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Research report

Increased masking response to light after ablation of the visual cortex in mice

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Abstract

Mice are known to suppress their wheel running when given a pulse of light in the night (masking response). The amount of suppression can be quantified; the response varies with the level of irradiance used during the light pulse. After ablation of the visual cortex, mice suppressed their activity more than sham-operated controls. In addition, the lesioned animals responded to lower levels of irradiance than controls. It is suggested that the visual cortex is not needed for the suppression of locomotor activity after a light pulse. Nevertheless it exerts an inhibitory influence on the masking response to light mediated by an irradiance detection system. When this inhibition is removed, even though pattern vision is lost, masking responses to ambient level of light are enhanced.

Theme: Neural basis of behavior

Topic: Biological rhythms and sleep

Keywords: Irradiance detection; Lateral geniculate; Locomotor activity; Masking; Mouse; Nonvisual photoreception; Retinal degeneration; Visual cortex

1. Introduction

Behavior and physiology are synchronized to the 24-h day by distinctive responses to light. First, light synchronizes a circadian clock in the hypothalamus which in turn drives most daily rhythms such as the sleep–wake cycle. This effect of light on the circadian clock is slow and requires protein synthesis [24]. Second, light can have a fast and direct effect on rhythmic variables. In a nocturnal rodent, for example, light at night causes an immediate reduction of wheel running. This fast effect of light on rhythmic variables is referred to as masking, because it masks or obscures control by the circadian clock (see [15] for terminology). Both processes, masking and entrainment, require only detection of irradiance, and may both be mediated by the same novel photoreceptors. This can be concluded from studies with mutant and transgenic mice which lack both rods and cones. These mice entrain normally to light–dark cycles and they also suppress their locomotor activity to light pulses [18], even though they must be considered blind. The irradiance detection system mediating both entrainment of circadian rhythms and masking is thought to start with photoreceptive cells in the inner retina. Melanopsin has been proposed recently as a candidate for the photopigment mediating these responses [5].

Although irradiance detection without rod and cone photoreceptors is sufficient for masking to occur, several observations indicate that the classical rod and cone system, in addition to its task in image formation, may also influence masking of locomotor activity. An enhanced masking response, that is, greater inhibition of activity by light of a given strength, has been seen with several different types of retinal degeneration. It has been found in

Abbreviations: IGL, intergeniculate leaflet; dLGN, dorsal lateral geniculate; ZT, zeitgeber time; SC, superior colliculus; SCb, brachium of the superior colliculus; LD, light–dark; SCN, suprachiasmatic nucleus; PRT, pretectum

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two strains of rd/rd (retinally degenerate) mutant mice, which loose nearly all their rods and cones [16], in rds/rds (retinally degenerate slow) mice old enough for the degeneration to be advanced [Mrosovsky, unpublished], and in transgenic mice with degeneration induced by a diphtheria toxin gene fused to a rod promoter [17]. Greater clock resetting after a light pulse has been also found in this strain of transgenic mice [9]. In addition, enhanced masking to light can occur after lesions of the thalamic intergeniculate leaflet (IGL) [23] or the dorsal lateral geniculate of the thalamus (dLGN) [3].

These results indicated that if input to the visual cortex, or possibly other visual centers past the geniculate, is interrupted, the suppression of locomotor activity by light was unimpaired and even enhanced. The results were similar whether visual input to the cortex was interrupted at the retinal level (in case of the various retinal degenerations) or along the visual pathway to the cortex (dLGN lesions). The enhanced masking seen after lesions of the IGL was therefore probably also the result of interruption of visual input to the cortex, as the IGL lesioning procedure undoubtedly resulted in accidental damage to the adjacent dLGN, which is very difficult to avoid because of the anatomical location of the IGL [20]. Although these studies suggested that deprivation of visual input to the cortex is causing the enhanced masking, the possibility remained that other areas receiving retinal input may have been responsible, such as the superior colliculus, a structure generally thought to be involved in visual reflexes.

The present experiments aimed to substantiate the assumption that deprivation of input to the visual cortex results in enhanced masking. We therefore tested how removal of the visual cortex affected masking of locomotor activity in mice. We also assessed the effects of combined lesions of the visual cortex and superior colliculus because the superior colliculus is a major projection area of the visual system in rodents.

2. Methods

2.1. Animals, housing, and experimental procedure

Seventy-three male C57BL/6JICO mice, aged 7.5±0.5 weeks, were obtained from IFFA Credo (L'Arbresle, France). They were housed in the INSERM laboratory at Bron, in groups in cages approx. 75×50×25 cm, and fed chow with apple supplements. The room where the mice were kept had windows; temperature was ~25 °C.

One group of mice (n=30) received visual cortex lesions, a second group (n=22) had their visual cortex ablated and in addition visual input to the superior colliculi was severed. A further group (n=17) was sham-operated. Survival rates were 24/30 cortically-lesioned mice, 22/22 for those with additional superior colliculus lesions, and 15/17 for the sham-operated animals. In addition, four mice died under anesthetic before the operations got under way. (For details of the surgical procedures, see below).

After 14±2 days for recovery, the animals were sent by air to Toronto for testing. From this time on they were kept in an LD 16:8 h cycle. Within the first 2 weeks of arrival in Toronto, the mice were put individually in cages equipped with running wheels for periods of a few days. This was to screen the mice for activity levels. Wheel revolutions were monitored with Dataquest III hardware and software (Mini Mitter, Sunriver, OR, USA). Purina 5001 rodent chow and water were available ad libitum.

On the basis of this initial screening, active mice were selected for testing: 16 cortically-lesioned mice, 16 with additional superior colliculus lesions, and the 15 sham-operated animals. Twenty-nine days after being sent to Toronto, these mice were placed in cages (polypropylene, 44×23×20 cm) with wheels (17.5 cm diameter) arranged in spatially matched positions within two rooms equipped with lighting for masking tests. During the tests the ambient temperature was 20±3 °C; the LD 16:8 h cycle was maintained (1300 lux in L phase).

After a further period of 15 days adaptation to these rooms, the masking tests began. At this stage the mice were about 16 weeks old, and had had 8 weeks for postoperative recovery. Nevertheless, only six mice with cortical ablation and six with additional superior colliculus lesions used their wheels enough to assess the effects of the different levels of light on locomotion. Because no obvious order effects were evident in pilot experiments or in those of Edelstein and Mrosovsky [3] and Mrosovsky et al. [16], tests were made in the order of decreasing illumination, ending with the sham (dark) pulse. At the end of the experiment presence of a pupillary response was confirmed.

2.2. Masking tests

The lighting system for masking tests made use of fluorescent lights (Sylvania Octron 4100K 32 W) suspended above the cages of the animals. These lights were enclosed in metal boxes, except for a transparent plastic base. Neutral density filters (Rosco, Cinegel) could be introduced on top of these plastic bases; for sham pulses, opaque cardboard was used (see [16] for details). Separate fluorescent lighting units outside of the metal boxes were used for the entraining light–dark cycle (providing light of ~1300 lux at cage level regardless of lighting level for the masking tests).

Masking lights were controlled from outside the room, and were programmed to come on 1.5 h after dark onset (i.e. ZT 13.5); Zeitgeber time (ZT) 12 is dark onset by convention. The light pulses lasted 1 h.

The responses to different levels of illumination were assessed in a series of tests, each with different numbers of neutral density filters between the light sources and the

animals. Each test required 3 days. On the first day (maintenance day), filters were added and general animal care was scheduled. On the second day (baseline day), the animals were left undisturbed, except in few instances when quick checks were needed during the light phase. On the third day (pulse day), the animals were given a light pulse. Sometimes a few additional days elapsed between tests for logistic reasons.

The number of wheel revolutions made during the 1-h pulse was compared to the number made in that same hour on the baseline day. Masking scores are given in percentage of baseline activity, with 0% indicating complete suppression of activity and 100% no change compared to baseline activity. The amount of running a mouse made during the 1-h baseline periods was quite variable and could drift up or down over a week or two. This was true also of sham-operated animals. It is to reduce the effect of gradual changes in baseline that responses to light are scored as percentage changes from the running in a baseline on the day immediately preceding the test [14,16].

Illumination was expressed in terms of the number of stops of the neutral density filters introduced to diminish the light [16]. For levels of illumination above the threshold of our light meter (ISO Tech ILM 350) lux levels were measured (0 stops: 500 lux, 3 stops: 55 lux, 6 stops: 9 lux, 9 stops: 2 lux). It is emphasized that the main aim, however, was not to specify thresholds in any particular units but to compare the responses to light of decreasing brightness between the experimental groups.

2.3. Surgery

Mice were anaesthetized with about 100 mg/kg of Ketalean (ketamine hydrochloride): 20–40 μl of a 3:1 parts by volume mixture of Ketalean and Rompun (xylazine) solutions were injected i.p., to give doses of 1.5–3.0 mg Ketalean and 0.1–0.2 mg of Rompun per mouse. Booster injections were administered when necessary. The occipital region of the cortex was exposed with a drill. The dura mater was opened and deflected. The cortex was then aspirated. Local bleeding was treated by applying surgical cotton over the lesioned area; suction through the cotton generally stopped bleeding rapidly. For animals receiving additional tectal lesions the cotton was removed and the brachium of the superior colliculus (SC) cauterized with an electrical probe. Following the lesions, the empty space was filled with sterile gelfoam and powdered streptomycin was applied. Sham-operated animals were treated as above up to the point of aspiration of the cortex.

2.4. Assessment of lesions

After the end of tests for masking, animals were given an overdose of barbiturate and perfused transcardially with physiological saline and 10% paraformaldehyde in phosphate buffer. After fixation, photographs were taken of the dorsal surface of the brain. The brains were later sectioned at 80 μm and stained with cresyl violet.

The photographs were digitized and an atlas [1] of the cortical areas of the mouse projected onto the digitized photographs (Fig. 1a). Boundaries of the visual cortex were drawn according to the atlas. An image analysis system (ANALYSIS, Soft Imaging System, Münster, Germany) was used to calculate the surface areas of the cortex, visual cortex and lesioned areas. Lesion extent was quantified by calculating the percentages of the primary (area 17) and secondary visual areas (areas 18a and 18b) that were damaged.

All brain sections were inspected by two observers for the extent of damage to the brachium of the SC (SCb). Particular attention was paid to noting possible additional damage to subcortical pretectal and geniculate structures. The observers were unaware of the surgical treatment or behavioral results.

3. Results

3.1. Description of lesions

The mice in the visual cortex group had 83.1% (±6.4 S.E.; $n=6$) and the group with additional SC lesions had 87.0% (±5.9 S.E.; $n=6$) of their visual cortex ablated. In mice with visual cortex lesions 13.7% (±3.4 S.E.) and in the mice with additional SC lesions 12.2% (±1.8 S.E.) of the cortex surface area outside the visual cortex was damaged (see Fig. 1). Mice with sham lesions ($n=15$) had intact cortices. In mice with visual cortex lesions only, slight additional damage to one side of the SC was found in four animals. In the same group, incidental minor damage to the pretectum was found in one mouse. Thus, no mouse from the group with visual cortex lesions only had any noticeable damage to the dLGN (Fig. 2a). In all of the mice receiving additional lesions of the SC the optic fibres of the brachium were interrupted. In addition, the severing of the brachium resulted in shrinkage of the SC in all cases. In some cases damage to adjacent structures was also evident. Three out of the six mice from this group showed some unilateral damage to the pretectum and the dLGN (Fig. 2b and d), and one other mouse had bilateral damage of these regions (Fig. 2c).

3.2. Behavioral results

A repeated measures two-way ANOVA (Statistica) revealed significant differences of the surgical treatment ($P<0.0001$) as well as significant effects of the lighting level of the masking pulses ($P<0.0001$). Because data for four cells were missing, we also analyzed the results with the more conservative nonrepeated measures 2-way ANOVA. The results were essentially the same (2-way ANOVA, $P<0.0001$, i.e. the three experimental groups

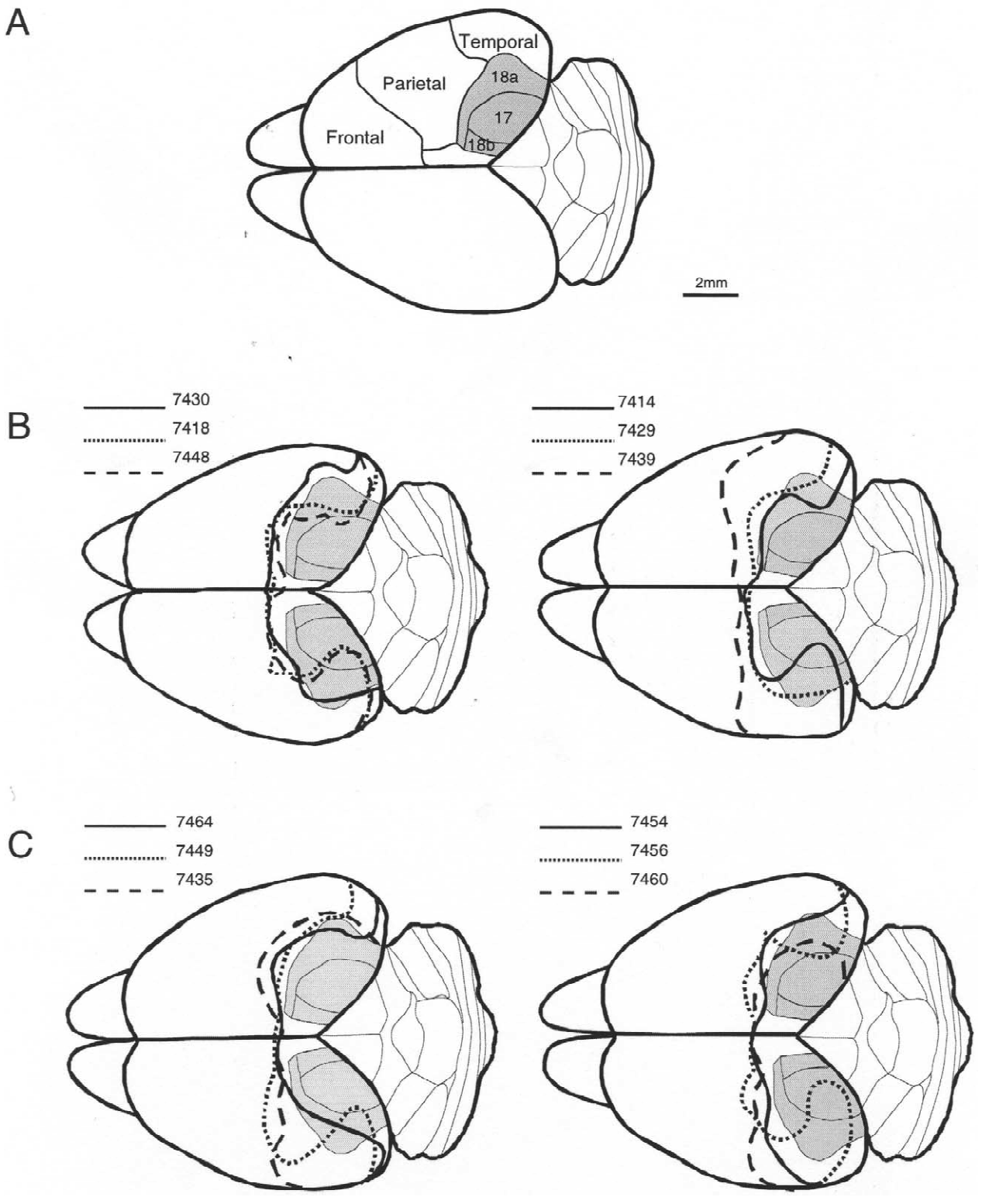

Fig. 1. Dorsal surface extent of cortical lesions. Lines show anterior border of damaged areas. (A) Visual cortex areas 17, 18a and 18b (shaded areas) in an intact mouse [1]. (B) Six mice with lesions almost restricted to the visual cortex. (C) Six mice with visual cortex lesions plus additional lesions (not illustrated here, but see Fig. 2) aimed at the brachium of the SC.

differed significantly). A posthoc Tukey's honest significant difference test for groups with different *n* values (out of a total of 132 datapoints 2 were lost in the visual cortex and 2 in the visual cortex+SC group) resulted in a significant difference between the sham-operated group and the visual cortex lesioned group ($P<0.01$). The sham

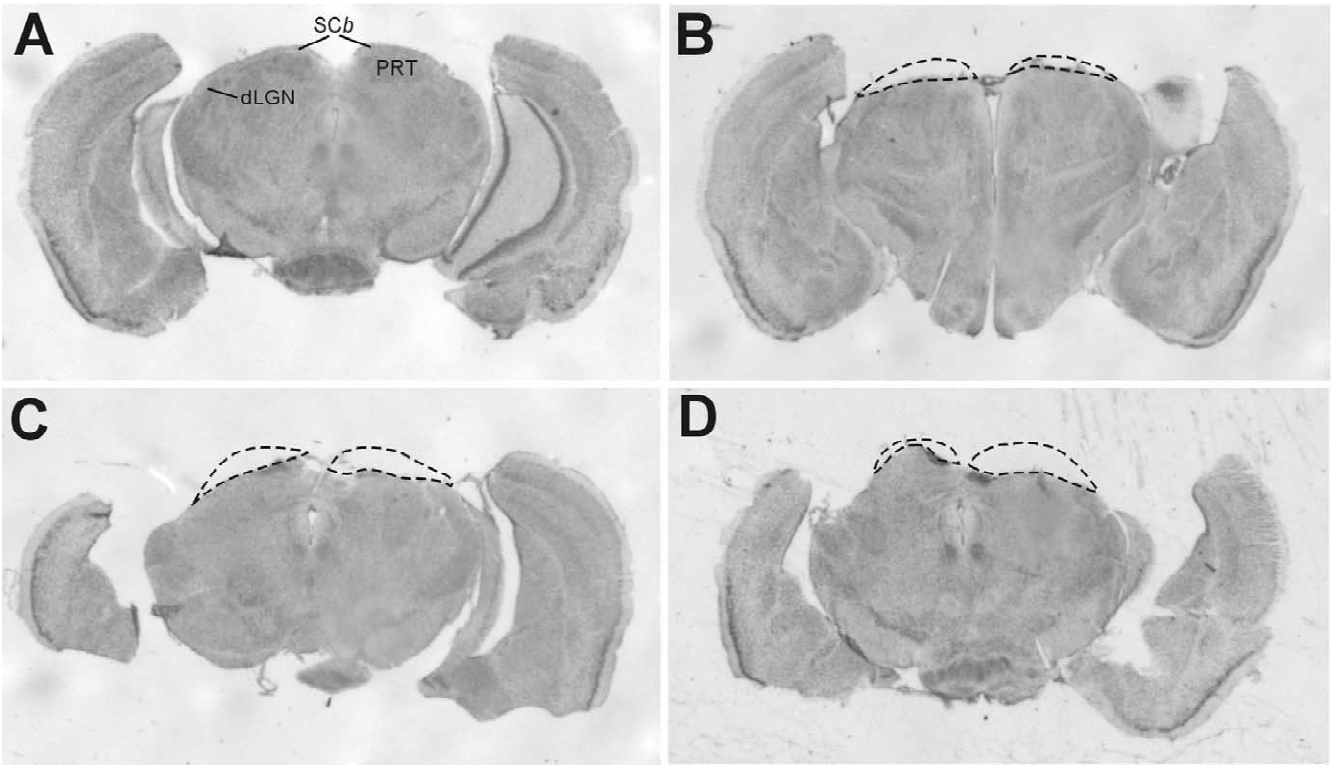

Fig. 2. Photographs of coronal sections illustrating lesions. (A) Mouse with visual cortex lesion. (B–D) Mice with both cortical and subcortical lesions, showing the variable extent of damage to the superior colliculus and incidental damage to other structures. (B) Damage to dLGN and PRT on left side. (C) Damage to dLGN on left and PRT bilaterally. (D) Damage to dLGN and PRT on right side.

group was also different from the group with additional SC lesions ($P<0.01$). No differences were found between the two groups with lesions ($P>0.9$). In conclusion, both lesion groups had a significantly enhanced masking response to the light pulses given (Fig. 4). All mice constricted their pupils when light was shone on the eyes at the end of the experiment.

A remarkable phenomenon occurred with some lesioned mice: a prolonged but paradoxical bout of running starting when the entraining lights came on (Fig. 3): it occurred in 2/6 of the mice with cortical ablations and in 2/6 of the mice with additional superior colliculus lesions. None of the 15 sham-operated animals had this pattern of activity.

4. Discussion

The results demonstrate that mice with visual cortex lesions or combined visual cortex and superior colliculus lesion showed a stronger reduction of their wheel running to light pulses than did sham-operated animals. This finding supports the view that the visual cortex influences the suppression of locomotor activity by light through a yet unidentified pathway.

Even though our lesion estimates based on brain atlas coordinates indicate that the visual cortex was not completely removed in all cases, it is obvious that the lesion extent was considerable. Furthermore, our finding of the enhanced masking response was not dependent on completeness of the lesions. Possible remaining input to the visual cortex after lesions was apparently not sufficient to prevent the effect of the lesion on masking.

Because a number of animals did not use the wheels sufficiently after the lesions, we cannot completely exclude the possibility that the lesion procedure resulted in selection of individuals with particular predispositions to mask. It is much more likely, however, that the nonspecific effects of the lesion and how well an animal recovered from the procedure were more or less random. Also, we could detect no tendency for animals that ran little to show greater suppression of activity to light. Therefore the greater response to light in the lesioned animals is unlikely to result from lowered activity levels. In the context of other studies finding enhanced masking after lesions of the visual system at the retinal and geniculate levels [3,16,17,23], the most plausible explanation is that in the present case the enhanced masking is produced by damage to the visual system.

It is also unlikely that a larger pupil size after the lesions was responsible for the enhanced masking. First, we know of no information suggesting that the cortex is important in the control of pupil size in rodents. Second, although the responses were not quantified, the pupils of all mice contracted when a light was shone on them.

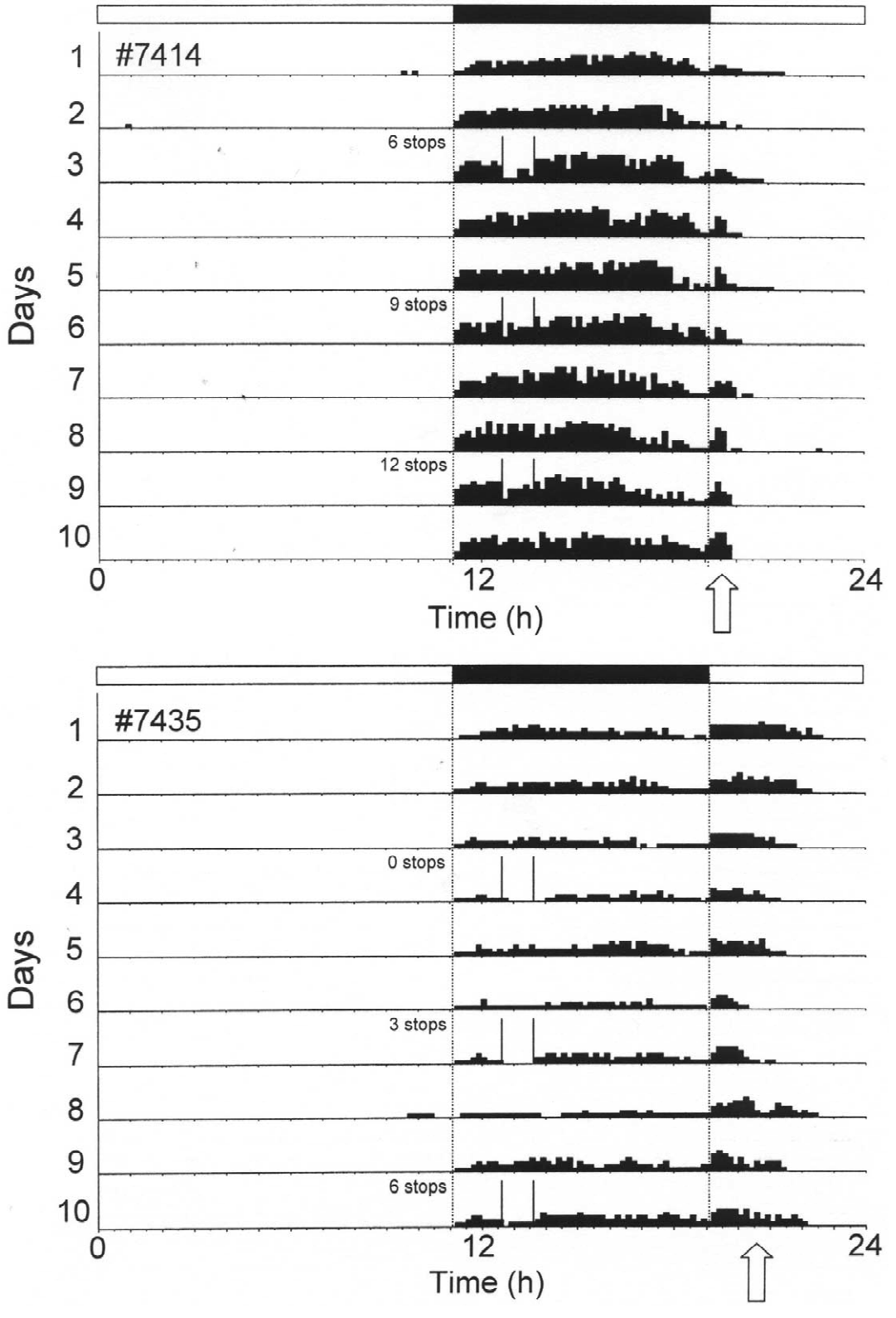

Fig. 3. Actograms showing the unusual pattern of wheel running during the masking tests by one mouse with cortical lesions (no. 7414) and another with cortical plus superior colliculus lesions (no. 7435). Open and solid bars at the top show light–dark cycle. Arrows at the bottom point to the enhanced activity bouts at light onset. Vertical lines show onset and offset of light pulses in the masking tests, with the corresponding stop levels. Each line of the actogram represents 1 day. Activity is plotted in 10-min bins in 15 quantiles, with the first including counts of 1–55 wheel turns/10 min, the second 56–110, etc.

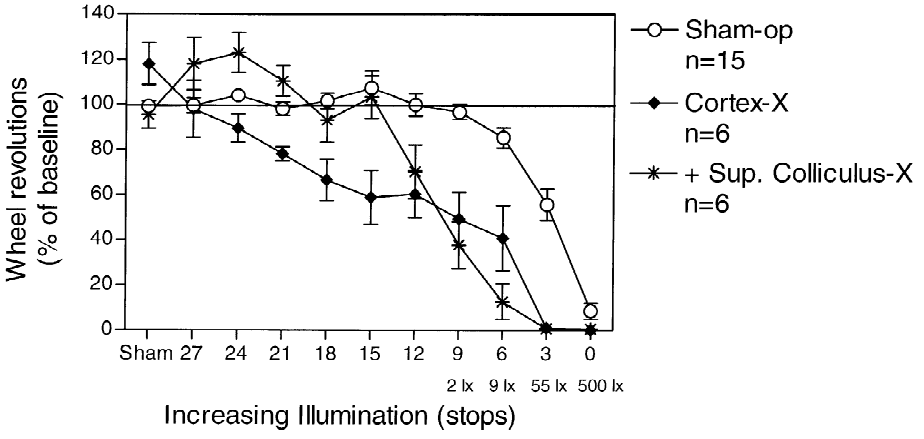

Fig. 4. Responses to light pulses. Masking scores are given in percentage of baseline activity, with 0% indicating complete suppression and 100% no change compared to baseline activity. Illumination is expressed by the number of stops of the neutral density filters introduced to diminish the light, lux levels are given for illumination in the measuring range of our light meter. Because of problems with microswitches, at 24 stops the baseline for one of the mice in the superior colliculus group comes from the day after the light pulse; the *n* value was only 5 for the 21-stop and sham pulse for the Cortex-X group and for the 6- and 9-stop pulse for the Superior Colliculus-X group.

With the inclusion of the present result, enhanced masking by light has now been found after damage to the visual system at three different levels: the retina, the thalamus, and the cortex. An enhanced response to light in an animal with extensive damage to its visual system can be understood if one distinguishes between a classical visual system for image perception and an irradiance detection system for telling night from day [19,10,2,14,8]. An additional assumption is necessary, that there is some interaction between these two systems [16,17]. Input to the classical visual system appears to inhibit the masking response to light which is mediated by the nonvisual irradiance detection system. Disruption of input to the classical thalamic and cortical systems evidently removes this inhibition and thus could result in enhanced masking.

The nature of this inhibition is not known but presumably depends on some corticofugal fibres projecting, directly or indirectly, to a brain area mediating masking. The visual cortex projects to almost all subcortical visual structures. Because both masking and clock resetting serve to confine activity to the night or the day, and because both require detection only of irradiance, initially it was thought possible that brain areas known to be important for biological rhythms, such as the suprachiasmatic nucleus (SCN) and the intergeniculate leaflet (IGL) might be involved in masking. Both these areas contain neurones that respond tonically to light, acting as dominance detectors [11,4] and are innervated by melanopsin containing cells in the retina [5].

However, in our studies with Syrian hamsters, lesioning the SCN or the IGL failed to abolish masking [22,23]. These results lead us to believe that the SCN or the IGL cannot be important masking areas unless masking by light involves redundant mechanisms. The present results provide additional information on brain areas that do not seem essential for masking: the visual cortex and the superior colliculus. In the case of the visual cortex, our lesions were extensive, destroying most of areas 17, 18a and 18b (Fig. 1). In the case of the additional SC lesions, these did not result in complete degeneration of this structure, but by cauterizing the brachium the optic fibres were interrupted in all the animals in the SC lesion group (Fig. 2).

Although the integrity of the SC and its retinal input does not seem necessary for masking, this area could modulate masking, rather than playing a primary role in mediating the response itself. Fibres from the SC project to the geniculate and the pretectum (PRT). The geniculate is not necessary for masking, since lesions here lead to enhanced masking, not a loss of masking [3,23]. If the PRT is important for masking, it might be inhibited either directly by the cortex, or indirectly via the SC. A possible role for the pretectum in masking of locomotor activity is particularly worth considering in view of the work of Miller et al. [12,13], who found that effects of light on sleep stages in rats were dependent on an intact pretectum. The pretectum was not a target for lesions in this study, but nevertheless accidental damage of this structure occurred in some animals. However, such damage was mostly unilateral and not extensive enough to permit conclusions on the function of the pretectum in masking.

A recent study [6] points to the hypothalamic subparaventricular zone (SPZ) as a masking center. After screening a hamster cDNA bank of SCN, the site of the circadian clock in mammals, they identified several novel factors secreted from the SCN. In a behavioral screen they subsequently identified transforming growth factor α (TGFα) as an inhibitor of locomotor activity. Furthermore, they found epidermal growth factor (EGF) receptors in the SPZ of the hypothalamus. TGFα is thought to act thought these receptors. Finally, they identified TGFα and EGF in

the retina. It seems possible that TGFα or EGF from retinal cells mediates masking in the SPZ. The SPZ is ideally located to integrate output from the SCN and photic information directly from the retina [7].

Further study of the function of the SPZ may also explain the enhanced masking seen after cortical lesions. Perhaps it might reveal a role for this structure in the surprising increased running in some animals when lights came on (Fig. 3). It should be emphasized that such bursts of activity occurred in light of 1300 lux, the level used for the entraining LD cycle, yet lower levels of illumination were effective in inhibiting activity when occurring in the 1-h test pulses given shortly after dark onset (Methods, Fig. 4). Bursts of activity at light onset have also been noted in the mutant mouse, wheels [21]. Perhaps this mutation affects some of the same systems as damaged by our lesions.

Much needs to be learned about simple behavioural responses to changes in illumination, such as the inhibition of locomotion. We are just beginning to learn about brain areas that are important for masking, e.g. the SPZ. The present study provides information on areas that influence the masking response. In particular, this study suggests that corticofugal fibres inhibit suppression of locomotion by light. Furthermore, this study supports the hypothesis that the suppression of locomotor activity by light in nocturnal rodents is not a function of the classical visual system, but is mediated by the recently described nonvisual photoreceptive system for detection of irradiance levels in the environment [8,5].

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