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Unequal Alternating Monocular Deprivation Causes Asymmetric Visual Fields in Cats

Abstract. *Kittens were reared so that each eye received normal patterned vision on alternate days. If the eyes received equal periods of stimulation, the visual fields were normal. If one eye received much more experience than the other, the field of the less experienced eye was restricted to the temporal hemifield. This change, which differs from that observed when one or both eyes are deprived continuously of patterned input, suggests that an imbalance in the duration of stimulation can influence the outcome of the normal competitive interaction between pathways from the two eyes and can cause a selective suppression of a portion of the input from the less experienced eye. This suppression may involve the ipsilateral retino-geniculo-cortical pathways or it may involve the entire cortical pathway from the less experienced eye, leaving the colliculus to control responses to visual targets.*

Binocular competition almost certainly occurs during the normal development of the visual pathways of higher mammals. Competition is easy to demonstrate, however, only when the stimulation to the two eyes is unbalanced. In experiments in which this imbalance is created by depriving one eye of all patterned input [monocular deprivation (MD)] (*1*), the effects of competition are difficult to separate from those of deprivation. We felt that competition could be more readily studied if the imbalance to the two eyes could be created without continuous deprivation of either eye (*2, 3*). Kittens were therefore reared by presenting each eye with patterned visual input but on alternate days and for different periods of time [unequal alternating monocular deprivation (AMD)]. This manipulation resulted in a striking behavioral asymmetry: the visual field of the less experienced eye was restricted. This asymmetry suggests that a difference in the duration of patterned visual stimulation is sufficient to place one eye at a competitive advantage. A difference in the quality of visual stimulation is not required. The pattern of the visual field deficit seen in cats with unequal AMD is different from those seen previously in MD or binocularly deprived (BD) cats (*4*) and suggests that either (i) the ipsilateral visual pathway is more susceptible to the effects of competition or (ii) competition can suppress the entire geniculo-cortical pathway from one eye.

Kittens were reared in the dark from 3 days to 4 weeks of age, when they were brought out into the light for daily periods of exposure with one eye occluded. For the four experimental animals, the right eye was exposed for 8 hours and, on alternate days, the left eye for 1 hour (AMD 8/1). Six control animals were exposed for equal periods with each eye: two of the animals for 8 hours (AMD 8/8) and four animals for 1 hour (AMD 1/1). Four normally reared cats served as additional control subjects.

Beginning at 2 months of age, the animals were tested for their ability to orient to targets in the visual field (*4*). Animals were taught to fixate on a target (a piece of food on a wire) presented straight ahead at a distance of 40 cm. A novel stimulus (a piece of food on another wire) was introduced at a distance of 20 cm along one of the guidelines, which were placed every 15° to the left or right of the fixation line (0°). A positive response was recorded when, upon being released, a cat turned and immediately approached the novel stimulus. A negative response was recorded if the cat approached the fixation object or if it scanned the field before approaching the novel stimulus (*5*). The novel stimulus was presented at each of 15 positions from 105° left to 105° right except at 0°. For the trials at 0°, only the fixation object was presented. On these trials, failure to directly approach the fixation object was scored as a negative response, and the number of these responses was used as an indication of the background level of nonspecific responses for the other trials. The order in which the trials were presented was determined by a table of random permutations. Each animal was tested monocularly with each eye 12 times at each position.

The visual field of each eye of a normal cat extends 120°, from 90° temporal to 30° nasal (Fig. 1). In control cats given equal periods of stimulation to the two eyes (AMD 8/8 and AMD 1/1), the visual fields for each eye were normal and of equal size (Fig. 1). In contrast, in all cats given unequal periods of stimulation to the two eyes (AMD 8/1), the visual fields for the two eyes were of unequal size (Fig. 1). The visual field of the 8-hour eye was normal. However, the visual field of the 1-hour eye of each of these animals was restricted to the temporal hemifield and extended from 90° temporal to the midline (*6*). None of these cats ever responded to a target in the nasal field of the 1-hour eye. The loss of responses in the nasal field was striking when compared with the responses of the 8-hour eye or to those of any of the cats receiving equal exposure to the two eyes. In particular, the AMD 8/1 cats made fewer responses with the left eye to targets at 15° and 30° nasal than did the AMD 1/1 cats, which had received the same length of exposure with the corresponding eye [t (6) = 11.7, $P < .001$, two-tailed]. Further, the AMD 8/1 cats showed a slight, but significant, reduction in responsiveness to targets presented at the temporal margin of the field of the 1-hour eye. Specifically, the AMD 8/1 cats made fewer responses with the left eye to targets presented at 90° temporal than did the AMD 1/1 cats [t (6) = 3.3, $P < .02$, two-tailed]. Thus, unequal periods of stimulation to the two eyes result in asymmetric visual fields. Since both eyes of the AMD 1/1 cats show normal fields, even though neither eye received any

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more exposure than the 1-hour eye of the AMD 8/1 cats, the restriction of the field of the 1-hour eye of AMD 8/1 cats cannot be due to a lack of visual experience (*7*) but must result from the imbalance in the duration of stimulation to the two eyes.

The visual fields of an MD cat are asymmetric and resemble those of an AMD 8/1 cat in three ways: (i) the field of the more experienced eye is normal, (ii) the field of the less experienced eye is restricted to the temporal hemifield, and (iii) the responsiveness at 90° temporal in the less experienced eye is reduced (*4, 8*). The pattern of responses to stimuli within the temporal hemifield of the less experienced eye differs, however. An MD cat responds to stimuli in the monocular segment where competition cannot occur, but responds rarely to stimuli presented within the binocular segment of the temporal hemifield (between 0° and 30° temporal) (*4, 8*), whereas an AMD 8/1 cat always responds to stimuli within the binocular portion of the temporal hemifield. The visual field changes resulting from unequal AMD thus differ from those produced by monocular deprivation.

This difference in the perimetry of AMD 8/1 and MD cats is unexpected. If the imbalance in stimulation has placed the 1-hour eye at a competitive disadvantage, it should be at the same disadvantage throughout the binocular segment. Thus, if competition has caused the 1-hour eye to lose control over visually guided behavior in any part of the visual field, it should lose control throughout the binocular segment, as does the deprived eye in MD cats. Since the main difference between MD and unequal AMD is that, in unequal AMD, both eyes receive some exposure to patterned light, our results suggest that providing patterned visual exposure to the disadvantaged eye permits the development or maintenance of those pathways that control visually guided behavior in the binocular segment of the temporal hemifield.

Either the retino-collicular pathway or the retino-geniculo-cortical pathway can control orientation to visual targets (*9*), and the locus of this control depends upon the early visual experience of the animal (*10, 11*). In normal adult cats, collicular lesions do not disrupt orientation to visual targets, whereas extensive cortical lesions render the animals blind (*9*). This blindness can be reversed by cutting the collicular commissures or by removing the superior colliculus on one side. The responses restored by these procedures are confined, however, to the temporal hemifield (*9*), and the visual fields resemble those of a BD cat (*4, 7*). In BD cats, extensive lesions of the cortex do not disrupt responses to visual targets, but collicular lesions do (*10*). Thus, while the visually guided behavior of normal adult cats is controlled by the cortex, the behavior of BD cats is controlled by the colliculus.

The asymmetry of the visual fields of the two eyes of the AMD 8/1 cats may reflect a division of control between cortex and colliculus. Except for the level of responsiveness, the visual field of the 1-hour eye of an AMD 8/1 cat resembles that controlled by the retino-collicular pathway, whereas the visual field of the 8-hour eye resembles that normally controlled by the retino-geniculo-cortical pathway. Thus, the 8-hour eye may be under cortical control and the 1-hour eye under collicular control.

The possibility that the control of visually guided behavior is split between the cortex and the colliculus suggests a novel role for competition: all of the retino-geniculo-cortical pathway from the 1-hour eye must have been suppressed, rather than, as in MD cats, the binocular segment alone. Yet this suppression must have resulted from competition. The cortex controls the visually guided behavior of both eyes of the AMD 1/1 and AMD 8/8 cats because their visual fields extend into the nasal hemifield. The possibility that competition might lead to the suppression of both the monocular and binocular segments of the retino-geniculo-cortical pathway has not, to our knowledge, previously been suggested.

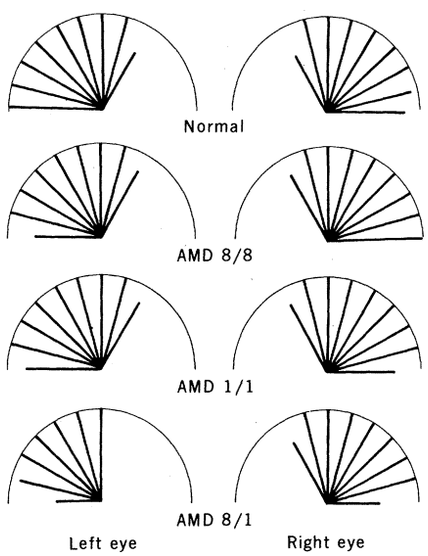

Fig. 1. Visual fields for the left and right eyes of cats in the different experimental groups. The visual fields are represented by polar plots showing the responses to stimuli presented at every 15° of the visual field. The semicircle represents a level of 12 positive responses in 12 trials. The data shown are averaged across all cats in each condition. The fields of the normal cats are shown in the top row. The next two rows show the fields for the cats reared with equal AMD. The fields of both eyes of these cats are similar to those of the normal cats. In the last row are shown the visual fields for the 8-hour (right) and 1-hour (left) eyes of the AMD 8/1 cats. With the more experienced, 8-hour eye, these cats exhibited a normal visual field. With the less experienced, 1-hour eye, they responded only to targets in the temporal hemifield.

An alternative to this division of control between the cortex and colliculus is that the cortex may control the behavior of both eyes of the AMD 8/1 cat but that the ipsilateral connections from the 1-hour eye are not functional. We favor this alternative for two reasons. (i) Providing patterned visual experience to either eye, as in MD cats, appears to be sufficient to permit the cortex to control orientation to visual targets with both eyes (*11*); it is therefore unlikely that the cortex would not control the behavior of both eyes when both eyes have received patterned input during development. (ii) There is considerable evidence that the phylogenetically newer, ipsilateral pathway is more sensitive to the effects of competition than the contralateral one (*12*). Such a differential sensitivity to the effects of competition would result if patterned visual stimulation were required for the development or maintenance of the retino-geniculo-cortical pathways and if the contralateral pathway had some inherent advantage over the ipsilateral pathway. When neither eye received patterned input, neither pathway would function, and the colliculus would control orientation to visual targets, as it does in BD cats (*10*). When the eyes received limited but equal patterned inputs, as in AMD 1/1, both the ipsilateral and contralateral pathways would develop, so that the animal would orient to targets in both the nasal and temporal fields. When the eyes received unequal patterned inputs, there would be advantages for both the contralateral eye and the eye receiving more exposure. A large imbalance in the stimulation of the two eyes, as in MD cats, would be sufficient to offset the contralateral advantage, so that the MD cat would fail to detect targets in the binocular segment of the temporal hemifield of its deprived eye. The lesser imbalance of unequal AMD would not be sufficient to prevent the development of the inherently stronger contralateral pathway from the less experienced eye, and, thus, the AMD 8/1 cat would respond to targets in the binocular segment of the temporal hemifield with its 1-hour eye. The ipsilateral pathway from the 1-hour eye would not develop,

however, because it would be competing against a contralateral pathway with the added advantage of more patterned stimulation.

A knowledge of the mechanisms underlying the visual field deficit of the less experienced eye may help us understand the basis of a similar deficit seen in certain amblyopic human patients, in whom responsiveness to stimuli in the nasal visual field is reduced relative to responsiveness to stimuli in the temporal visual field (*13*).

NINA TUMOSA
SUZANNAH BLISS TIEMAN
HELMUT V. B. HIRSCH
Neurobiology Research Center,
State University of New York,
Albany 12222

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7. The visual field of the 1-hour eye resembles the visual fields of a BD cat in two respects. (i) The fields of BD cats are restricted to the temporal hemifield. (ii) The BD cats show a relative reduction in responsiveness to targets presented at 90° (*4*). However, BD cats respond at reduced levels throughout their visual fields, whereas the AMD 8/1's responded normally throughout the temporal hemifield except at 90°.
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Rebound Insomnia

Kales *et al.* (*1*) recently presented evidence for rebound insomnia, a "worsening of sleep" occurring subsequent to the withdrawal of three benzodiazepine hypnotics—flunitrazepam, nitrazepam, and triazolam. The report by Kales *et al.* raised an important question: Is rebound insomnia a consideration that would preclude the use of these three benzodiazepines, and possibly others, in the symptomatic relief of insomnia?

In addition to the six sleep laboratory studies cited by Kales *et al.* (*2-4*), at least nine additional sleep laboratory studies of flunitrazepam, nitrazepam, and triazolam in both normal and insomniac populations have included a baseline, drug, and withdrawal period (*5-7*). In none of this additional literature are the three objective parameters used by Kales *et al.* to define rebound insomnia—sleep latency, number of awakenings, or wakefulness after sleep onset—significantly elevated above the baseline during drug withdrawal. These studies, which used drug administration periods ranging from 2 (*5*) to 21 (*6*) days, raise the question of whether rebound insomnia may be considered a generalized phenomenon occurring after short- and intermediate- as well as long-term periods. Furthermore, even within a single study, the generalizability of rebound insomnia is at issue. Bixler *et al.* (*3*) found that withdrawal of 1 mg of flunitrazepam produced a significant increase in sleep latency and wakefulness after sleep onset, but withdrawal of a 2-mg dose did not produce these changes. Also, within a single study, sleep parameters do not consistently demonstrate exacerbation of the insomnia during drug withdrawal. For example, Roth *et al.* (*4*) showed a significant increase above the baseline during the withdrawal period in the percentage of total time spent awake but not in sleep latency, number of awakenings, or minutes of wakefulness occurring during the sleep period.

Additionally, the mechanism of rebound insomnia must be reconsidered. Kales *et al.* attributed rebound insomnia to a "lag in the production and replacement of endogenous benzodiazepine-like compounds" (*1*, p. 1040), which is a consequence of the short action of flunitrazepam, nitrazepam, and triazolam. There are, however, major differences in the half-lives of these three compounds. Triazolam has a half-life of 4 to 5 hours (*8*), whereas nitrazepam has a half-life of about 30 hours (*9*). Other short-acting benzodiazapines—for example, temazepam, which has a half-life of 8 to 10 hours (*10*)—also do not cause drug-withdrawal insomnia (*11*).

The report by Kales *et al* has drawn our attention to a potentially important clinical phenomenon which has direct implications for the physician who prescribes drugs for the symptomatic relief of insomnia. More complete data are needed, however, before either the generalizability or specificity of rebound insomnia can be determined. Issues that must be considered include the type of insomniacs who exhibit rebound insomnia, the severity of the insomnia before the drug was prescribed, the specificity of drug-withdrawal insomnia to different drug classes, the relationship between rebound insomnia and drug half-lives, and the critical duration of drug administration necessary to produce rebound insomnia upon withdrawal.

KRISTYNA M. HARTSE
THOMAS ROTH
PAUL M. PICCIONE
FRANK J. ZORICK
Sleep Disorders and Research Center,
Henry Ford Hospital,
Detroit, Michigan 48202

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