	0	0%
	4	1	1	92	0	0%
	6	1	2	36	0	0%
8a	2	0.5	1	0	0	78%
	4	1	1	39	120	85%
	10	1	1	214	133	0%

¹The immediate postinjection effects are measured for the first 30 minutes after injection and include approach behavior as manifest by circling behavior toward the side contralateral to the injection and avoidance behaviors reflecting the sum of three components—hissing, pawing, and circling behavior away from some feared stimulus (i.e., backward circling). Circling and pawing behavior are represented as the overall preference for the side contralateral to the injection site (i.e., the difference between the contralateral and ipsilateral preference). Circling was measured as a continuous variable meeting the criterion of the animal completing a complete revolution without changing direction. Approach behavior reflects the overall preference for circling toward the contralateral side, whereas avoidance behavior reflects the overall preference for circling away from the contralateral side (i.e., backward circling). Pawing was measured as a continuous variable meeting the criterion of a swiping movement close to or above the head. This behavior was very stereotyped and distinct from grooming movements. The criterion for hissing, also a continuous variable, was an opening of the mouth followed by a hissing noise. For visual behavior, data from visual perimeter testing are shown. The data show the percent correct responsiveness, collapsed across the entire hemifield, for visual stimuli in the previously hemianopic field at the time of maximal effectiveness of the drug, x-y hours after injection. All data are normalized to account for spontaneous scanning behavior in the absence of visual stimuli on control trials.

some aspect of the mechanism of recovery or it could reflect some artifact of the experimental paradigm. In terms of the mechanism of recovery, it is unclear if a specific cell type within the SC must be disinhibited, if a particular layer or region of the SC must be disinhibited, or how large an area of the SC must be disinhibited to induce a recovery. Differences along these dimensions may distinguish animals that recover from those that do not.

In terms of experimental artifact, one can easily rule out the possibility that drug delivery failed in some cases and not in others, potentially explaining the pattern of failures and recoveries. As mentioned in Materials and Methods, precautions were taken during drug delivery to ensure the absence of air bubbles or any blockage within the injection apparatus. Furthermore, most animals exhibited immediate postinjection effects regardless of the presence or absence of a subsequent recovery. The presence of immediate postinjection behaviors are consistent with a successful injection of solution for cases that recovered and those that failed to recover.

A more serious consideration is any artifact introduced by the bicuculline methiodide itself. Previous studies of motor responses subsequent to intracerebral injections of bicuculline methiodide have noted effective and ineffective injection sites in close proximity and inconsistent effects of the drug with delivery at the same site on different occasions (e.g., Crossman et al., 1988; Yoshida et al., 1991; Onn and Grace, 1995; Matsumura et al., 1995).

The possibility that the pattern of recoveries and failures could be explained by bicuculline methiodide differentially inducing depolarization versus depolarization block is also unlikely. Evidence does suggest that an overexcitation of nerve cells via dopamine agonists or of muscle cells via acetylcholine agonists can induce a depolarization

block (Taylor, 1990; Grace, 1992; Henry et al., 1992; Onn and Grace, 1995; Zhang and Jackson, 1995). However, no evidence exists demonstrating a postsynaptic depolarization block for antagonists of the neurotransmitter GABA. Furthermore, dopamine cells are exceptionally susceptible to depolarization block, and depolarization block is an extreme condition resulting from prolonged and continuous drug treatment. In the present experiments, the GABA antagonist was administered acutely, not chronically. Finally, none of the animals in the present study displayed behaviors that would be expected if one colliculus had been inactivated via depolarization block. Thus, no cases exhibited the ipsiversive posturing and circling tendencies seen after procedures that inactivate the SC (e.g., Albano et al., 1982; Wallace et al., 1989; Rosenquist et al., 1996). There is the possibility of a differential induction of depolarization versus depolarization block subsequent to the 1-hour period of immediate postinjection effects. Currently, there is no evidence for such a temporal delay in the induction of depolarization block. In addition, there is no conceptual framework for a mechanism that would induce depolarization block versus depolarization selectively for cases that recovered versus those that did not. Thus, the pattern of recoveries and failures is unlikely to be explained by the differential induction of depolarization versus depolarization block by bicuculline methiodide.

Characteristics of the recovery. In animals that did recover, the temporal progression of the effects was such that there was a tendency for the central aspect of the hemifield to recover first, followed by the more peripheral aspect, until the entire hemifield had been restored. It is possible that the central-to-peripheral and the all-or-none characteristics of the pharmacologically induced recovery reflect diffusion of the drug through the SC over time (Crossman et al., 1988; Yoshida et al., 1991; Dean and Redgrave, 1992).

Neurons in the intermediate and deep layers of the SC have a movement field and discharge before a range of saccades of particular amplitudes and directions (e.g., Schiller and Koerner, 1971; Wurtz and Goldberg, 1971, 1972; Sparks, 1975, 1978; Sparks et al., 1976, 1990; Sparks and Mays, 1980). Detailed microstimulation studies have characterized the motor map of the SC (e.g., Robinson, 1972; Schiller and Stryker, 1972; Wurtz and Goldberg, 1972). Neurons involved in eye movements are topographically organized across the surface of the SC such that disinhibition of increasingly posterior areas of the SC releases increasingly peripheral horizontal movements of the eyes. Animals that recovered had injections centered in the more anterior aspect of the SC; thus, diffusion of the drug over time—from more anterior to more posterior areas—may underlie the central-to-peripheral shift seen in recovery. Furthermore, in the several hours required for recovery of the entire hemifield, the drug could have diffused throughout the majority of the SC, thus explaining the all-or-none aspect of recovery.

If the all-or-none tendency and central-to-peripheral shift of recovery can be explained simply by the anterior to posterior spread of disinhibition in the SC that accompanies diffusion of the GABA antagonist (Crossman et al., 1988; Yoshida et al., 1991; Dean and Redgrave, 1992), then (1) recovery should have been observed in all animals with anterior injection sites (however, cases 4–7, with anterior injection sites, failed to recover), and (2) recovery should have been observed that progressed from the peripheral to

the central hemifield for more caudal injections that diffuse rostrally. Such a result has yet to be observed. The only animal with a posterior injection site, case 3, failed to recover; thus, the progression of the recovery could not be observed, assuming that recovery is possible at this location.

Furthermore, the diffusion explanation of recovery fails to account for the spread of disinhibition to neurons in the rostral pole of the SC, in the area centralis of the cat SC (Peck, 1989; Munoz and Guitton, 1991). Neurons in the rostral pole discharge during visual fixation rather than during visual orienting. In the monkey, disinhibition of such neurons by application of bicuculline methiodide suppresses saccade generation, with a maximal effectiveness 7–10 minutes after injection (Munoz and Wurtz, 1993).

It is unclear how disinhibition of these “fixation” cell types in the rostral SC of a cat with a cortical lesion could account for a recovery effect (i.e., the release rather than the suppression of visual orienting). However, in the present study, three animals with fairly rostral injections close to the “fixation” cells did recover visual orienting behavior, and behavioral effects were maximal over 1 hour after injection rather than the 7–10 minutes in the monkey. The duration of bicuculline methiodide effects seen in this study are consistent with those reported by other authors subsequent to intracerebral injections (Maksay and Ticku, 1984; Hikosaka and Wurtz, 1985a; Crossman et al., 1988; Yoshida et al., 1991; Matsumura et al., 1995) and with the binding characteristics of this drug, especially when compared with GABA (Olsen and Snowman, 1983; Maksay, 1994).

Finally, pharmacologically induced recovery shares several characteristics with recoveries induced by destruction of the SC, CSC, or SNpr. Thus, whether recovery is induced by lesion or by pharmacology, animals display an increase in scanning behavior if they recover and there is a tendency to recover the entire hemifield over the course of time, whether time is measured in hours after injection or days after lesion. Studies suggest that disinhibition may play an important role in lesion-induced recovery. Acute physiologic (Anderson, 1970; Goodale, 1973; Saraiva et al., 1978; Nagata et al., 1980) and metabolic (Hovda et al., 1987; Hovda and Villablanca, 1990) studies in several species demonstrate that a cortical lesion results in increased inhibition on cells in the ipsilateral SC. This increased inhibition is reduced (i.e., there is a disinhibition) following ablation of the contralateral SC (Anderson, 1970; Goodale, 1973; Saraiva et al., 1978; Nagata et al., 1980). However, it is unclear if a unitary mechanism can explain the recovery seen following pharmacological disinhibition of the SC and that seen after transection of the CSC or ablation of the contralateral SC or SNp.

The importance of plasticity. The present results suggest that the recovery process is far from understood and is far more complicated than initially thought. One main consideration is that previous work demonstrating the topography of SC maps and the role of the SC in visual orienting and fixation was done in the intact animal. However, the function of SC neurons is altered following a cortical lesion, and this may account for some of the properties of the recovery of visual orienting. Subsequent to various lesions of visual cortex, the superficial layers of the SC ipsilateral to the lesion remain responsive to visual stimuli yet exhibit increased responsiveness to stationary

stimuli, a loss of direction selectivity, and a loss of the effectiveness of the ipsilateral eye in driving SC neurons (Wickelgren and Sterling, 1969; Rizzolati et al., 1970; Rosenquist and Palmer, 1971). The deeper layers of the SC ipsilateral to a lesion or to inactivation of the lateral suprasylvian cortex show a loss in the proportion of visually responsive cells (Hardy and Stein, 1988) and an increased inhibition on these cells (Ogasawara et al., 1984). Thus, cortical inactivation induces a number of alterations in the SC.

Bicuculline methiodide may also induce plasticity in the system. In the intact rat, disinhibition of the SC via bicuculline methiodide alters the sensory specificity of neurons such that neurons responding exclusively to somatosensory stimuli become visually responsive (Dean and Redgrave, 1992). Such an alteration in the sensory specificity of SC neurons following injection of bicuculline methiodide may contribute to the recovery of visual orienting in animals with cortical lesions. Thus, the GABA antagonist may alter the sensory specificity of neurons such that either cells that had become unresponsive to visual stimuli following a visual cortical lesion regain visual responsiveness or cells that were initially unresponsive or only weakly responsive to visual stimuli gain responsiveness.

The finding that direct pharmacological disinhibition of the SC ipsilateral to a cortical lesion can result in recovery stands in contrast to the failure to see recovery following ibotenic acid lesion of the SNpr ipsilateral to the cortical lesion (Ciaramitaro et al., 1997). It is assumed that destruction of the SNpr should result in disinhibition of the ipsilateral SC. Compensatory mechanisms induced by the cortical lesion may also elucidate the reason for the failure of ipsilateral SNpr lesions to result in recovery.

What is recovered?

The nature of what is actually restored is poorly understood. To better understand the nature of the recovery, we need to better understand the nature of the deficit. Within the present behavioral paradigm, an animal indicates detection of a visual stimulus by initiating a movement. There is thus an intrinsic confound between assessing the animal's ability to detect or attend to visual stimuli (i.e., sensitivity and/or attention) and the ability or tendency to initiate a movement (i.e., response and/or criterion).

Motor (response). If the deficit is motor in nature, then it may be specific to visuomotor processing rather than to sensorimotor processing in general. The hemianopic animal may present with deficits in orienting to auditory or somatosensory stimuli in the hemianopic field (Sprague, 1966b; Wallace et al., 1989). In the present study, these nonvisual impairments often resolved over time. Thus, animals able to initiate orienting movements to somatosensory and auditory stimuli remained unresponsive to visual stimuli. An important consideration is the potential confound in comparing responsiveness to different sensory stimuli, given the unknown parameter of the relative saliency of stimuli across sensory modalities required to elicit a given level of responsiveness.

Criterion. The deficit could be the result of a change in criterion. Thus, there may be a change in the probability that the animal will initiate a response given a particular signal that is sufficiently different from noise. Increases in scanning behavior seen preferentially in the three cases that recovered may reflect an alteration in response crite-

tion. However, as stated previously, the maximal increase in scanning was not seen during the period of maximum recovery, when a change in criterion would most bias the interpretation of the data. Additionally, in two of three cases, increased scanning was not biased toward the hemianopic field. Rather, the same maximal increase in scanning was seen in both hemifields (Table 2).

Sensory (sensitivity). If the deficit is sensory in nature, it could be due to a loss of sensitivity for visual stimuli. Thus, the signal may no longer be sufficiently different from noise for the animal to detect it. Studies mentioned previously suggest that various visual cortical lesions alter the sensitivity of SC neurons for visual stimuli in the acute, anesthetized animal (Wickelgren and Sterling, 1969; Rizzolati et al., 1970; Rosenquist and Palmer, 1971; Ogasawara et al., 1984; Hardy and Stein, 1988). Work in the behaving animal also demonstrates impairments in visual function following various visual cortical lesions. Thus, permanent destruction or temporary inactivation of various visual cortical areas—such as area 17, area 18, lateral suprasylvian cortex, middle suprasylvian cortex, or ventral-posterior suprasylvian cortex—have been shown to result in visual impairments (i.e., deficits in contrast sensitivity, direction discrimination, spatial resolution, form discrimination, pattern discrimination, motion detection, and velocity discrimination; Pasternak et al., 1989, 1995; Pasternak and Maunsell, 1992; Lomber et al., 1994, 1996).

The deficits in visual function following the unilateral removal of all visual cortical areas, as used in the present paradigm, have not been addressed, and the quality of the visual information in the recovered animal also remains unknown. The SC has been implicated in visual discrimination behavior (Sprague et al., 1973). It is known that an animal with bilateral removal of visual cortical areas shows no decrement for light-dark discrimination while demonstrating a loss of visual function on visual perimetry (Sherman, 1977) and pattern or orientation discrimination (Loop and Sherman, 1977). CSC transection restores visual perimetry performance yet fails to restore pattern discrimination, suggesting that cortical areas are necessary for tasks involving more complex visual stimuli. Thus, the recovery of the ability to detect or attend to fairly rudimentary visual stimuli is sufficient to initiate an orienting movement; however, orienting is "sluggish and relatively poorly directed" (Sherman, 1977). How readily these results relate to visual function in an animal with a unilateral lesion of all visual cortical areas is unclear.

Attention. The deficit in visual orienting following a visual cortical lesion could be due wholly or in part to an attentional deficit. Lesions to various cortical areas result in attentional deficits. The physiological properties that may underlie attentional gating of visual input to the SC are also altered following a cortical lesion. The simultaneous presentation of two stimuli in opposite hemifields inhibits the superficial layers of the SC in the anesthetized cat (Rizzolati et al., 1973, 1974). This inhibitory effect, which could alter the relative salience of the two stimuli and allow the animal to attend to one stimulus versus the other, is reduced subsequent to a cortical lesion (Buchtel et al., 1979). In other words, a stimulus presented in the blind hemifield will fail to inhibit responsiveness for a stimulus in the good hemifield. Thus, one would predict that an animal would not respond to novel stimuli if responding required a shift or "disengagement" of atten-

tion from stimuli in the good hemifield. A similar deficit in "disengaging" attention is seen in humans with parietal lobe lesions (Posner et al., 1984).

Studies in the intact, behaving animal have suggested that the SC participates in visual attention (Sprague and Meikle, 1965; Goldberg and Wurtz, 1972; Butter et al., 1978; Rafal et al., 1988; Desimone et al., 1990). Reversible deactivation of one SC in the monkey increases manual reaction time for validly and invalidly cued targets in the contralateral hemifield (Robinson and Kertzman, 1995) and decreases percent correct performance, in the absence of eye movements, for targets in this hemifield in the presence of another stimulus—a distractor—in the ipsilateral hemifield (Desimone et al., 1989). Stimulation studies also demonstrate the role of the SC in attention (Kustov and Robinson, 1996). If an animal is presented with a cue indicating future target location, stimulation of the SC during the period between cue presentation and saccade initiation results in an evoked movement biased in the direction of the attentional shift (i.e., the location specified by the cue). The direction of the bias is dependent on whether the cue is valid or invalid (i.e., in the same or the opposite hemifield from the location of the target, respectively). The extent of the bias is dependent on the time of stimulation relative to the time of cue onset and the time of target onset. Deviations in stimulated eye movements are observed for tasks requiring an eye movement after target presentation and for tasks requiring maintained fixation and manual release of a lever following target presentation (Kustov and Robinson, 1996).

Attentional mechanisms are known to affect recovery. In the recovered animal, a test for extinction reveals that responsiveness to visual stimuli presented in the recovered hemifield is lost when a competing stimulus is presented in the good hemifield (Wallace et al., 1989). Thus, the recovered field reveals a permanent relative neglect for visual stimuli, suggesting that the SC can only subservise some component of attentional processes in the absence of visual cortex.

The deficit observed in the present study is unlikely to be purely one of attention. If the deficit were purely attentional, then bilateral cortical inactivation should result in no deficit due to a cancelling out of competitive attentional effects across hemifields. Bilateral cooling of the posterior-middle suprasylvian sulcal cortex does not result in deficits in visual orienting (Lomber and Payne, 1996). However, bilateral ablation of most visual cortical areas does result in visual orienting deficits in both hemifields (Sherman, 1977). The differences observed in bilateral cooling versus ablation of the cortex remain unresolved.

In summary, GABA-mediated disinhibition of the SC ipsilateral to a visual cortical lesion can transiently restore visual orienting behavior into the previously hemianopic field. The exact mechanisms underlying recovery are still far from understood, and it is unclear if similar mechanisms can account for not only this pharmacologically induced recovery but for lesion-induced recovery as well. The nature of what capacities are restored also remains ambiguous given the limitations of the behavioral paradigm used in the present study. Understanding the mechanisms responsible for recovery and the nature of what is restored will ultimately advance our understanding of sensorimotor integration and of findings in the human literature on attention and neglect.

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