Behavioral/Systems/Cognitive

Cortical Lesion-Induced Visual Hemineglect Is Prevented by NMDA Antagonist Pretreatment

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Large unilateral visual cortex lesions produce enduring contralesional visual orientation deficits. To examine whether glutamate excitotoxicity is involved in establishing these deficits, cats were pretreated with the NMDA receptor antagonist dizocilpine (MK-801) 30 min before unilateral visual cortex ablation. Pretreated MK-801 animals were trained first in an orientation task in which they were required to fixate directly ahead and then orient to stimuli introduced at various eccentricities throughout the visual field. They did not display the characteristic ipsilesional head and neck asymmetries and/or spontaneous ipsiversive rotational behaviors or show the profound contralesional visual neglect seen postoperatively in nonpretreated control animals. Rather, pretreated animals were able to orient to visual stimuli in the contralesional hemifield immediately following surgical recovery. Postmortem histology revealed severe retrograde degeneration of the ipsilesional lateral geniculate nucleus in both experimental groups, suggesting that postlesion visuomotor behavioral competencies in pretreated animals are attributable to preserved function in nongeniculocortical visual pathways. These observations are consistent with the hypothesis that visual cortex lesions normally induce secondary alterations via NMDA-mediated excitotoxicity in these other pathways that prevents them from supporting visuomotor behaviors. The similar behavioral competencies of MK-801-pretreated animals and those whose lesion-induced deficits are ameliorated by removing basal ganglia afferents to the ipsilesional superior colliculus are consistent with this hypothesis and highlight the normal functional capabilities of this circuit. It is likely that MK-801 pretreatment acts, at least in part, by preserving the normal interhemispheric control dynamics with which the basal ganglia influence superior colliculus-mediated orientation behaviors.

Introduction

Unilateral removal of all primary and contiguous regions of visual cortex in cats produces a profound deficit in their ability to orient to contralesional visual cues (Sprague and Meikle, 1965; Sprague, 1966; Sherman, 1974, 1977; Wallace et al., 1989, 1990). The animals behave as if they are unaware of objects in visual space contralateral to the lesion. Remarkably, this visual hemineglect can be ameliorated with a second lesion made in either the opposite superior colliculus (SC) or in the anterior aspect of the opposite substantia nigra, pars reticulata (SNr). Either midbrain lesion effectively severs crossed basal ganglia outputs via nigrocollicular afferents en route to the SC ipsilateral to the damaged cortex (Wallace et al., 1989, 1990). These observations indicate that the remaining ipsilesional neural architecture has both the capacity to detect visual stimuli and to select appropriate motor programs to respond to them in the neglected hemifield. However, it is actively prevented from doing so by inhibitory processes that emanate from the opposite basal ganglia via crossed nigrocollicular projections.

The unique physiological properties of these crossed nigrocollicular projections provide one component of a pair of complementary circuits that the basal ganglia use for the interhemispheric coordination of visuomotor behaviors (Jiang et al., 2003). Presumably, the dynamic interplay between basal ganglia circuits that mediate focal disinhibition of the ipsilateral SC (via uncrossed nigrocollicular projections) and global inhibition of its contralateral counterpart (by crossed nigrocollicular fibers) is altered by large visual cortex lesions. The effect is to render the ipsilesional SC functionally inoperative. These observations suggest that the cortical lesion has dual effects: a primary and immediate effect that results in the loss of all functions directly attributed to visual cortex itself, and a cascade of secondary alterations that render its ipsilateral midbrain target, the SC, inoperative.

These secondary alterations may be initiated by lesion-induced glutamate excitotoxicity. Glutamate excitotoxicity mediated via NMDA receptors is known to be an important contributor to deficits associated with cerebral ischemia and traumatic brain injury (Faden et al., 1989; Obrenovitch and Urenjak, 1997; Dirnagl et al., 1999; Lee et al., 1999). It can produce secondary alterations in structures far removed from the original insult site and, perhaps, in structures that are not even directly connected with the damaged area. If such secondary alterations are involved in the orientation deficits that follow visual cortex removal, then agents that selectively block NMDA receptors might mitigate these effects and preclude this consequent behavioral deficit. One such agent, the noncompetitive glutamate antagonist dizocilpine (MK-801), has been shown to enhance posttraumatic behavioral capabilities in experimental animals performing a variety of tasks (Bullock and Fujisawa, 1992; McIntosh, 1994; McIntosh et al.,

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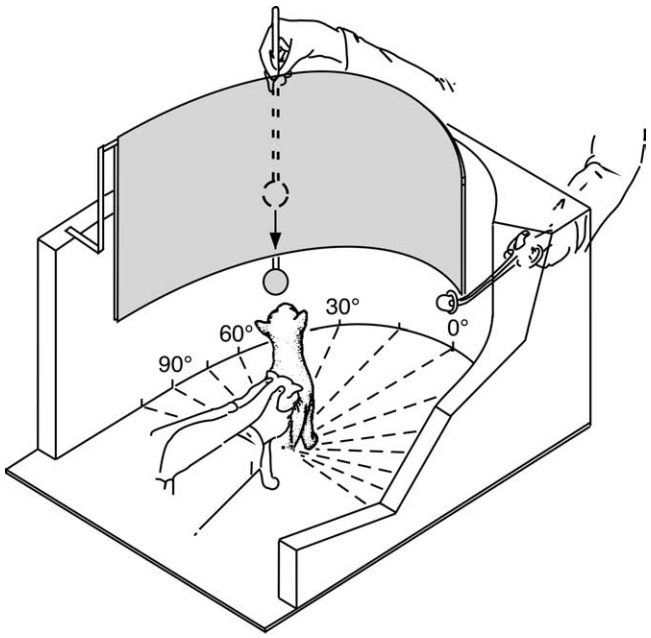

Figure 1. Each cat was trained to fixate on a morsel of food presented at eye-level directly ahead (0°). When released from restraint, it moved briskly forward toward the food reward. On select trials, a ping-pong ball at the end of a rod was introduced from behind a curtain at one of 14 equally spaced radial positions (105° left to 105° right), coincident with the animal's release. A food reward was given when the animal either oriented to the ping-pong ball or moved to the fixation point if no stimulus was presented (or detected). A food reward was given when the animal either oriented to the ping-pong ball or, if no stimulus was presented (or detected), it moved to the fixation point.

1996). Testing this possibility was the objective of the present study.

Materials and Methods

Nine mature domestic cats of either sex, obtained from a USDA-licensed commercial animal breeding facility (Liberty Labs), were used in the present study. All experimental procedures were performed in compliance with the National Institutes of Health (NIH) *Guide for the Care and Use of Laboratory Animals* (NIH Publications No. 80-23, revised 1996) and approved by the Institutional Animal Care and Use Committee at Wake Forest University School of Medicine. All efforts were made to minimize the number of animals used and to alleviate any discomfort.

Visual orientation testing procedures. Visual orientation was evaluated using previously applied methods (Hardy and Stein, 1988). Testing was conducted in a semicircular orientation arena. The arena was subdivided into 15° sectors, extending from 105° left to 105° right. Visual test stimuli (a white ping-pong ball on the end of a wand) were delivered manually, emerging from behind a black curtain hung parallel to the black arena walls. This arrangement, depicted in Figure 1, minimized extraneous visual cues associated with stimulus delivery and eliminated anticipatory movements. The apparatus was housed in a standard laboratory environment with normal ambient light and sound levels (~31 dB, SPL). A food-restricted cat was gently restrained by an animal handler so that its head and eyes were directed toward the 0° fixation mark, 58 cm away. The handler was blind to the location of test stimuli to preclude him from inadvertently providing the animal with target-related cues. Each cat was trained to fixate directly ahead on a food reward held in a pair of forceps that protruded through a hole in the forward wall of the apparatus. A trial began when the experimenter, who also was monitoring the animal's head/eye position, determined that the animal was fixating and gave the verbal command "Go." At that time the animal was released and could move toward the food reward. On some trials, visual test stimuli emerged from behind the curtain coincident with the Go command. If the animal oriented briskly toward the test stimulus, it received a food reward at that position. If the animal did not orient to test stimuli, or if no test stimuli were delivered (i.e., "catch" trials), it could move ahead to receive a food reward at the 0° fixation mark. These quasirandomly presented catch trials effectively minimized "scanning" or spontaneous orientations (Wallace et al., 1989). Thus, the cat was rewarded regardless of its response and made few spontaneous responses. Test stimulus locations were assigned quasirandomly at 15° eccentricities along the horizontal meridian throughout the field. Typically, each eccentricity was tested 4 times during a daily session. After a variable period of training, intact cats responded to stimulus delivery on nearly every trial, albeit with lowered accuracy at peripheral locations. Criterion performance was 95% correct responses, averaged throughout the field.

Before each daily testing session, cats were food-restricted for 24 h but had *ad libitum* access to water at all times. As a reward during training and testing, cats received 40 g of high caloric value food (Science Diet Kitten Original, Hill's Pet Nutrition) in the orientation arena and, following each session, were allowed to feed on the remainder of their daily ration while in the testing area. Body weight was monitored daily during the week, with no excessive weight loss noted. No testing was conducted on weekends, when the cats were permitted to feed *ad libitum* on a daily ration of standard animal chow.

After collecting a minimum of 100 normative tests at each eccentricity, an animal was prepared for unilateral visual cortex ablation, with or without MK-801 pretreatment (see below). If normative testing revealed a particular cat had a tendency toward better performance in one hemifield (generally reflected as greater accuracy in the periphery of that field), the visual cortex subserving that hemifield (i.e., contralateral) was selected for removal. Following cortical extirpation and surgical recovery, the presence, duration, and magnitude of any spontaneous circling and/or head deviation was noted and in some cases recorded on videotape. Once any postsurgical motor asymmetries had resolved, animals were retested on the visual orientation task.

Surgical procedures. All surgery was conducted aseptically. Animals were food-deprived for 24 h before surgery and administered a corticosteroidal anti-inflammatory (dexamethasone; 1 mg/kg, i.m.) preoperatively to minimize cerebral edema. Sedation was induced with ketamine hydrochloride (20–30 mg/kg, i.m.), and a preoperative dose of an analgesic (butorphanol, 0.1–0.4 mg/kg, i.m.) was given. An endotracheal tube was inserted, and a surgical plane of anesthesia was induced with isoflurane (1–4%). In some cases, nonpretreated cats were anesthetized with pentobarbital (22–30 mg/kg, i.p. or i.v.). Core body temperature, expiratory CO_2, blood pressure, and heart rate were continuously monitored (VSM7, VetSpecs) and maintained within normal physiological bounds. Animals were placed in a stereotaxic head-holder, wrapped in a heating pad, and the saphenous vein catheterized. Pretreated animals received a dose of MK-801 (3 mg/kg, i.v.; dizocilpine maleate; Sigma-Aldrich) 30 min before cortical extirpation. A midline scalp incision was made, and a craniotomy exposed the cortical areas to be removed. The dura was reflected, and the cortical blood vessels were heat coagulated to minimize bleeding. The gray matter then was extirpated by subpial aspiration. The following cortical areas were removed: 17, 18, 19, 20a, 20b, 21a, 21b, DLS, VLS, PS, PMLS, PLLS, AMLS, ALLS, 5, 7, and SVA (Rosenquist, 1985). Moist gelfoam was placed within the aspiration defect, the cranial bone plate was replaced, and the scalp closed with sutures. An antiseptic agent was applied topically around the sutured wound margin, and the animal received an injection of a broadband antibiotic (cefazolin, 20 mg/kg, i.m.). Physiological saline (50–200 ml, s.c. or i.v.) was given to compensate for fluid loss. The animal then was removed from the stereotaxic frame and placed in a darkened recovery cage.

The degree of neuroprotection is determined by drug concentrations not in the plasma but in specific brain areas vulnerable to injury at critical times during the trauma (Chen et al., 1991; Wallace et al., 1992). While we are unaware of data on the specifics pharmacokinetics and tissue binding of MK-801 in cats, the dose we employed (i.e., 3 mg/kg, i.v., see above) is similar to that previously reported as efficacious in this species (Ozyurt et al., 1988; Miyabe et al., 1997). Given that MK-801 can quickly reach maximal concentrations in the brain within 10–30 min of injections (Vezzani et al., 1989; Wallace et al., 1992) and its brain uptake is dominated by the level of blood flow (Wallace et al., 1992), it is likely that

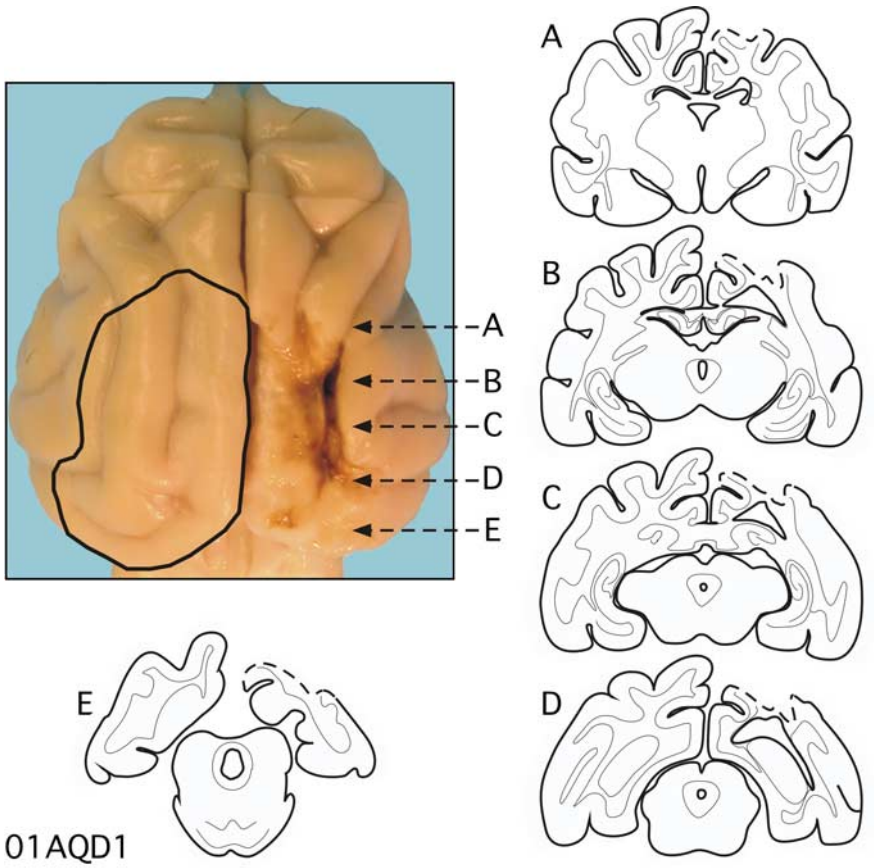

Figure 2. A whole-brain macrophotograph from a MK-801-pretreated cat reveals the extent of cortical tissue removal. Because the remaining cortex shifts medially to fill the aspiration defect, the actual extent of the lesion is minimized. The approximate extent of the lesion is outlined on the intact hemisphere. Five evenly spaced coronal sections (***A–E***) throughout the rostrocaudal extent of the lesion are shown. Dashed lines in these sections depict the extirpated tissue border. The behavior of this cat (01AQD1) is shown in Figure 4.

maximal brain concentrations would have been achieved before tissue extirpation and disruption of cortical blood flow.

Because of the long-term sedating effect of the drug, MK-801-pretreated cats had significantly longer recovery times than nonpretreated animals and required considerable postoperative monitoring and maintenance while on the respirator. Observations were made every 30 min for the duration of the recovery period, which lasted from 12 to 48 h. During this time, the animals' posture was adjusted, and vital functions monitored and maintained. Once alert and ambulatory, they were given a prophylactic dose of analgesic (butorphanol tartrate; 0.1–0.4 mg/kg, i.m.) and antibiotic (cefazolin, 20 mg/kg, i.m.) and returned to the home cage. Analgesics were continued for 18–24 h. Dexamethasone was administered, in progressively lower doses, for 5 d, twice a day.

Histological evaluation of cortical lesions. After all data were collected, animals were sedated with ketamine (20 mg/kg, i.m.) and, following the loss of pinna reflexes, injected with lethal doses of pentobarbital (100 mg/kg; i.p.). They then were exsanguinated by transcardial perfusion with 0.9% saline followed by an aldehyde fixative. Brains were removed, photographed, cut on a cryostat, and processed using routine histological procedures. The extent of each cortical lesion was determined by charting the damage in serial coronal sections onto drawings made of intraoperative photographs of the intact hemisphere, following procedures outlined by Wallace et al. (1989). The reconstructed lesion then was compared with standard physiological and anatomical maps to assess the extent of the lesion (Rosenquist, 1985). Microscopic examination of neutral red-stained sections through the dorsal lateral geniculate nucleus (LGN) were conducted to determine the extent of retrograde degeneration (Sherman, 1977; Wallace et al., 1989) and quantified by calculating the reduction in total volume compared with the intact side.

Results

Consistent with previous observations (Sprague and Meikle, 1965; Sprague, 1966; Sherman, 1974, 1977; Wallace et al., 1989, 1990), all cats exhibited brisk orientation to visual stimuli between 105° left and right of fixation before lesioning. Following cortical lesions, no behavioral performance differences were noted that could be ascribed to the particular hemisphere involved. Thus, the data here have been normalized for clarity to appear as if all lesions were made in the right cortex.

Histological analysis

Figure 2 illustrates a representative lesion reconstruction for one of the MK-801-pretreated animals. In this, and every other case, approximately the posterior three-fourths of both the lateral and suprasylvian gyri were completely removed along with some of the posterior ectosylvian gyrus. The gray matter of the medial aspect of the hemisphere posterior to the cruciate gyrus was removed above the splenial sulcus. In this, and in all other cases, the anterior ectosylvian sulcus (AES) was left intact, thereby sparing its visual and visual-multisensory representations (Mucke et al., 1982; Jiang et al., 1994a,b).

Lesion effects on nonpretreated animals

Immediately following recovery from surgical anesthesia, all ($n = 4$) nonpretreated animals displayed marked tonic head deviation toward the side of the lesion and ipsiversive circling behavior. These motor biases resolved gradually over the following 2–5 d, but they prevented quantitative assessment of visual orientation during this time. However, neurological evaluation during this period revealed a lack of blink-to-threat reflex for contralesional stimuli, with no indication of orientation to either visual or auditory stimuli at any position within the contralesional hemifield. Responses to contralesional tactile stimuli were preserved. Contralesional auditory orientation deficits were present, but they resolved within the first posttrauma week. Blink-to-threat deficits and visual neglect remained.

Once ipsiversive circling had resolved, postsurgical quantitative behavioral testing revealed a profound contralesional visual orientation deficit in all animals (Fig. 3). The contralesional visual orientation deficits lasted through the subsequent testing periods, the longest of which was 68 weeks. The long-term nature of such deficits was previously described by Sprague (Sprague, 1966), who considered them permanent (Wallace et al., 1989). In contrast, no visual orientation deficits were present in the ipsilesional hemifield of any of these animals (Fig. 3, bottom). In fact, their overall behavioral performance to stimuli in the intact hemifield improved with subsequent testing, as there was a progressive decrease in number of missed responses to peripheral visual stimuli.

Lesion effects on pretreated animals

The visual performance of animals pretreated with MK-801 ($n = 5$) was in striking contrast to that of their counterparts described

above. There were far fewer motor anomalies present immediately following recovery from surgery and those that were noted were comparatively mild. Although the ipsilesional pupil was usually dilated for several days, tonic head deviations were either absent or just noticeable and lasted only a few days. Similarly, the duration of ipsiversive circling was minimal and was resolved within 1–2 d of surgery. Blink-to-threat reflexes in the contralesional field were preserved, and visual or auditory stimuli delivered in the contralesional hemifield evoked brisk orientation of the eyes, pinnae, head and body. In several cats, postsurgical recovery was so rapid that it was possible to begin quantitative behavioral testing the following day.

In no instance ($n = 5$) did immediate postsurgical testing reveal any contralesional visual orientation deficits (Fig. 4). Equivalently brisk responses were made to visual test stimuli presented in both the ipsilesional and contralesional visual hemifields, and no obvious kinematic impairments were evident in responses to contralesional visual stimuli. In every respect, visual orientation behaviors appeared to be normal and appeared too quickly to be attributable to the spontaneous recoveries that sometimes occur after 4–8 postoperative weeks (Wallace et al., 1989).

The sparing of visual orientation behavior occurred in these animals despite massive retrograde degeneration of the ipsilateral lateral geniculate nucleus (LGN). The histology of two such pretreated cats, whose behavior is depicted above, is illustrated in Figure 5. Reconstruction of the lesion revealed that virtually all regions of primary visual cortex and adjacent extraprimary visual cortex had been removed (cf., Fig. 2). Postmortem microscopic inspection of the thalamus confirmed that the LGN was severely damaged, with few remaining cell bodies and substantial collapse of its nuclear dimensions. Thus, it is likely that the residual visual capabilities in pretreated cats reflect nongeniculocortical function.

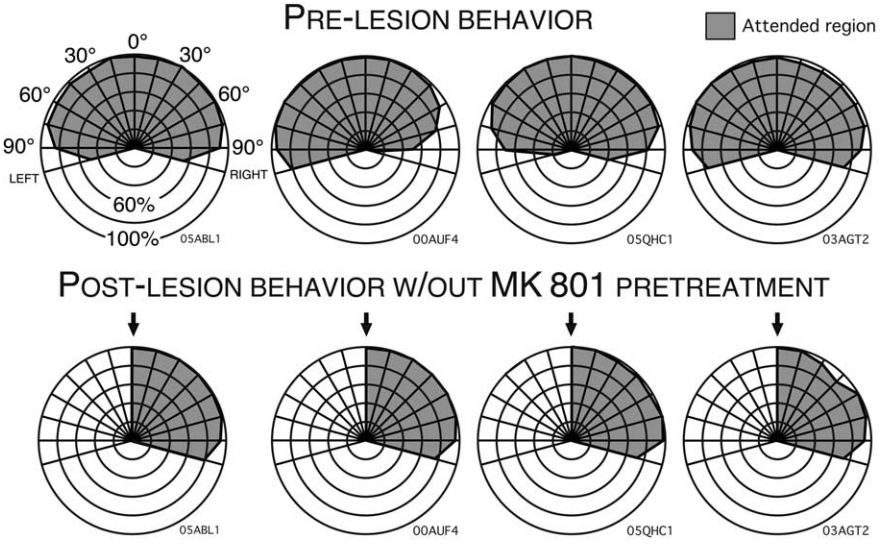

Figure 3. Large unilateral visual cortex lesions produce a profound visual orientation deficit in nonpretreated cats. Dark gray shaded areas of visual perimetry diagrams indicate correct responses seen at each tested position in each cat before (upper) and after (lower) cortical extirpation. The outer circle of the perimetry diagram represents 100% correct responses.

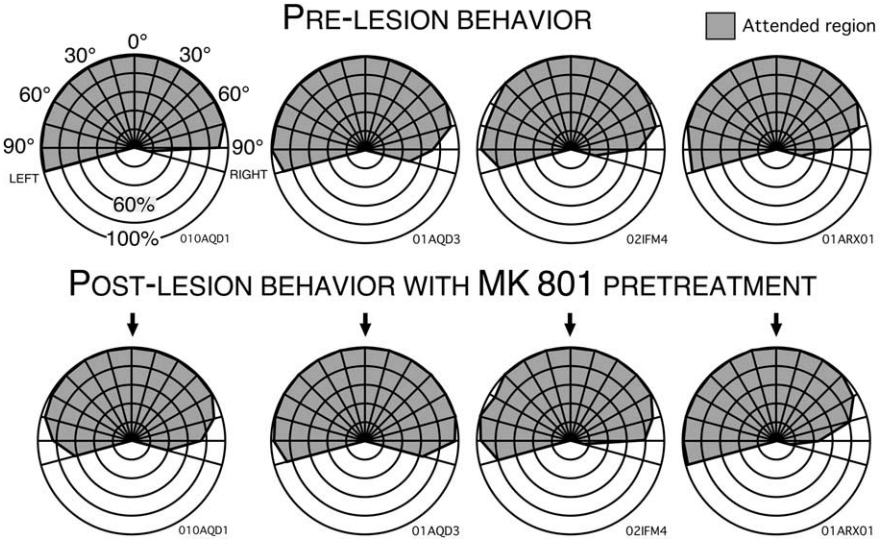

Figure 4. Pretreatment with the NMDA antagonist MK-801 prevents lesion-induced visual orientation deficits. Dark gray shaded areas of perimetry diagrams indicate percentage of correct responses before (top) and after (bottom) cortical extirpation. Note that the prelesion and postlesion orientation behavior was the same: the expected visuomotor deficits were absent. All cats were capable of normal visual orientation behaviors immediately following surgical recovery.

One of the MK-801-pretreated animals deviated from the pattern observed in the other 4. Instead it failed to maintain the spared visual functions that were present during initial postsurgical tests. This animal showed a progressive decline in visual orientation responses as shown in Figure 6. It differed in other ways as well. Its recovery was far slower than that of others in this group, so that its first orientation tests could not take place until 8 d after surgery. Although the animal could orient in much of the contralesional hemifield, a large percentage of the time its performance fell far short of the postoperative capabilities of the other pretreated animals. During the ensuing weeks, its visual performance progressively declined until it was no longer able to orient to contralesional visual stimuli and its performance was indistinguishable from that of nonpretreated controls. The specific reasons for the performance differences of this animal were not immediately apparent from its behavioral training history, responsiveness or histological examination of its tissue.

Discussion

The present data reveal that the profound contralateral visual hemineglect produced by unilateral visual cortex lesions is prevented by pretreatment with the NMDA receptor antagonist MK-801. These findings support the hypothesis that such lesions induce secondary NMDA-mediated excitotoxic alterations that prevent the remaining subcortical structures from supporting visuomotor behaviors. It is not yet possible to evaluate the breadth of the brain structures (including the SC itself, thalamic tecto-recepient nuclei, etc) that were affected by this pretreat-

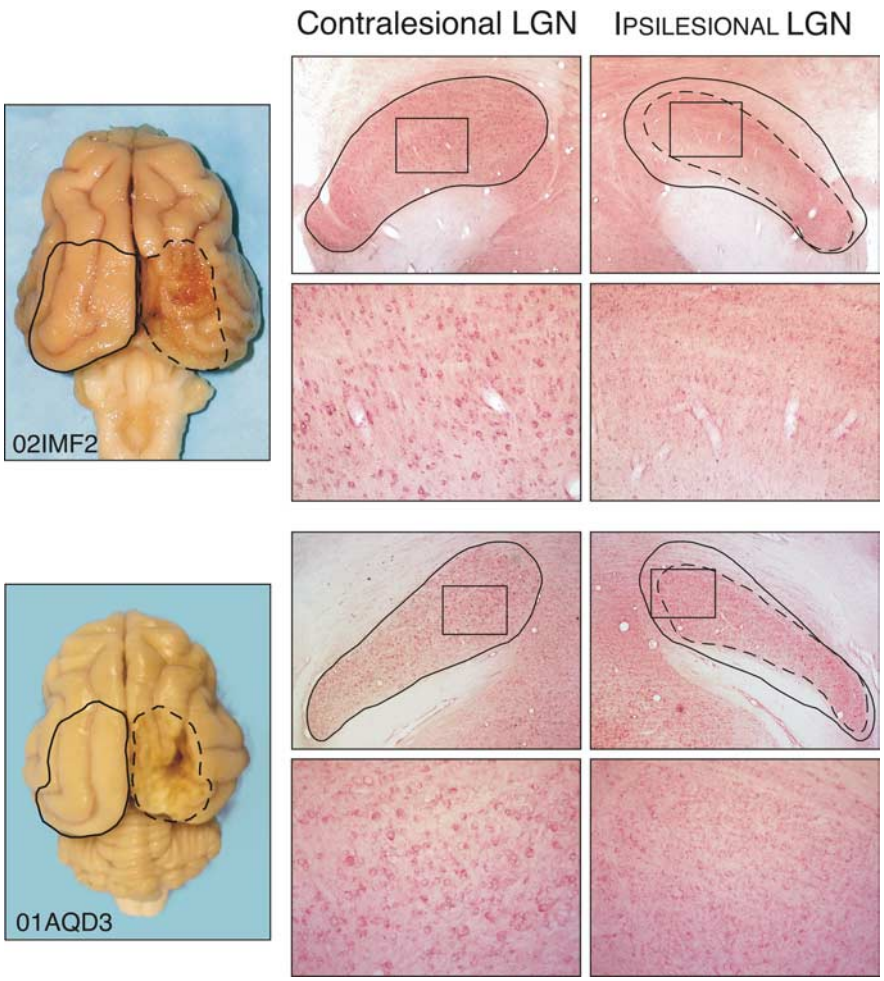

Figure 5. Pretreatment with MK-801 prevented visual orientation deficits despite massive retrograde degeneration of the ipsilesional lateral geniculate nucleus. Postmortem analysis in two MK-801-pretreated animals reveals the extent of cortical damage (left) and corresponding pairs of neutral red stained sections in the contralesional and ipsilesional LGN (right). Dashed outline shows the reduction in nuclear size, and area in box is show at higher magnification. Note the lack of stained cell bodies in the ipsilesion LGN and the collapse of nuclear borders. Thus, while MK-801 pretreatment preserved visual orientation capabilities, it did not prevent retrograde degeneration in the lateral geniculate nucleus. It is likely, therefore, that any residual visual capabilities cannot be ascribed to an intact geniculocortical system.

ment procedure. However, one parsimonious explanation is that pretreatment minimized lesion-induced alterations within the basal ganglia–SC circuit, thereby preserving the normal interhemispheric dynamics by which the basal ganglia bilaterally regulate SC activity.

Neurological dysfunction as a two-stage process

The pathophysiology underlying lesion-induced deficits arise by two distinct processes. Primary effects of injury are due to immediate physical disruption of tissue and the loss of its associated neural circuitry. Secondary effects evolve as a consequence of the release of excess glutamate into structures targeted by the damaged region. The resultant NMDA receptor-mediated calcium influx can kill its constituent neurons or compromise their normal function due to biochemical sequelae triggered by high intracellular calcium (Rothman and Olney, 1986; Choi et al., 1987; Choi, 1988; Choi and Rothman, 1990). As originally articulated by von Monakow (von Monakow, 1914; Feeney and Baron, 1986), these secondary alterations can cause functional disruption of structures remote from the initial injury but related to it via multisynaptic circuits. Administration before cortical extirpation ensured that MK-801 was bound to receptors before any pathological glutamate release. It is likely, however, that posttraumatic delivery within a restricted temporal window also may be effective, as MK-801 enhances posttrauma behavioral capabilities (McIntosh et al., 1989, 1996; Bullock and Fujisawa, 1992).

A distributed network underlies visual orientation

Although the SC plays a central role in visual orientation (Stein and Meredith, 1993; May, 2006), it is dependent on integrated inputs from both the basal ganglia and visual cortex. Deep SC neurons effecting visual orientation via connections to the brainstem and spinal cord (Stein and Meredith, 1993; May, 2006) receive visual cortex projections (Rosenquist, 1985; Harting et al., 1992) necessary for normal visual activity (Ogasawara et al., 1984; Hardy and Stein, 1988). Similarly, these same SC neurons receive GABAergic inputs from basal ganglia output pathways (Chevalier et al., 1984; May and Hall, 1984; Chevalier et al., 1985; Harting et al., 1988) that modulate both their sensory (Chevalier et al., 1984, 1985) and motor (Hikosaka and Wurtz, 1983; Joseph and Boussaoud, 1985) activity. Thus, it is likely that the preservation of visual orientation in pretreated animals is due, in large part, to the retention of functional integrity within this basal ganglia–SC network.

The striatum as a site of excitotoxicity

The basal ganglia are particularly vulnerable to excitotoxic damage. The major input structure of the basal ganglia, the striatum, receives glutamatergic input from widespread regions of the cortex. Corticostriatal interactions are highly plastic and mediated via NMDA receptors (Calabresi et al., 1996). Damage to nonvisual cortex is known to produce secondary striatal alterations (Schallert et al., 1990; Jones and Schallert, 1992; Hara et al., 1993; Hoffman et al., 1994; Hoane et al., 1997), and posttrauma administration of NMDA antagonists reduces the degree of these alterations (Gill et al., 1987; Barth et al., 1990; Hara et al., 1993; Feldman et al., 1996; Hoane et al., 1998), facilitating behavioral recovery (McIntosh et al., 1989; Barth et al., 1990; Hoane et al., 1997, 1998).

Similar events likely follow visual cortex lesions. Visual cortex, especially those extrastriate regions whose disruption produces visual neglect (Hardy and Stein, 1988; Payne et al., 1996), sends dense excitatory projections to the striatum (Norita et al., 1991; McHaffie et al., 1993; Niida et al., 1997). That such lesions alter the internal milieu of the striatum is suggested by the presence of ipsiversive circling following visual cortex lesions (Sprague and Meikle, 1965; Wallace et al., 1989, 1990). This transient phenomenon is associated with the development of asymmetries in striatal dopaminergic receptor subtypes (Glick et al., 1988) which is thought to alter the activity of SNr neurons (Weick and Walters, 1987; Jaspers et al., 1989; Rohlfs et al., 1997), presumably includ-

ing those that project to the SC. Furthermore, excitotoxic lesions of the striatum produce sequential metabolic alterations at the level of the SNr and SC that lead to behavioral alterations (Jaspers et al., 1989).

Basal ganglia control of SC-mediated visuomotor behaviors

Although SNr afferents to the SC are bilateral (Beckstead et al., 1981; Harting et al., 1988), the more numerous ipsilateral projections (Beckstead et al., 1981; Gerfen et al., 1982) are the most thoroughly studied. Uncrossed SNr neurons have relatively small visual receptive fields that are in topographic register with those of their ipsilateral SC target neurons. Their high spontaneous activity is phasically inhibited by visual stimuli (Hikosaka and Wurtz, 1983; Chevalier et al., 1984, 1985; Joseph and Boussaoud, 1985; Jiang et al., 2003), thereby disinhibiting their SC targets, which in turn mediate contralaterally directed visuomotor behaviors. Crossed SNr neurons have distinctly different physiological properties (Jiang et al., 2003): they have large receptive fields in the hemifield opposite those of their contralateral SC target neurons and display relatively low spontaneous activity that is phasically excited by visual stimuli. Because their axon terminals are broadly distributed in the SC (Jiang et al., 2003; Gabriele et al., 2007), they facilitate global inhibition. Given that cortical perturbations preferentially affect striatal cells of origin of the indirect pathway (Berretta et al., 1997; Parthasarathy and Graybiel, 1997), which increases basal ganglia output activity (Mink, 1996), the net consequences of cortical lesions might be increased activation of crossed output neurons.

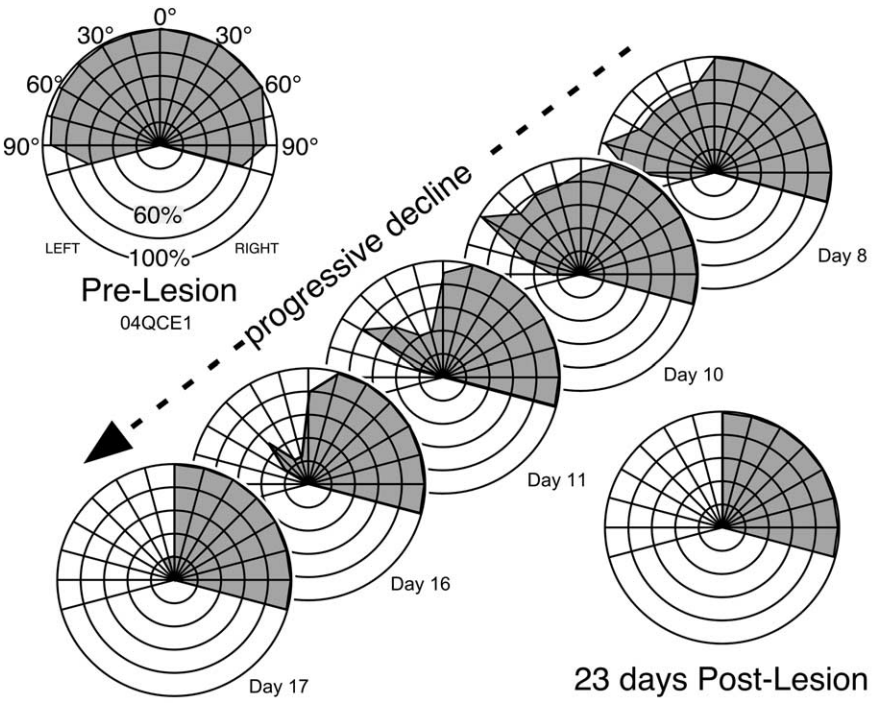

Figure 6. Only one MK-801-pretreated animal failed to maintain the spared orientation capabilities that were present during initial postsurgical testing. This animal showed a progressive decline in visual orientation responses that eventually resulted in a complete neglect of contralesional stimuli that was indistinguishable from that of nonpretreated controls.

A "simple" physiological model

We suggest that cortically induced visual hemineglect is produced by NMDA-mediated excitotoxic events in the striatum that alter transbasal basal ganglia pathways. This ultimately compromises the functional integrity of the ipsilesional SC by upregulating the spontaneous activity of crossed nigrocollicular neurons (Fig. 7). Consequently, their normal widespread phasic inhibitory role (Jiang et al., 2003) is transformed to one of widespread tonic inhibition, preventing the ipsilesional SC from mediating visual orientation. Such changes are analogous to basal ganglia alterations that account for hypokinetic or akinetic dysfunction associated with Parkinson's disease (DeLong, 1990; Albin et al., 1995).

This hypothesis also provides a physiological basis for the Sprague Effect, a paradoxical phenomena whereby visuomotor deficits induced by visual cortical lesions are ameliorated by a second lesion of the contralesional SC (Sprague, 1966; Sherman, 1974, 1977) or SNr (Wallace et al., 1989, 1990). Thus, a presumptive source of pathophysiological inhibition is eliminated by severing crossed SNr axons as they pass through the contralesional SC en route to the SC ipsilateral to the damaged cortex. This facilitates ipsilesional SC activity, rendering it responsive to previously ineffectual visual inputs and capable of once again supporting visual orientation. The observation that ipsilesional SC bicuculline injections temporarily ameliorates hemineglect (Ciaramitaro et al., 1997b), but lesions of the ipsilesional SNr do not (Ciaramitaro et al., 1997a), underscores the specific contribution of the crossed GABAergic projection.

Precisely how unilateral lesions induce contralesional basal ganglia alterations is not yet clear. Anatomical data indicate that crossed nigrothalamic neurons only become evident following unilateral cortical lesions and a period of lesion-induced circling (Pritzel and Huston, 1981; Neumann et al., 1982). This suggests that normally quiescent crossed neurons are poor transporters of retrograde tracers and are effectively "invisible" to anatomical techniques until rendered tonically active by cortical perturbations. Interestingly, manually delaying circling behavior also delays these anatomical changes (Morgan et al., 1983). Since nigrothalamic neurons often have collaterals to the SC (Anderson and Yoshida, 1977, 1980), crossed nigrocolliculus neurons may be similarly affected. It is not yet possible, however, to eliminate the possibility that the activity changes induced in this pathway are secondary to changes induced in the SC itself. Clearly, further experiments detailing striatum and SC alterations as well as direct electrophysiological evidence from the crossed neurons are necessary to confirm this hypothesis.

The source of visual input that facilitates SC-mediated orientation in the absence of cortex is another critical question. One obvious route is via direct monosynaptic retinal projections to the deep SC (Beckstead and Frankfurter, 1983), which, although modest, can activate deep SC neurons (Berson and McIlwain, 1982). Another possibility is via descending projections from the superficial SC, which retains its visual activity following visual cortex lesions (Wickelgren and Sterling, 1969; Rosenquist and Palmer, 1971; Ogasawara et al., 1984) because of direct retinal input (Kanaseki and Sprague, 1974; Harting and Guillery, 1976). Superficial layer SC activity has both monosynaptic and polysynaptic access to deep SC neurons (Lee et al., 1997; Doubell et al.,

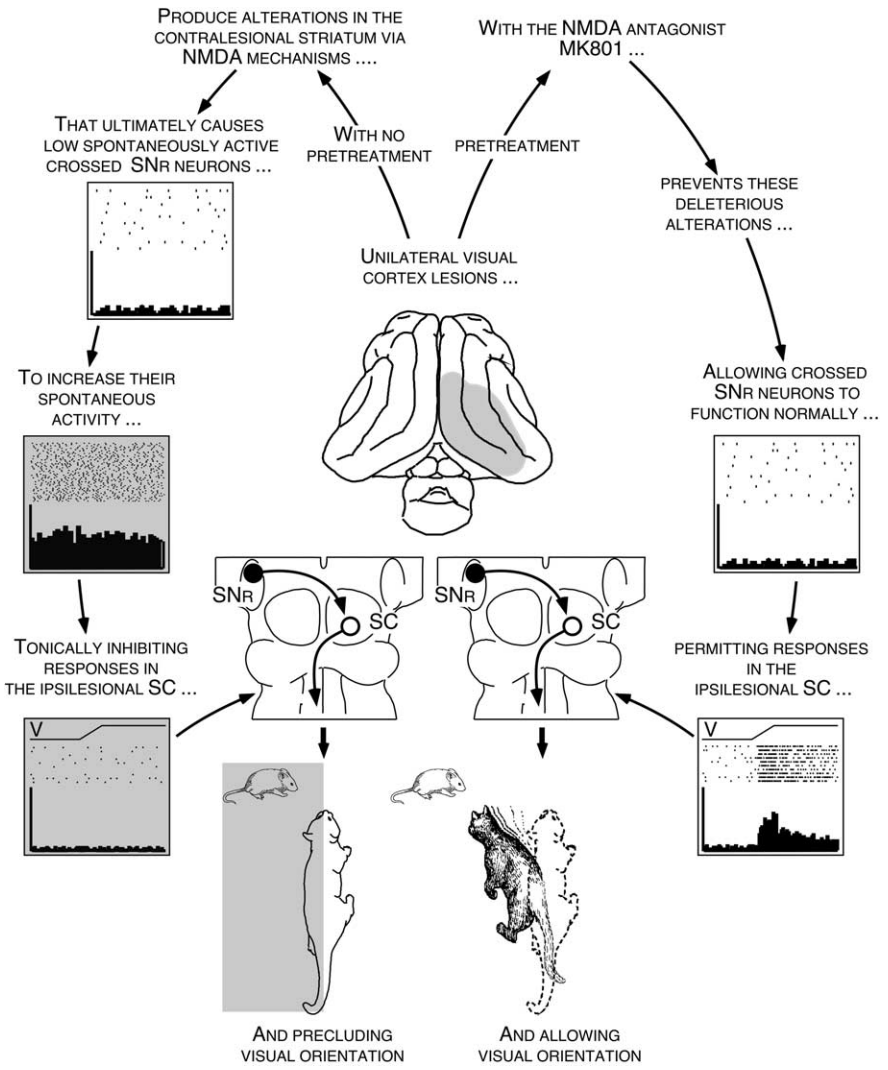

Figure 7. We suggest that the cortical lesions induce a persistence contralateral visual field defect because secondary NMDA-mediated excitotoxic events in the basal ganglia ultimately upregulate the normally low spontaneous activity of crossed nigrocollicular neurons. This changes their functional role from one of phasic global inhibition to one of tonic global suppression of their target SC and prevents SC-mediated visuomotor behaviors.

2003), a route thought to mediate short-latency express saccades (Lee et al., 1997). Another potential route is the SC–basal ganglia–SC loop (May and Hall, 1986; McHaffie et al., 2005). Here ascending projections from the superficial SC layers convey visual information to the striatum via the thalamus (Harting et al., 2001a, 2001b), and descending striatal outputs regulate deep SC neurons via SNr projections (Chevalier et al., 1985; Harting et al., 1988). This closed-looped architecture provides the means for detecting and localizing visual stimuli, as well as for selecting and coordinating the appropriate motor programs required for orienting (McHaffie et al., 2005).

These data raise the possibility that other visual capabilities are present in pretreated animals. Although hemineglect animals whose deficits have been ameliorated by midbrain lesions still lack visual discrimination abilities (Loop and Sherman, 1977), the postlesional behaviors of pretreated animals might be more sophisticated than the orientation tasks employed here revealed. This notion finds support in recent evidence indicating that superficial SC neurons possess basic feature analysis properties in the absence of visual cortex (Girman and Lund, 2007). If so, any residual visual discrimination capacity would provide important insights into the subcortical architecture that subserve blindsight (Stoerig and Cowey, 1997; Ptito et al., 2001).

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