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Effects of delay and duration of light deprivation on recovery of function from neglect induced by unilateral medial agranular prefrontal cortex lesions in rats

KAREN J. BURCHAM and JAMES V. CORWIN
Northern Illinois University, DeKalb, Illinois

Forty-eight hours of postoperation light deprivation (LD) has been found to produce complete and permanent behavioral recovery of function from neglect induced by unilateral lesions of medial agranular cortex (AGm) in rats. The two experiments in the present study parametrically examined the postoperation delay prior to LD and the duration of LD necessary to produce recovery from severe neglect. Subjects in both experiments received unilateral AGm lesions and were tested for the degree of neglect of visual, tactile, and auditory stimuli prior to and after experiencing LD. The results of the study of delay of LD indicated that LD administered 4 h postsurgery produced dramatic immediate recovery from severe neglect, and the recovery lasted for the duration of behavioral testing (3 weeks) following LD. The longer delay groups (52 and 100 h) and the no-manipulation controls did not demonstrate behavioral recovery. The 28-h delay group demonstrated an intermediate effect following LD. The results of the study of duration of LD indicated that the therapeutic effect of LD was duration dependent. Forty-eight hours of LD produced a significant reduction in the severity of neglect, but shorter durations (4 and 24 h) did not. The results of the present study indicate that a critical postoperative period exists in which LD must be initiated in order to produce recovery from severe neglect and that LD has to be administered for a period of at least 24 h to produce any evidence of recovery of function. These findings may have clinical implications for the treatment of neglect in humans.

Unilateral lesions in humans can produce the neglect syndrome, which is characterized by an inability to orient, respond, or attend to stimulation located on the contralesional side of space (Halligan, Marshall, & Wade, 1989; Heilman, Watson, & Valenstein, 1993). In the most severe cases, patients diagnosed with neglect are totally unresponsive to the side of space opposite the lesion. The vast majority of all cases of neglect in humans are secondary to cortical damage (Heilman et al., 1993), specifically to the dorsolateral frontal cortex (Damasio, Damasio, & Chang Chui, 1980), the tempero-parieto-occipital junction (Ogden, 1985; Vallar & Perrani, 1987), or the cingulate gyrus (Heilman & Valenstein, 1972). The symptoms of neglect may persist for years, and, as a consequence, patients with severe neglect are often dependent on care givers (Henley, Pettit, Todd-Pokropek, & Tupper, 1985; Robertson, Halligan, & Marshall, 1993). At present, there are no generally accepted therapies for patients with neglect, and the treatment programs often do not generalize to other tasks and settings, even when tasks seem very similar in nature (Robertson et al., 1993).

A rodent cortical model of neglect has been developed to examine the neural basis of neglect and behavioral recovery from neglect (Chandler, King, Corwin, & Reep, 1992; Corwin et al., 1986; Crowne & Pathria, 1982; King & Corwin, 1990, 1992, 1993; Reep, Chandler, & Corwin, 1994; Reep, Corwin, Hashimoto, & Watson, 1984, 1987; Reep, Goodwin, & Corwin, 1990; Vargo, Bromberg, Best, Corwin, & Marshall, 1995; Vargo, Corwin, King, & Reep, 1988; Vargo, Richard-Smith, & Corwin, 1989). Unilateral destruction of the medial agranular cortex (AGm), the rodent analogue of area 8 in primates (Reep et al., 1984, 1987; Reep et al., 1990), has been found to produce severe neglect that shares a number of behavioral (Corwin et al., 1986; Corwin & Vargo, 1993; Crowne & Pathria, 1982; Crowne, Richardson, & Ward, 1983; Heilman et al., 1993) similarities with neglect produced by cortical damage in humans, including multimodal neglect of visual, auditory, and tactile stimuli, and allesthesia/allokinesia resulting in inappropriate orientations to the nonneglected body side when stimulated on the neglected body side. As in humans, significant spontaneous recovery from neglect occurs over the course of weeks to months (Crowne & Pathria, 1982; Crowne et al., 1983; King & Corwin, 1990; Vargo et al., 1988), and acute behavioral recovery from severe neglect in rodents (Corwin et al., 1986; King & Corwin, 1990; Vargo, Lal, & Marshall, 1996) and humans (Fleet, Valenstein, Watson, & Heilman, 1987) can be produced by the administration of dopamine receptor agonists.

More recently, it has been demonstrated that accelerated recovery of function from severe neglect in rodents can be produced by an environmental manipulation, 48 h

Correspondence should be addressed to K. J. Burcham, Department of Psychology, Northern Illinois University, DeKalb, IL 60115 (e-mail: kjburcham@msn.com).

of light deprivation (LD; Corwin & Vargo, 1993; Crowne et al., 1983; Harrell & Balagura, 1974). Corwin and Vargo (1993) examined the effects of LD on recovery from severe neglect induced by unilateral destruction of AGm by testing the subjects for the presence of severe neglect 4 h after injection of the surgical general anesthetic and prior to being placed in the dark. The results indicated that 48 h of LD produced virtually complete behavioral recovery from severe neglect. Subjects that experienced a normal light:dark cycle or that were placed in constant light for 48 h to control for the disruption of circadian rhythms did not demonstrate accelerated recovery from neglect.

In all of the investigations in which LD has produced behavioral recovery, LD has been administered in the preoperative or the immediate postoperative period. The temporal parameters associated with the effectiveness of LD have never been examined. Direct and indirect evidence from pharmacological studies indicates that the perisurgical time period for the therapeutic effectiveness of LD may be brief. Schallert, Hernandez, and Barth (1986) have found that the mechanisms that underlie spontaneous recovery from neglect induced by unilateral medial prefrontal lesions may be particularly susceptible to pharmacological manipulation for only a short time span following brain damage (96 h). Furthermore, in a review of the literature on the potential therapeutic use of *N*-methyl-D-aspartate (NMDA) receptor antagonists for the treatment of brain injury, Albers (1990) concludes that treatment with NMDA antagonists would likely have to be administered in the immediate postlesion period. These studies support the importance of temporal factors during the postlesion interval for promotion or interference with behavioral recovery from brain damage. Therefore, we reason that the effects of LD and other environmental manipulations on behavioral recovery from severe neglect may be subject to similar perisurgical temporal constraints.

The present experiments examined two temporal factors that could be related to the therapeutic effectiveness of LD. Experiment 1 examined the effects of delaying the onset of LD on recovery of function from neglect following unilateral AGm destruction by systematically varying the time between injection of the surgical general anesthetic and placement into 48 h of LD. A better understanding of this "window of opportunity" during which LD is effective is essential both for any potential clinical use and to aid in guiding future investigations of the neural mechanisms through which LD produces recovery. Experiment 2 examined the duration of LD necessary to produce recovery of function from neglect induced by unilateral AGm destruction. Prior studies have examined only the effectiveness of 48 h of LD (Corwin & Vargo, 1993; Crowne et al., 1983). The results of this "duration–response" study will serve to further characterize the effects of LD on recovery of function from severe neglect, and it may provide information for future examinations of the neural mechanisms involved in recovery that must operate within that time frame.

EXPERIMENT 1

Experiment 1 was an investigation of the effects of postsurgical delay of the onset of 48 h of LD on recovery of function from severe neglect. All of the LD groups received 48 h of LD, but the time interval between injection of the surgical general anesthetic and initiation of LD was varied among the groups.

Method

Subjects

The subjects were 35 male Long-Evans hooded rats bred from stock purchased from Harlan Sprague-Dawley (Indianapolis). Prior to the surgical procedure, the subjects were handled daily for 2–4 weeks in order to reduce struggling or "freezing" responses during behavioral testing. Throughout the study, the subjects were individually maintained on free food and water under standard colony conditions.

Surgical Procedures

The subjects were anesthetized with a ketamine–xylazine mixture (87:13 mg/ml) at a dosage of 70 ml/kg, i.p. When totally unresponsive, as determined by lack of responsiveness to a mild tailpinch and absence of a corneal reflex, the subjects were placed into a stereotaxic instrument equipped with blunt-tipped ear bars in order to prevent damage to the tympanic membrane. Using sterile gloves and instruments, a craniotomy was performed at the desired coordinate location in the left hemisphere (Corwin & Vargo, 1993; Vargo et al., 1988). Under visual guidance, either the AGm or the lateral agranular cortex (AGl) was aspirated down to the white matter with the use of a fine-gauge pipette. For the animals receiving AGm lesions, the coordinates used were 5.0 mm rostral to 2.5 mm caudal to Bregma and from 0.0 mm to 2.5 mm lateral to the sagittal suture. The coordinates utilized for the animals placed into the AGl control lesion group were 5.0 mm rostral to 2.5 mm caudal to Bregma and 2.5 mm to 5.0 mm lateral to the sagittal suture. Gelfoam was gently placed into the lesion site, and the incision was closed with either surgical clips or a sterile nylon suture. Following completion of surgery, the subjects were kept warm and were monitored during recovery. All surgeries were performed between 0900 and 1300 during the light phase of the light:dark cycle.

Behavioral Testing

For all behavioral testing, the experimenter was blind with respect to the group affiliation of the subjects. The subjects were tested for the presence of neglect 4 h after injection of the surgical anesthetic. Corwin and Vargo (1993) indicated that this is a sufficient recovery period to allow for behavioral testing for neglect. Furthermore, severe neglect obtained at 4 h almost invariably (>95%) predicts severe neglect on a subsequent behavioral test at 48 h (Corwin & Vargo, 1993). The time from injection of anesthetic was used as a marker for the onset of LD in order to maintain a constant reference point for behavioral testing and administration of LD. Throughout the study, testing was conducted in a room with standard overhead fluorescent lighting at approximately the same time during the light phase of the light:dark cycle (1300–1700) in order to equate for circadian rhythms.

Testing for neglect was identical to that used in previous studies (Corwin, Burcham, & Hix, 1996; Corwin & Vargo, 1993; King & Corwin, 1990; Vargo et al., 1989) and was a modification of that developed by Crowne and Pathria (1982). Each subject was placed in its home cage on the testing platform for a 1-min period of adaptation. After adaptation, the subject was taken out of its cage and placed directly on a test platform on which markings delineated 0°, 30°, 45°, and 60° angles in either direction from a central line run-

ning the length of the testing board. The subject was gently restrained by hand from behind without restricting head movement and was aligned with the center line on the board running down the midline of the rostral–caudal axis. Stimuli were presented only when there was no evidence of struggling and no asymmetry of body posture and when the head was oriented in direct line with the body. Typically, the animal's body had to be realigned several times during testing.

The visual stimulus consisted of the presentation of a silver metallic rod 10.0 cm in length, which was waved in a small circle (approximately 5.0 cm in diameter) five times within the animal's visual field at a distance of 7.5–10.0 cm from the animal and at a rate of approximately one revolution/second. The auditory stimulus was a single 114-dB (SPL) click generated by a clicking device held at midbody. The tactile stimulus was a single caudal-to-rostral stroke through the vibrissae with a 15-cm wooden Puritan applicator (Harkwood Products, No. 807).

Each test session was composed of three cycles of testing. One cycle consisted of the single presentation of each of the three stimuli to each body side. The side of initial presentation was randomly determined. The order of presentation was visual, tactile, and auditory, with each stimulus presented first to one body side, then to the other. Previous studies have shown that the order of stimulus presentation does not influence behavioral results (Vargo et al., 1988). Stimulus presentations were separated by approximately 5 sec.

The experimenter rated the degree of head turning toward (appropriate responding) or away from (allesthetic/allokinetic responding) the stimuli as measured by the position of the tip of the snout over the test platform markings. Head turns of less than 30° were scored as 0, between 30° and 45° as 1.0, between 45° and 60° as 1.5, and greater than 60° as 2.0. Orientations made more than 2 sec after either the tactile or the auditory stimulation received a score of 0. Orientations to the visual stimulus after the third revolution (3 sec) could only receive a maximum score of 1.5. Appropriate and allesthetic/allokinetic orientations were scored separately. Using this scoring method, the maximal score for appropriate responding was 6.0 for each of the three different stimuli, or 18.0 in total for each body side. The subject had to achieve a total score of at least 5.5 on one body side and respond in two stimulus modalities in order to be considered responsive. Previous studies from our laboratory (Corwin et al., 1986; King & Corwin, 1990; King, Corwin, & Reep, 1989) have found that the use of this scoring procedure produces an interrater reliability of 1.0 for the direction of orientation and greater than 0.90 reliability for the magnitude of orientation.

Two total orientation scores (one for each body side) were obtained for each test by summing all scores representing appropriate responding. Total neglect ratios were calculated for each test session by dividing the total contralesional orientation score by the total ipsilesional orientation score. The use of the neglect ratio allows for an indication of severity of neglect by taking into account responsiveness on both body sides.

Individual modality neglect ratios were calculated for each test session by (contralesional responses − ipsilesional responses)/(contralesional responses + ipsilesional responses). This ratio was utilized due to the large number of zero scores obtained in the individual modalities.

Prior studies have indicated that unilateral cortical lesions that produce neglect can also produce significant allesthesia/allokinesia on the neglected body side (Corwin et al., 1986). This allesthesia/allokinesia occurred only when combined for all modalities. Therefore, total allesthesia/allokinesia summed across all modalities was examined for the ipsilesional and contralesional body sides.

Grouping Procedure

AGm operates that demonstrated severe neglect at 4 h postinjection of the surgical general anesthetic were randomly assigned to one of five groups: (1) no manipulation (NM) control ($n = 6$), (2) 4-h delay ($n = 5$), (3) 28-h delay ($n = 5$), (4) 52-h delay ($n = 7$), and (5) 100-h delay ($n = 4$). Severe neglect was operationally defined as a total neglect ratio $\leq .33$. Approximately 72% of the AGm operates demonstrated severe neglect at the first test.

An additional group of subjects received unilateral lesions of the AGl ($n = 8$) to act as cortical lesion controls in order to provide a baseline by which to measure the effectiveness of LD in producing complete recovery of function. Prior studies have indicated that unilateral lesions of AGl do not produce neglect (King & Corwin, 1990; Vargo et al., 1988; Vargo et al., 1989). The NM group served as a control group in which the normal time course of spontaneous recovery from neglect could be demonstrated. The 4-h delay group served two functions: (1) to replicate the findings of Corwin and Vargo (1993), and (2) to provide a comparison group for the other manipulation groups. The subjects in the 4-h delay group experienced 48 h of LD immediately after the behavioral assessment of severe neglect at 4 h postinjection. The subjects in the 28-h group were tested both at 4 and 28 h postinjection. The animals that demonstrated severe neglect during both tests were placed into 48 h of LD. The subjects in the 52-h delay group were tested at 4 and 52 h postinjection. The animals that demonstrated severe neglect during both tests were placed into LD for 48 h. The animals in the 100-h delay group were tested at 4, 52, and 100 h postinjection. The subjects that demonstrated severe neglect during both the 4-h and the 100-h test were placed into 48 h of LD.

In order to be included in this experiment, the subjects in the 4-h delay group had to demonstrate severe neglect only once prior to LD, whereas the subjects in the other delay groups had to demonstrate severe neglect on two behavioral tests prior to the onset of LD. This raises the issue that the selection criteria for the longer delay groups may have resulted in the animals with more severe neglect being placed into these groups. In the present experiment and in Corwin and Vargo's (1993) study, the presence of severe neglect on the first behavioral test at 4 h postinjection predicted severe neglect on the subsequent test 48 h later (one exception in the present experiment). Therefore, it is doubtful that the subjects included in this experiment were different prior to the onset of LD.

Light-Deprivation Procedure

After determination of severe neglect and after the appropriate delay of onset of LD based on group membership, all animals except those in the NM and AGl groups underwent 48 h of LD. The subjects were housed in one of three dark rooms, separate from the colony for 48 h. The door of the room was taped with masking tape to prevent extraneous light and to block entrance. NM and AGl animals were maintained under a 12:12-h light:dark schedule in the same rooms separate from the colony as were the animals that experienced LD. For each of the groups, only 1–3 animals experienced a particular environmental manipulation at any given time, so that the environmental exposure for each of the groups could be counterbalanced to control for the possibility of temporal variation.

Post–Light-Deprivation Testing

After 48 h of environmental exposure, the subjects were transferred back into the colony and allowed to adapt to ambient light for 15 min. After the adaptation period, the subjects were tested for neglect as described previously. Subsequently, the subjects were tested for neglect three times per week for a 3-week period.

Histological Procedures

After behavioral testing was completed, the subjects were given an overdose (65 mg) of sodium pentobarbital (Nembutal). When totally unresponsive (no response to a tailpinch and the absence of a corneal reflex), the subjects were intracardially perfused with a 0.9% saline solution, followed by 10% formalin. The brain was removed from the skull, placed into 10% formalin for at least 3 days,

and then frozen and sectioned on a coronal plane at 40 μm. Every 10th section throughout the extent of the lesion and every 5th section throughout the thalamus was saved, mounted, and stained with Cresyl violet.

All lesions were examined to determine the extent of damage to the AGm or AGl and to adjacent areas. Absolute lesion sizes were measured by tracing the extent of the lesions through an image analysis software program (Optimus, BioScan, Inc., Edmonds, WA). Maximum and minimum lesion extents were traced onto standard brain diagrams (Paxinos & Watson, 1986). The thalamus was examined for evidence of retrograde degeneration. All histology was performed with the experimenter blind with respect to the behavioral performance and group membership of the subjects.

Results

An alpha level of .05 was utilized for all statistical analyses. When statistical significance was indicated by an overall analysis of variance (ANOVA), lower order ANOVAs and Student–Newman-Keuls (SNK) analyses were performed. A Levene's test for homogeneity of variance was performed for each ANOVA calculated. When significant heterogeneity occurred, the alpha level was adjusted to .01 to control for Type I errors.

Histological Analyses

As indicated in Figure 1, the typical AGm lesion included substantial damage to the caudal AGm, with more variable damage to the rostral AGm. Typically, there was additional damage: rostrally to the dorsal anterior cingulate cortex, laterally to the lateral agranular cortex, and caudally to the retrospenial agranular cortex. There was no damage to the contralateral hemisphere and none of the lesions extended ventrally through the white matter; however, in approximately 74% of the subjects distributed among the groups, there was some superficial damage to the white matter. The pattern of retrograde degeneration in the thalamus of the AGm operates was similar to that found in other studies, and it indicated minimal evidence of gliosis in the lateral part of the mediodorsal nucleus and centralis lateralis (King & Corwin, 1990, 1992, 1993). As found in previous studies from our laboratory (King & Corwin, 1990; Vargo et al., 1988), the typical lesion of AGl produced extensive damage to the lateral agranular cortex, with variable amounts of damage to the hindlimb and forelimb cortices caudally and very slight damage to the most lateral part of AGm rostrally. The largest lesions of AGl produced some white matter damage, which, in the largest lesion, included the forceps minor. Examination of the thalamus revealed extensive gliosis and cell loss in the ventrolateral nucleus (Paxinos & Watson, 1986).

A one-way ANOVA revealed no significant difference in total lesion extent among the groups. Furthermore, a one-way ANOVA comparing the percentage of AGm damage indicated that there were no significant differences among the AGm groups. Because statistical analyses indicate that the groups were not different with regard to lesion extent or percentage of AGm damage, statistical outcomes based on behavioral results are not explainable by differences in total lesion extent or percentage of damage to AGm.

Behavioral Analyses

Total neglect ratios. To examine the effects of delaying the onset of LD on recovery from severe neglect, a group $\times$ test mixed ANOVA was performed on the total neglect ratios. The results indicated significant main effects for group [$F(5,29) = 27.36, p < .0009$] and test [$F(9,261) = 5.31, p < .0009$] and a significant interaction [$F(45,261) = 1.69, p < .008$].

A series of one-way ANOVAs done to compare total neglect ratios among the groups at each day of testing revealed that there was a significant difference among the groups at each test day (all $ps < .001$). In order to further assess the significant outcomes, an SNK analysis was performed for each test day (all $ps < .05$).

The first test day (T1) was the pre-LD behavioral test. As illustrated in Figure 2, prior to LD, SNK analyses revealed that the AGl surgical control group demonstrated significantly less severe neglect than all other groups. The second behavioral test was the first post-LD test. The SNK revealed that the AGl and 4-h groups demonstrated significantly less severe neglect than the 52-h, 100-h, and NM groups. Thus, LD significantly decreased the severity of neglect on the first post-LD behavioral test at the shortest delay (4 h).

The results of the SNK analyses on subsequent test days indicated that the effectiveness of LD in producing behavioral recovery was maintained. As indicated in Figure 2, the AGl lesion control group and the 4-h group never differed. The AGl group demonstrated less severe neglect than the NM and 52-h groups on each of the test days and less severe neglect than the 100-h group at all but 2 test days (T5 and T8).

The 4-h group demonstrated significantly less severe neglect than the NM group on all post-LD tests, than the 52-h group on all but T7, and than the 100-h group on all but T5 and T7.

LD produced an intermediate recovery effect in the 28-h group; this group demonstrated significantly less severe neglect than the NM group (T3, T6, and T8), the 52-h group (T3, T5, T6, and T9), and the 100-h group (T3, T6, and T9). However, the 28-h group demonstrated significantly more severe neglect than the AGl group (T4, T7, T9, and T10) and the 4-h group (T2, T4, and T10).

One-way within-subjects ANOVAs were performed for each of the groups in order to examine the performance of the groups across test days. Significant differences among the days were obtained for the AGl group [$F(9,63) = 2.21, p < .033$], the 4-h group [$F(9,36) = 8.43, p < .000$], and the 52-h group [$F(9,54) = 3.15, p < .004$].

SNK analysis of the AGl group indicated that there were no significant differences between any of the test days.

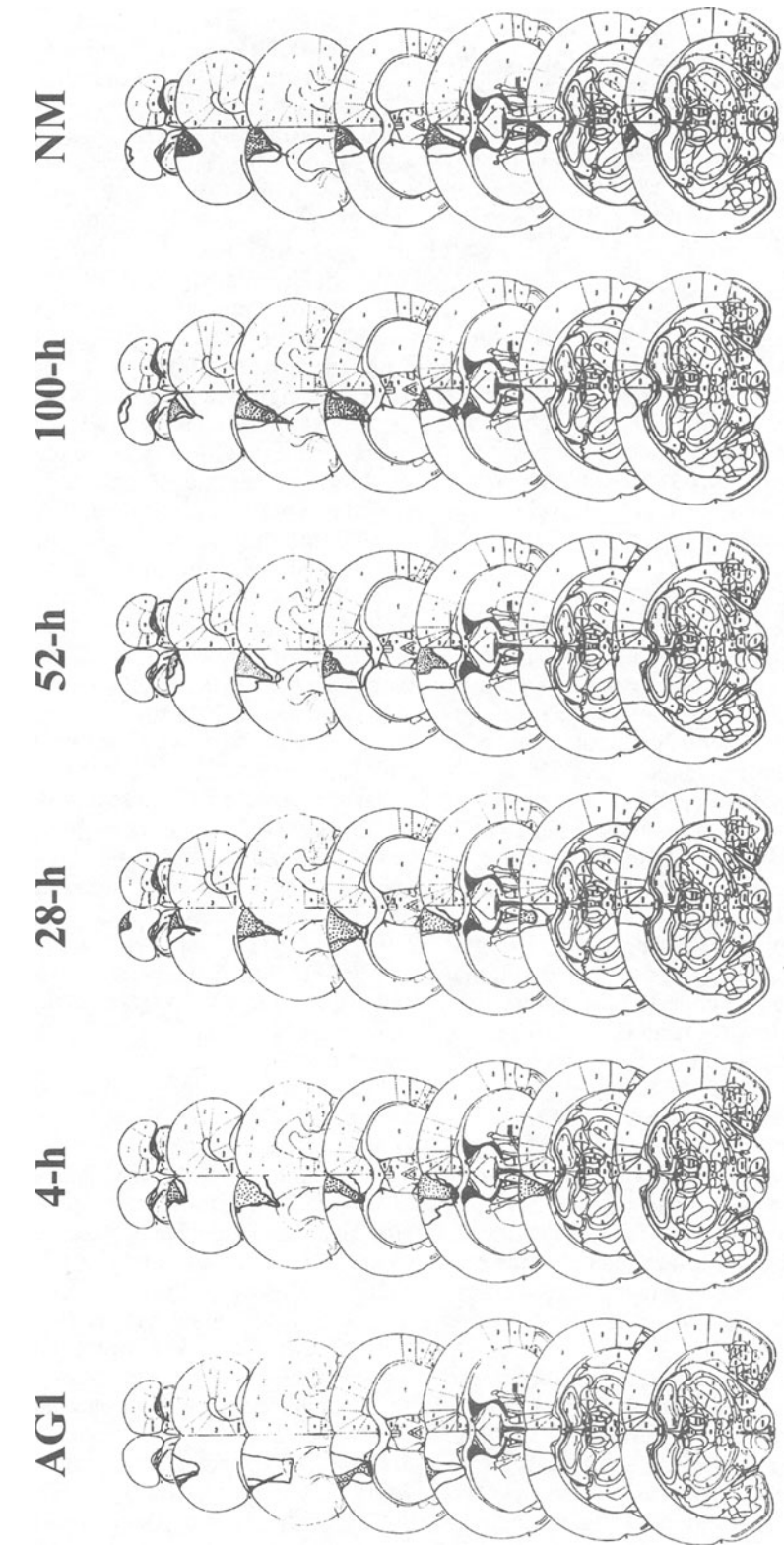

Figure 1. Reconstructions of the largest (dark outline) and smallest (stipple) lesions for the delay groups.

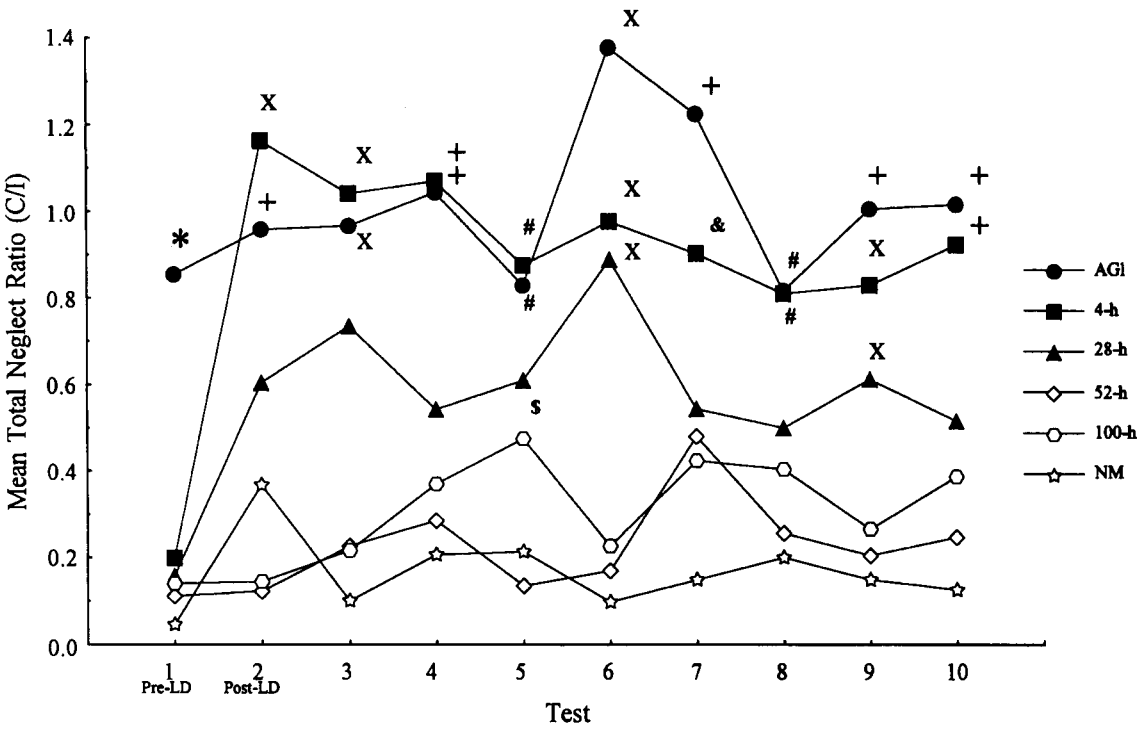

Figure 2. Effects of 48 h of LD on total neglect ratios in each of the delay groups. A ratio of 1.0 represents symmetrical responding. Test 1 was administered prior to LD (pre-LD), whereas Tests 2–10 were given after exposure to LD (post-LD). "+" indicates a significant difference from the 96-h, 48-h, 24-h, and NM groups. "*" indicates a significant difference from all other groups. "#" indicates a significant difference from the 48-h and NM groups. "X" indicates a significant difference from the 96-h, 48-h, and NM groups. "$" indicates a significant difference relative to the 48-h group. "&" indicates a significant difference relative to the NM group. All *ps* < .05, as indicated by SNK analyses.

SNK analysis for the 4-h group revealed that neglect prior to LD (T1) was significantly more severe than all post-LD tests. This finding indicates that the LD-induced recovery was maintained for the duration of behavioral testing. SNK analysis across the weeks in the 52-h group indicated only that neglect on T7 was significantly less severe than on T1, T2, T5, T6, and T9.

In summary, the results of the analyses of the total neglect ratios revealed that 48 h of LD administered at 4 h postinjection produced significant recovery relative to NM controls on all post-LD behavioral tests. Furthermore, the within comparisons across days indicated that the recovery was maintained throughout testing. Delaying the onset of LD by 24 h reduced the effectiveness of LD and produced an intermediate effect of recovery that only occasionally reached significance relative to controls. Delays longer than 24 h did not result in recovery from neglect.

Raw score totals. Because changes in the neglect ratios utilized in the previous analyses may have been a result of changes in the responsiveness on the contralateral side only, the ipsilateral side only, or both sides, we performed separate analyses of the total contralateral and ipsilateral raw scores summed across all modalities.

Contralesional raw scores. A group × test mixed ANOVA done to compare the responsiveness of the groups on the contralesional (neglected) body side indicated significant effects of group [$F(5,29) = 22.08, p < .000$] and test [$F(9,261) = 5.49, p < .000$] and a significant interaction [$F(45,261) = 1.47, p < .034$].

As done for the ratios, one-way ANOVAs were performed to compare the groups at each test day. The results revealed significant differences among the groups at each test day (all *ps* < .004). An SNK analysis was performed for each test day to evaluate specific between-groups differences. The findings were virtually identical to the ratio data (all *ps* < .05).

At T1 (pre-LD), the AGl group was more responsive on the contralesional side than all of the other groups. At T2, the first post-LD test, the 4-h group was significantly more responsive than the 52-h and 100-h groups, and the 4-h group did not differ from the AGl operates, supporting the contention that the effects of LD on recovery are present immediately post-LD. On subsequent test days, the 4-h group differed from NM and 100-h groups on all tests but T8, from the 52-h group on all but T7 and T8, and from the 28-h group on several tests (T3, T6, T7, T9, and T10). The 4-h group and AGl groups did not differ on any post-LD tests.

Comparisons done to evaluate group performance across days indicated significant differences among the days in the 4-h group [$F(9,36) = 4.555, p < .001$] and the

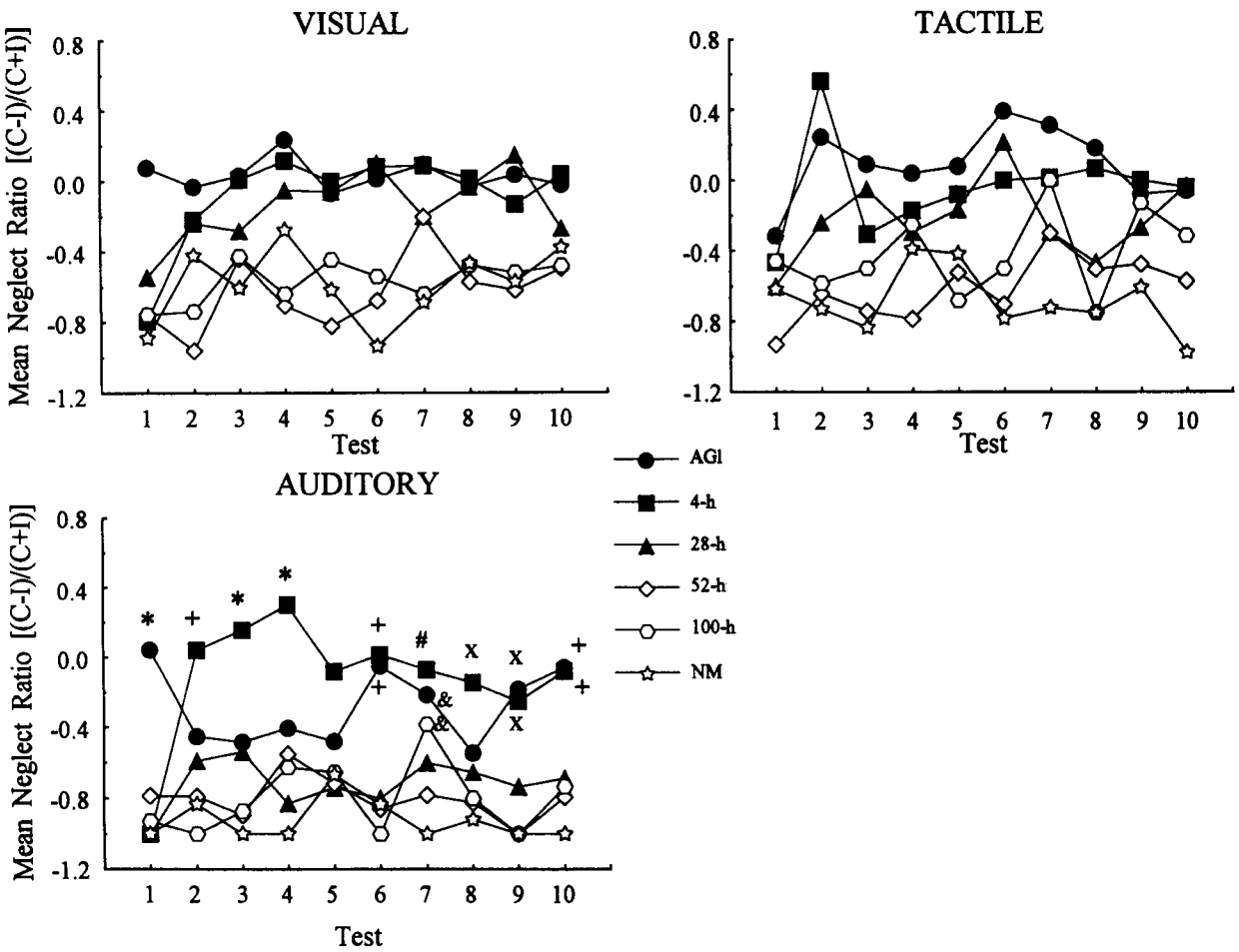

Figure 3. Effects of delay of 48 h of LD on modality neglect ratios. A ratio of 0.0 represents symmetrical responding. "+" indicates a significant difference from the 96-h, 48-h, and NM groups. "*" indicates a significant difference from all other groups. "#" indicates a significant difference from the 48-h and NM groups. "X" indicates a significant difference from the 96-h, 48-h, 24-h, and NM groups. "&" indicates a significant difference relative to the NM group. Error bars represent standard errors. All *p*s < .05, as indicated by SNK analyses.

52-h group [$F(9,54) = 2.284, p < .030$]. As found for the neglect ratio analyses, the SNK analysis indicated that the 4-h group demonstrated less contralesional responsiveness at pre-test (T1) than on any of the post-LD tests.

Ipsilesional raw scores. A group × test mixed ANOVA was done to compare the ipsilesional total responsiveness among the groups. The analysis revealed a significant main effect of group [$F(5,29) = 3.40, p < .02$] and test [$F(9,261) = 2.50, p < .009$]. There was no significant interaction. In order to further examine the significant group effect, two one-way ANOVAs were performed comparing the groups prior to LD (T1) and following LD (collapsed across all post-LD days, T2–T10). The results indicated that the AGl and 4-h groups were significantly less responsive than the 52-h group prior to LD. However, no differences in ipsilateral responsiveness emerged following the environmental manipulation. No significant differences were indicated when follow-up analyses to the significant within effect were performed.

In summary, the results of the raw score analyses indicate that LD, when administered at 4-h postinjection, produced significant increases on the neglected (contralesional) body side; however, LD had no systematic effects on the nonneglected (ipsilesional) side.

Modalities. As is illustrated in Figure 3, in order to further examine the effects of delay of LD on recovery from neglect, each of the individual stimulus modalities was examined.

Visual. A group × test ANOVA done to examine the effects of delay of LD on visual neglect indicated that there were significant main effects of group [$F(5,29) = 12.77, p < .000$] and test [$F(9,261) = 3.54, p < .000$]. There was no significant interaction. An SNK analysis done to examine the main effect of group revealed that the AGl group demonstrated less severe visual neglect at T1 than all other groups. However, the AGl, 4-h, and 28-h groups demonstrated less severe neglect than the 100-h, 52-h, and NM groups following LD. To follow up the

significant effect of test, SNK analyses were performed comparing tests collapsed across all groups. No significant differences between tests were indicated.

Tactile. A mixed group × test ANOVA was performed to determine the effects of delay on recovery from tactile neglect. The results of the analysis revealed only a significant effect of group [$F(5,29) = 14.355, p < .001$]. Separate one-way ANOVAs performed for T1 and for the data collapsed across all post-LD test days (T2–T10) indicated significant differences among the groups ($ps < .05$). SNK analysis at T1 revealed no differences between groups. For T2–T10, the AGl group was significantly less impaired than all but the 4-h group, the 4-h group was less impaired than all but the AGl and 28-h groups, and the 28-h group was less impaired than the 52-h and NM groups.

Auditory. A group × test ANOVA was done to examine the effects of LD on neglect in the auditory modality. The result indicated a significant main effect for group [$F(5,29) = 27.15, p < .000$] and a significant group × test interaction [$F(45,261) = 1.68, p < .007$].

In order to further examine the interaction, a series of one-way analyses were done to examine between-groups differences at each of the test days. The results indicate that there was a significant difference among the groups at each test (all $ps < .01$) except T5 and T8. During T1 (pre-LD), the AGl group had less severe auditory neglect than all of the other groups. At T2, the 4-h group had significantly less severe neglect than all groups, but AGl did not differ from any of the groups. The 4-h group had significantly less severe neglect than the NM and 52-h groups on all tests (except T5 and T8), than the 100-h group on all tests but T5, T7, and T8, than the 28-h group on T3, T4, T6, and T10, and than the AGl lesion controls on T3 and T4.

Comparisons across test days in each group indicated a significant difference in the 4-h group [$F(9,36) = 4.970, p < .001$], although no specific differences between days were indicated by post hoc SNK.

Postsurgical Analyses

The prior analyses were done using post-LD behavioral testing to evaluate the delayed effects of LD. However, when time post-LD is the reference point and the groups differ in the time of onset of LD, there is an unavoidable difference among the groups in postsurgical recovery time. To quickly assess if there was an influence of time postsurgery on recovery, independent of delay of LD, analyses of the total neglect ratios were performed using tests relative to the time of surgery rather than tests post-LD as the reference point. Because of the different delays experienced by the groups, only Tests 5–10 postsurgery could be examined. The results of the analyses of total neglect ratios postsurgery were virtually identical to those for the time post-LD analyses.

The mixed group × test (Postop Tests 5–10) ANOVA indicated significant main effects of group [$F(5,29) = 18.863, p < .001$] and test [$F(5,145) = 2.965, p < .014$]. SNK analysis to follow up the significant effect of group revealed that the AGl group demonstrated less severe neglect than all but the 4-h group, the 4-h group demonstrated less severe neglect than the 52-h, 100-h, and NM groups, and the 28-h group demonstrated less severe neglect than the 52-h and NM groups. Within analysis comparing postop test days collapsed across all groups were performed to further examine the significant test effect; however, SNK analysis indicated that there were no significant differences between test days.

Discussion

The results of Experiment 1 indicate that 48 h of LD administered 4 h after the injection of surgical anesthetic was effective in producing significant behavioral recovery of function from neglect induced by unilateral destruction of the AGm. LD produced increased responsiveness on the neglected body side, which was evident on the first test following LD and was maintained for the 3 weeks of behavioral testing. Furthermore, recovery of function from neglect was obtained across all modalities. These results replicate those of Corwin and Vargo (1993), and they are consistent with the findings from pharmacological studies that indicate that manipulations must be performed within a short period of time postlesion to affect recovery (Albers, 1990; Schallert et al., 1986; Zivin & Choi, 1991). The 4-h delay group was the only group to demonstrate significant recovery immediately following LD.

LD appears to produce an intermediate, though not significant, therapeutic effect if administered at 28 h postinjection. Delaying the onset of LD for 28 h did not produce significant recovery at the first post-LD behavioral test. However, the 28-h delay group was significantly less impaired than the 52-h, 100-h, and NM groups on at least 3 of the test days. Delaying the onset of LD for durations longer than 28 h completely abolished the therapeutic effect of LD.

Differences in recovery among the groups were not based on different postsurgical recovery times, as evidenced by comparing the performance of the groups relative to time postsurgery rather than to time post-LD. The patterns of statistical results of both sets of analyses were virtually identical. These results suggest that LD, when administered at a 4-h delay, produced significant recovery from verified severe neglect.

EXPERIMENT 2

Experiment 2 examined the duration of LD required to induce accelerated behavioral recovery of function from neglect induced by unilateral destruction of the AGm. In Experiment 2, postoperative delay of the onset of LD was held constant at 4 h postinjection of surgical general anesthetic, and the duration of exposure to LD was varied among the groups.

Method

Subjects

The subjects were 30 male Long-Evans hooded rats bred from stock purchased from Harlan Sprague-Dawley (Indianapolis, IN). The subjects from the 4-h delay (48-h duration) group ($n = 5$), the no-manipulation (NM) control group ($n = 4$), and the AGl control lesion group ($n = 8$) from Experiment 1 were included in this experiment to reduce needless repetition of surgical manipulations. Throughout the experiment, the subjects were maintained in the same fashion as the subjects in Experiment 1 were.

Surgical Procedures

The surgical procedures were identical to those in Experiment 1.

Behavioral Testing

The behavioral testing methods were identical to those used in Experiment 1.

Grouping Procedure

The subjects that demonstrated severe neglect (operationally defined as a total neglect ratio ≤. 33) at 4 h postinjection of the surgical anesthetic were randomly assigned to one of two duration groups: 4 h ($n = 6$) or 24 h ($n = 7$).

Light-Deprivation Procedure

After determination of severe neglect, all animals (on the basis of group membership) underwent the appropriate duration of exposure to LD. The conditions for LD were identical to those described in Experiment 1.

Post-Light-Deprivation Testing

After exposure to LD, the lights were turned on, and the subjects were transferred back into the colony and allowed to adapt to ambient light for 15 min. After the adaptation period, the subjects were tested for neglect, as described previously. It should be noted that the subjects in the 4-h group, unlike the other duration groups, were tested twice on the same day. However, prior studies in which subjects were tested twice within the same day have found that recovery from neglect is not affected (Corwin et al., 1986; King & Corwin, 1990). Subsequently, all subjects were tested three times per week for a 3-week period. For all behavioral testing, the experimenter was blind with respect to the group affiliation of the subjects.

Histological Procedures

The histological procedures were identical to those used in Experiment 1.

Results

Statistical analyses of behavioral data were performed in a manner identical to that described in Experiment 1.

Histological Analyses

As in Experiment 1, the typical AGm lesion encroached medially to varying extents on the dorsal anterior cingulate cortex and caudally on the retrospenial agranular cortex. Laterally, lesions tended to produce variable amounts of damage to the lateral agranular cortex and in hindlimb cortex. There was no damage to the contralateral hemisphere and none of the lesions extended ventrally through the white matter; however, typically, some minor damage occurred to the white matter.

The histological findings for the AGl group are described in the Results section of Experiment 1.

As in Experiment 1, total lesion extents for each subject were traced onto standard brain diagrams (Paxinos & Watson, 1986) and measured using image analysis (Optimus, BioScan, Inc., Edmonds, WA). Figure 4 illustrates the individual subjects in each group with the largest and smallest lesions. A one-way ANOVA revealed no significant difference in total lesion extent among the groups. Furthermore, a one-way ANOVA indicated that there was no significant difference in the percentage of AGm damage among the AGm groups.

Behavioral Analyses

Total neglect ratios. A group × test ANOVA was performed to compare the effects of duration of LD among the groups. The results indicate significant main effects for group [$F(4,26) = 18.69, p < .000$] and test [$F(9,36) = 3.50, p < .000$] and a significant interaction [$F(36,234) = 1.79, p < .006$].

A series of one-way ANOVAs was done to examine group differences at each test. The results indicated that there were significant differences among the groups at each day of testing (all $ps < .005$) except T3 (due to Bonferroni adjustment of p value to control for significant heterogeneity of variance). SNK analyses were done at each of the test days to examine specific between-groups differences. The analyses indicated that the AGl lesion control group was not impaired and demonstrated less severe neglect than all other groups at T1 (pre-LD). On the first behavioral test following LD (T2), the AGl and 48-h groups did not differ from one another, but both were significantly less impaired than the 4-h, 24-h, and NM groups. Furthermore, the AGl and 48-h groups had less severe neglect than the NM group during T4–T10 and than the 4-h group during T4–T9. The 48-h group had significantly less severe neglect than the 24-h group at T4 and T9. The AGl group demonstrated less severe neglect than the 24-h group at T4, T6, T7, and T9.

One-way ANOVAs performed to determine how the groups behaved across days of testing revealed significant overall differences across days for only the AGl group [$F(9,63) = 2.213, p < .033$] and the 48-h group [$F(9,36) = 8.43, p < .001$]. SNK analysis indicated that no significant differences between days occurred in the AGl group and that the animals in the 48-h group demonstrated significantly more severe neglect at T1 than on any other behavioral test (all $ps < .05$).

To summarize, the results of the statistical analyses performed on the total neglect ratios indicate that LD must be administered for a period of at least 48 h in order to produce significant recovery from severe neglect. As previously described in Experiment 1, the 48-h group did not differ from the AGl group at any time following LD.

Raw score totals. In order to examine the effects of varying the duration of LD on contralesional and ipsilesional responsiveness, analyses were performed on the raw score totals for behavioral testing.

Contralesional responsiveness. The effects of LD duration on contralesional responsiveness were examined

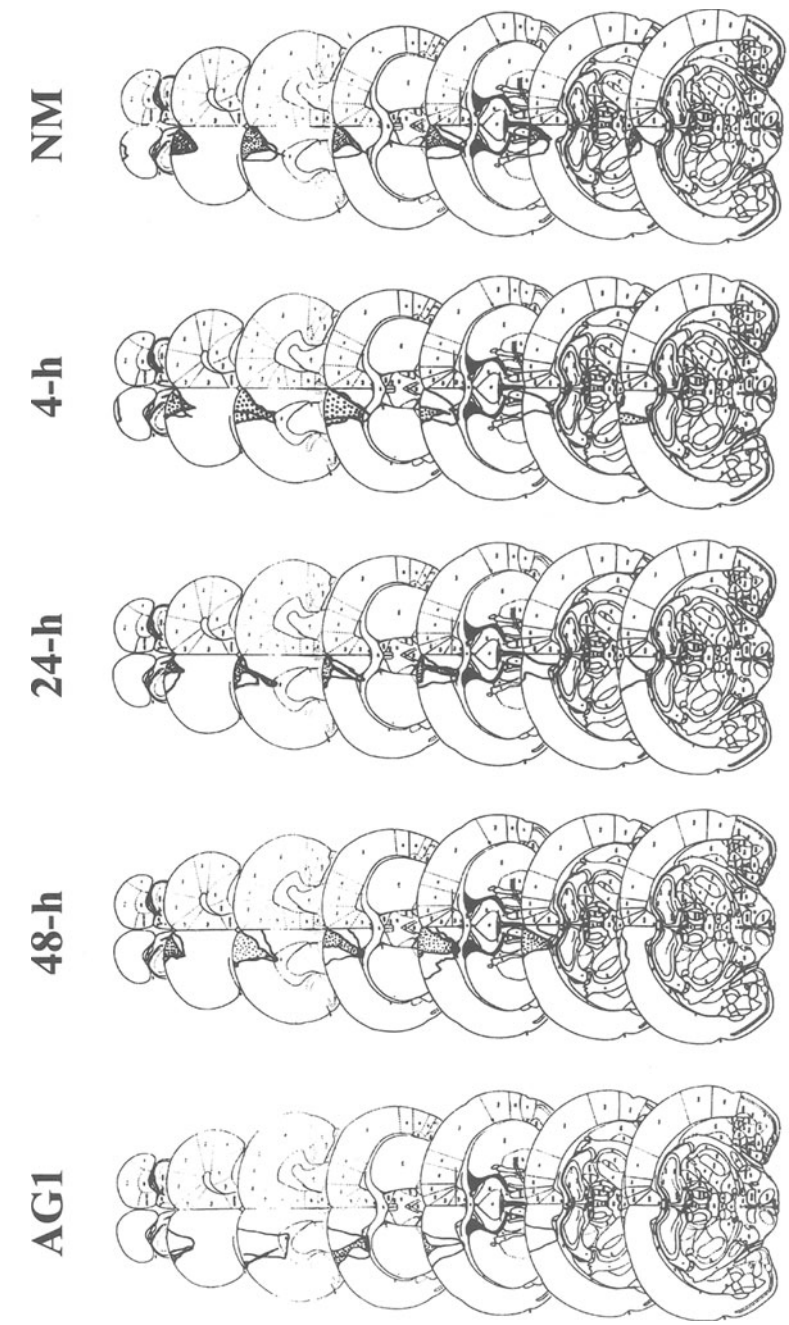

Figure 4. Reconstructions of the largest (dark outline) and smallest (stipple) lesions for the duration groups.

by a group × test ANOVA. The results indicate significant main effects of group [$F(4,26) = 14.417, p < .001$] and test [$F(9,234) = 4.980, p < .001$] and a significant group × test interaction [$F(36,234) = 1.836, p < .004$].

A series of one-way ANOVAs and SNK analyses were performed to compare the groups at each of the test days. The results indicated that the groups were significantly different on all test days (all $ps < .05$). On T1, the AGl group was significantly more responsive on the contralesional body side than all other groups. The AGl and 48-h groups were significantly more responsive than the NM group on all subsequent tests and more responsive than the 4-h group on T2, T3, T4, T6, T8, and T10. The 24-h group was less responsive than the AGl and 48-h groups on T2, T3, T4, and T6.

One-way ANOVAs comparing days were performed for each group, and they revealed that both the 24-h and the 48-h group demonstrated a significant change across days. SNK analysis for the 48-h group indicated significantly less contralesional responsiveness on T1 than on any of the subsequent tests. However, in the 24-h group, none of the between test days comparisons reached statistical significance.

Ipsilesional responsiveness. To determine the effects of LD duration on ipsilesional responsiveness, a group × test mixed ANOVA was performed. The results indicate a significant main effect of group [$F(4,26) = 4.090, p < .011$]. SNK analysis revealed that the only significant finding was that the AGl group was less responsive on the ipsilesional body side than the NM group ($p < .05$).

In summary, the results of the analyses of contralesional and ipsilesional responsiveness support the results of the total neglect ratio analyses. The 48-h group did not differ significantly from the AGl group at any test following LD. In addition, the 48-h group was the only group to demonstrate a significant increase in contralesional responsiveness following exposure to LD. The analyses performed using the ipsilesional raw score totals indicate that LD had very little, if any, affect on ipsilesional responsiveness. Therefore, LD produced behavioral recovery of function when administered for 48 h solely by increasing responsiveness on the contralesional body side.

Individual modalities. As illustrated in Figure 5, the effects of duration of LD were examined in each of the modalities across the 3 weeks of testing. The results obtained in the analyses of the individual modalities were virtually identical to those obtained for the total neglect ratios; therefore, they will be summarized. Significant between-groups differences were obtained for each modality (all $ps < .001$). Separate analyses revealed that, as in Experiment 1, the AGl and 48-h groups exhibited significantly less severe neglect than the other groups on at least 3 test days in each of the individual modalities (all $ps < .05$). Furthermore, as in Experiment 1, only the 48-h group demonstrated significant recovery to pre-LD

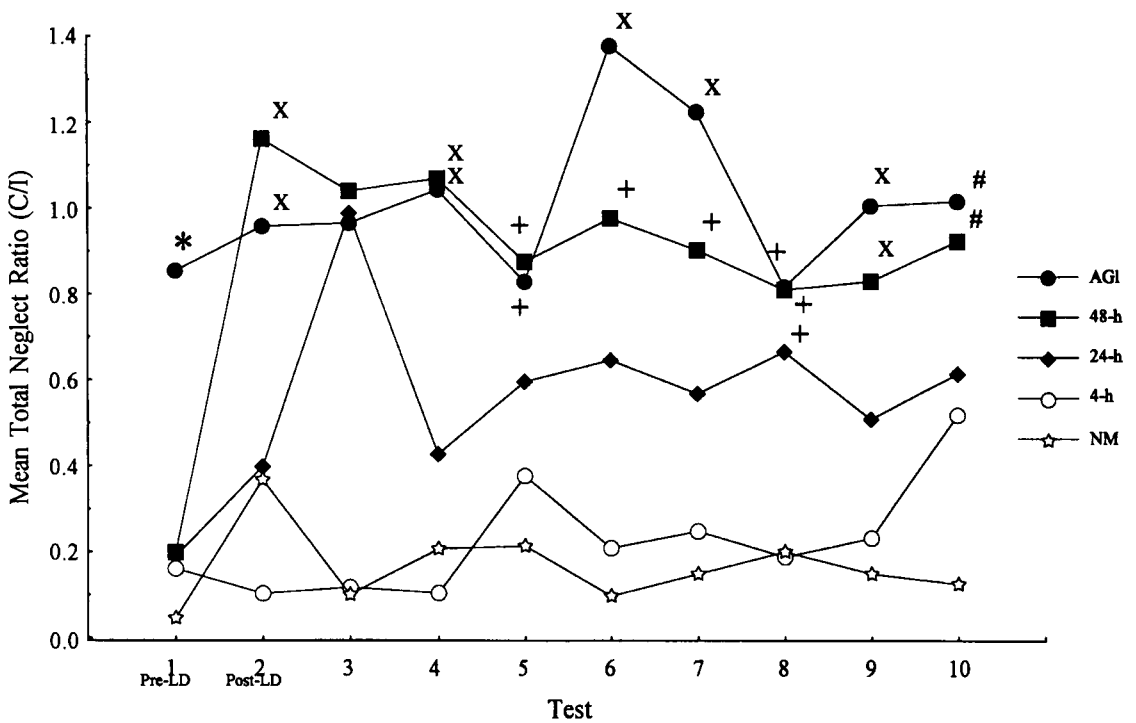

Figure 5. Effects of duration of LD on total neglect ratios. A ratio of 1.0 represents symmetrical responding. Test 1 was administered prior to LD (pre-LD), whereas Tests 2–10 were given after exposure to LD (post-LD). "+" indicates a significant difference from the 4-h and NM groups. "*" indicates a significant difference from all other groups. "X" indicates a significant difference from the 4-h, 24-h, and NM groups. "#" indicates a significant difference relative to the NM group. All $ps < .05$, as indicated by SNK analyses.

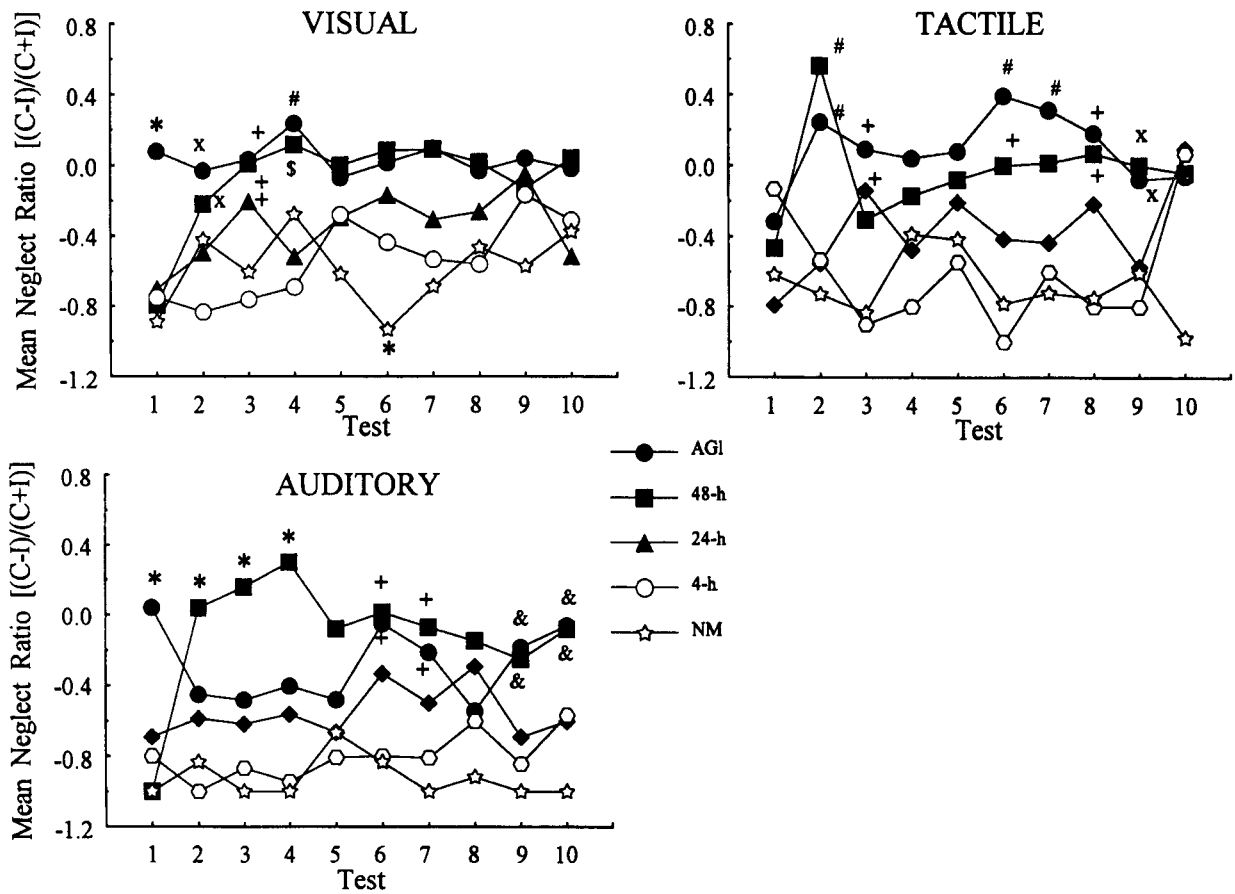

Figure 6. Effects of duration of LD on modality neglect ratios. A ratio of 0.0 represents symmetrical responding. "+" indicates a significant difference from the 4-h and NM groups. "*" indicates a significant difference from all other groups. "#" indicates a significant difference from the 4-h, 24-h, and NM groups. "X" indicates a significant difference from the 4-h group. "&" indicates a significant difference from the NM group. "$" indicates a significant difference from the 4-h and 24-h groups. All *ps* < .05, as indicated by SNK analyses.

levels of neglect in the tactile and auditory modalities (all *ps* < .05).

Postsurgical Comparisons

As in Experiment 1, the results of the analyses previously reported using removal from LD as the reference point are potentially confounded by differential recovery times based on group membership. That is, the subjects in the 4-h group were allowed 8 h to recover before being tested for neglect, whereas the subjects in the 48-h group were allowed 52 h.

To examine whether these differences in recovery time had an affect, the effects of LD on the total neglect ratios were examined using time postsurgery as the reference point. As in Experiment 1, only Tests 5–10 relative to the time of surgery could be included in these analyses. A group × postoperative tests (T5–T10) analysis was performed to determine how the groups behaved relative to time postoperatively. The results indicate only a significant main effect of group [$F(4,26) = 16.169, p < .001$]. Post hoc SNK analysis performed using the postoperative test means (T5–T10) indicate that the AGl group was significantly less impaired than the 24-h, 4-h, and NM groups. Furthermore, the 48-h and 24-h groups had significantly less total neglect than the 4-h and NM groups.

Discussion

The results of Experiment 2 indicate that LD, when administered 4 h postinjection of the surgical anesthetic, has a duration-dependent effect on recovery of function from neglect induced by unilateral AGm destruction. The 48-h group demonstrated a significant reduction in the severity of neglect, which was present immediately after LD and was maintained throughout testing. Twenty-four hours of LD did produce a meliorative effect on the severity of neglect relative to that for the 4-h and NM groups, although the groups differed significantly only during the 3rd week post-LD. Durations of LD less than 24 h did not affect behavioral recovery.

Although analyses were performed comparing the groups relative to time postsurgery, the results of these analyses did not differ from those performed relative to LD. These results suggest that the differences in recovery among the duration groups were a result of differences

in exposure to LD, and not due to differential postsurgical recovery times.

GENERAL DISCUSSION

The results of the present study support and extend the findings of prior studies (Corwin & Vargo, 1993; Crowne & Pathria, 1982; Crowne et al., 1983), which indicate that LD can have a dramatic therapeutic effect on neglect induced by unilateral AGm destruction. Experiment 1 demonstrated that 48 h of LD must be administered within a critical period of time in order to produce recovery of function from severe neglect in rats. When 48 h of LD was administered 4 h following unilateral AGm destruction, the subjects exhibited immediate recovery that lasted for the duration of behavioral testing. Significant recovery of function from severe neglect was not found at longer delays. In Experiment 2, the duration of LD was varied and the onset of LD was held constant at 4 h postinjection of the surgical anesthetic. The results indicate that the effects of LD were duration dependent. The animals in the 48-h LD duration group demonstrated complete and permanent recovery. The subjects in the 24-h LD duration group demonstrated a small, but significant, recovery relative to controls postoperatively (T5–T10). The 4-h LD duration group did not demonstrate recovery from severe neglect.

The results of the present study and prior studies of the effects of environmental manipulations on neglect point to a brief postlesion period during which LD, and perhaps other environmental manipulations, may be effective in producing recovery. Rose, Davey, Love, and Dell (1987) examined the effects of enriched housing on recovery from neglect. Their results indicate that both the enriched and the impoverished group performed no differently from subjects housed under standard conditions. However, in contrast to the present experiment, the subjects in the Rose et al. study were kept in individual cages under standard conditions for 10–12 days immediately following surgery and prior to environmental manipulation. The results from our Experiment 1 suggest that environmental manipulations for the treatment of neglect may be therapeutically effective only when administered within 24 h following brain damage.

At present, little is known about the mechanisms that underlie LD-induced recovery. However, LD has been found to produce recovery of function in situations in which the behavioral deficit is related to a disruption of dopaminergic mechanisms (Burcham, Corwin, & Van Vleet, in press; Corwin et al., 1996; Corwin & Vargo, 1993; Harrell & Balagura, 1974; Schallert, 1989). Several studies have found that acute recovery from neglect can be produced by dopamine receptor agonists in both rats (Corwin et al., 1996; Corwin et al., 1986; King & Corwin, 1990) and humans (Fleet et al., 1987), and that dopamine receptor antagonists can reinstate neglect in rats that have spontaneously recovered from neglect (Vargo et al., 1996; Vargo et al., 1989). However, whether LD produces recovery via dopaminergic mechanisms has yet to be directly tested.

Recent studies of neglect following unilateral lesions of AGm have found that severe neglect is correlated with asymmetries (ipsilesional < contralesional) in immediate early gene expression (c-fos, zif/268, junB) in the dorsolateral striatum (Vargo & Marshall, 1996). In subjects demonstrating spontaneous recovery, striatal immediate early gene expression was symmetrical (Vargo & Marshall, 1995, 1996). In a subsequent study in AGm operates, it was (1996) found that, as for spontaneous recovery, LD-induced recovery was correlated with symmetrical c-fos expression in striatum (Vargo et al., 1996). Furthermore, Vargo et al. (1996) found that, during LD, behavioral activity levels were significantly lower in both lesioned animals and unlesioned controls relative to subjects that experienced a standard 12:12-h light:dark cycle. Lower activity levels during LD were associated with greater recovery from neglect and less asymmetry in striatal c-fos expression. The results of these studies suggest that the mechanisms for spontaneous and LD-induced recovery may be similar, and that recovery may result from a reduction of asymmetries in subcortical functioning, perhaps in the striatum. However, it remains to be determined whether LD is acting directly to produce recovery or whether the effects of LD on recovery are indirectly produced by decreased levels of activity during LD. Further studies of the general effects of LD on activity must be undertaken to examine in greater detail the changes in activity produced by LD across the entire 24-h light:dark cycle.

There are some issues that would need to be resolved in regard to the potential applicability of LD to humans suffering from neglect. In Experiments 1 and 2, neglect was induced by unilateral aspiration of the AGm. In humans, cerebrovascular accidents are the predominant cause of neglect (Heilman et al., 1993). Ischemic lesions may produce changes in brain function that are not susceptible to environmental manipulation. Investigations of neglect in rats produced by ischemic unilateral lesions of AGm must be performed to indicate more clearly whether LD might also be effective in inducing recovery of function from neglect produced by stroke in humans. Furthermore, it is currently unknown whether or not the effects of LD will generalize to other contexts. For example, it is important to determine whether LD will be effective in producing recovery from neglect in aged subjects. This issue may be clinically important, because strokes (and, as a consequence, neglect) occur most often in older individuals. Recent pilot data from our laboratory (Corwin & Burcham, 1998) indicate that LD can produce recovery of function from neglect in aged rats (24 months), but that the duration of LD required to produce a therapeutic effect may be 72 h rather than 48 h. Another important consideration is whether LD is effective in producing recovery from neglect induced by lesions of cortical areas other than AGm. We have recently examined this issue in subjects with severe neglect in-

duced by unilateral destruction of PPC, the rodent analogue of the inferior parietal lobule. As found for AGm operates, 48 h of LD administered at 4 h postsurgery produced significant recovery from neglect induced by unilateral PPC lesions (Burcham et al., in press). This finding is of some importance because, in humans, neglect is most commonly associated with damage to the inferior parietal lobule (Ogden, 1985; Vallar & Perrani, 1987).

A major consideration related to the therapeutic applicability of LD to humans is that rats are a nocturnal species, whereas humans are diurnal. Therefore, it is not obvious whether one should expect LD, or any light-related manipulation, to have similar effects on recovery from neglect in humans. Dark deprivation (placement into constant light), rather than LD, might prove to be effective in alleviating the symptoms of neglect in human patients. Furthermore, only animals that demonstrated severe neglect were included in this study. The use of animals with severe neglect provided a conservative test of the effectiveness of LD. However, it is important to determine the effectiveness of LD in animals that do not demonstrate severe neglect, because many humans suffer from a relatively milder asymmetry in orientation.

A number of studies have pointed to the need for immediate intervention to promote recovery from brain damage (Albers, 1990; Corwin et al., 1986; Schallert et al., 1986). Yet, in humans, drug therapies are typically delayed due to the concern that administration during the period immediately following brain damage may interfere with spontaneous recovery and plasticity (Albers, 1990; Schallert et al., 1986). In contrast, LD, perhaps through eye patching, is an inherently simple manipulation that could be implemented immediately on determination of cerebral insult. Although not specifically examined in this study, LD did not appear to produce any obvious side effects (e.g., changes in motor behavior or affect) during post-LD behavioral testing, as may be produced when certain drugs are given to promote recovery (Feeney, Gonzales, & Law, 1981, 1982; Feeney & Sutton, 1987; Schallert et al., 1986). Therefore, LD may be an alternative form of treatment that may avoid these side effects for stroke patients. Given the absence of any generally accepted therapeutic treatments for human patients with neglect (Robertson, 1993; Robertson et al., 1993), it is essential to examine any promising therapeutic intervention. Future research should be aimed at determining the specific mechanisms that mediate LD-induced recovery.

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