

Electrophysiological Evidence that Abnormal Early Visual Experience Can Modify the Human Brain

Abstract. *Visual resolution in humans is nearly equal for vertically and horizontally oriented detail, but for some subjects there is a substantial difference in resolving power for these orientations. Although subjects who exhibit this difference invariably have ocular astigmatism, optical explanations of the effect can be ruled out. Direct evidence has been found for an electrophysiological correlate to the psychophysical finding. Subjects who have reduced resolution for a pattern of a particular orientation also show a decreased evoked potential response elicited by a target of the same orientation. The results are consistent with the hypothesis that a deficiency of specific features in the early visual input can alter the organization of the visual pathways.*

The absence of visual form during early stages of development of the nervous system can have profound physiological, anatomical, and behavioral consequences (1, 2). Furthermore, recent studies demonstrate that the effects of deprivation can be both predictable and well circumscribed. Kittens raised in an environment consisting entirely of vertical or horizontal contours adjust their neural circuitry to the orientation of visual exposure (3). Following the rearing periods, the adjustment is manifested both behaviorally and physiologically with respect to the receptive field organizations of cortical neurons. The cells appear to be tuned to the orientation they have experienced. Additional evidence of specific neural alteration to an imposed abnormal visual input has been found in kittens raised with prisms that created vertical disparities (4).

Visual exposure biased toward a particular orientation, as in the animal studies mentioned above, occurs in some humans as a result of ocular astigmatism. An astigmatic eye has a continuously varying refractive power in different meridians so that every point in object space is imaged as two mutually perpendicular focal lines. The focal lines are typically formed in vertical and horizontal planes, and they are separated by a distance determined by the magnitude of astigmatism. In certain cases, a particular focal line will be relatively distant from the retina. Consequently, contours of a specific orientation will be blurred. If the astigmatism is present during early years, the lack of exposure to well-defined stimuli of this orientation could readily affect neuronal maturation, and higher centers could be imprinted to favor detail imaged at different orientations. Thus, there is the unique opportunity to look for limited and specific neural changes arising from abnormal visual input in the human visual system.

Results compatible with the notion of selective neuronal modification to an astigmatic visual world have been presented by Freeman and co-workers (5, 6). They found that certain subjects exhibit pronounced differences in their abilities to resolve vertical and horizontal detail. Although, without exception, the subjects have considerable ocular astigmatism, these differences cannot be of optical origin because the refractive errors have been completely neutralized with lenses. Moreover, the resolution asymmetries persist when the subjects are tested by a method in which optical influences are obviated (7).

In this report, we present evidence that there is a measurable neurophysiological correlate to the psychophysical finding. Subjects who have the dissimilarities in meridional resolution described above also have corresponding differences in a component of the brain's electrical activity. We have made electrophysiological observations (visual evoked potential) and psychophysical observations (grating resolution) on subjects who viewed a pattern oriented horizontally, vertically, or obliquely. In the subjects who show a reduction in resolution for horizontal or vertical patterns, there is also a diminished evoked response to a stimulus of the same orientation. The results locate the visual asymmetry at or before the site of origin of the evoked potential.

For the evoked potential experiments, subjects binocularly fixated the center of a grating whose bright and dark bars were alternated, that is, phase shifted through 180°, at a temporal frequency of 10 hertz (8). To avoid time-locked artifacts control trials were performed during which the target was not viewed. Evoked potentials from a standard electrode configuration were recorded on tape, and power spectra were derived by computer analysis. The index we used was the signal power at the second

harmonic of temporal stimulation (9).

Psychophysical data were obtained by using sinusoidal gratings generated on the face of an oscilloscope (10). At a fixed contrast the maximum resolvable number of cycles per unit visual angle was determined binocularly for horizontal, vertical, and oblique orientations.

Figure 1 contains photocopies of the power spectra, printed out by the computer, to illustrate the evoked potential data. The results for a nonastigmatic subject (PT) and an optically corrected astigmatic subject (DA) are shown in the left and right columns, respectively. The spectra at the top are for the control condition, during which the subject observes a blank field. Each of the other spectra is the response to the target orientation indicated between the columns. For every spectrum, the stimulation frequency and its second harmonic are shown by arrows.

The results for the evoked potential and the resolution capacity, expressed in normalized form, are presented in Fig. 2 (11). The findings at the top are for the same nonastigmatic subject shown in Fig. 1. The reduction for the oblique orientation ($\pm 45^\circ$ from vertical) is well established psychophysically (7), and it provides confirmation of the results of other evoked potential studies (12). Immediately below, data are shown for the same subject PT. Only here, she viewed the stimuli through a cylindrical lens that had a minimal effect on the horizontal meridian but caused extensive blur in the vertical meridian. So a condition of ocular astigmatism was simulated. Correspondingly, the amplitude of the evoked potential and the visual resolution are both substantially reduced. This agrees with the results of other investigations of the evoked potential and ocular refractive state (13). Subjects DA and AD have equal bilateral astigmatism of 3.5 and 3.0 diopters, respectively. Carefully determined ophthalmic lens corrections were used for the experiments. Nevertheless, the results for vertical and horizontal orientations are very different. For subject DA, also shown in Fig. 1, there is a clear depression for vertical stimuli. For subject AD it is just the reverse. In each case, the reduced sensitivities correspond to the orientation which, when optically uncorrected, would be considerably defocused.

The results shown in Fig. 2 have been confirmed with other subjects. Individuals with negligible astigmatism

do not have significant vertical-horizontal differences. But astigmatic subjects who exhibit marked meridional resolution asymmetries also have corresponding asymmetries in the evoked potential. Moreover, the differences are always ordered in that the meridian with reduced sensitivity has the maximum blur in the absence of corrective lenses. This fulfills an important prediction of the idea that early discordant visual input causes matching physiological alterations in the visual pathways (14). If it is assumed that the astigmatism is present when the visual system is especially vulnerable to the nature of its input (15), these results

support the view that ocular astigmatism can cause selective visual deprivation with concomitant neural changes that are specific and lasting (16).

Our evoked potential results constitute direct electrophysiological evidence of a neuronal correlate to meridional resolution differences. The position that limited deprivation is indeed the causative agent resulting in the evoked potential asymmetries has support from other studies. Wiesel and Hubel (1) found a highly abnormal evoked potential response from a kitten eye deprived of vision. An abnormally depressed evoked response has also been reported in children with reduced resolution attributed

to visual disuse or prolonged suppression (17).

Now it is relevant to consider the possible physiological processes that can be invoked to account for the selectively diminished psychophysical and electrophysiological responses. There are, a priori, two plausible explanations. Cells intended to process information received from the deprived meridian become "dropouts" and atrophy. Or, cells originally intended for that plane are converted and become tuned to the meridian receiving clearly imaged stimuli. The question is, of course, not easy to deal with in the case of humans. But the available evi-

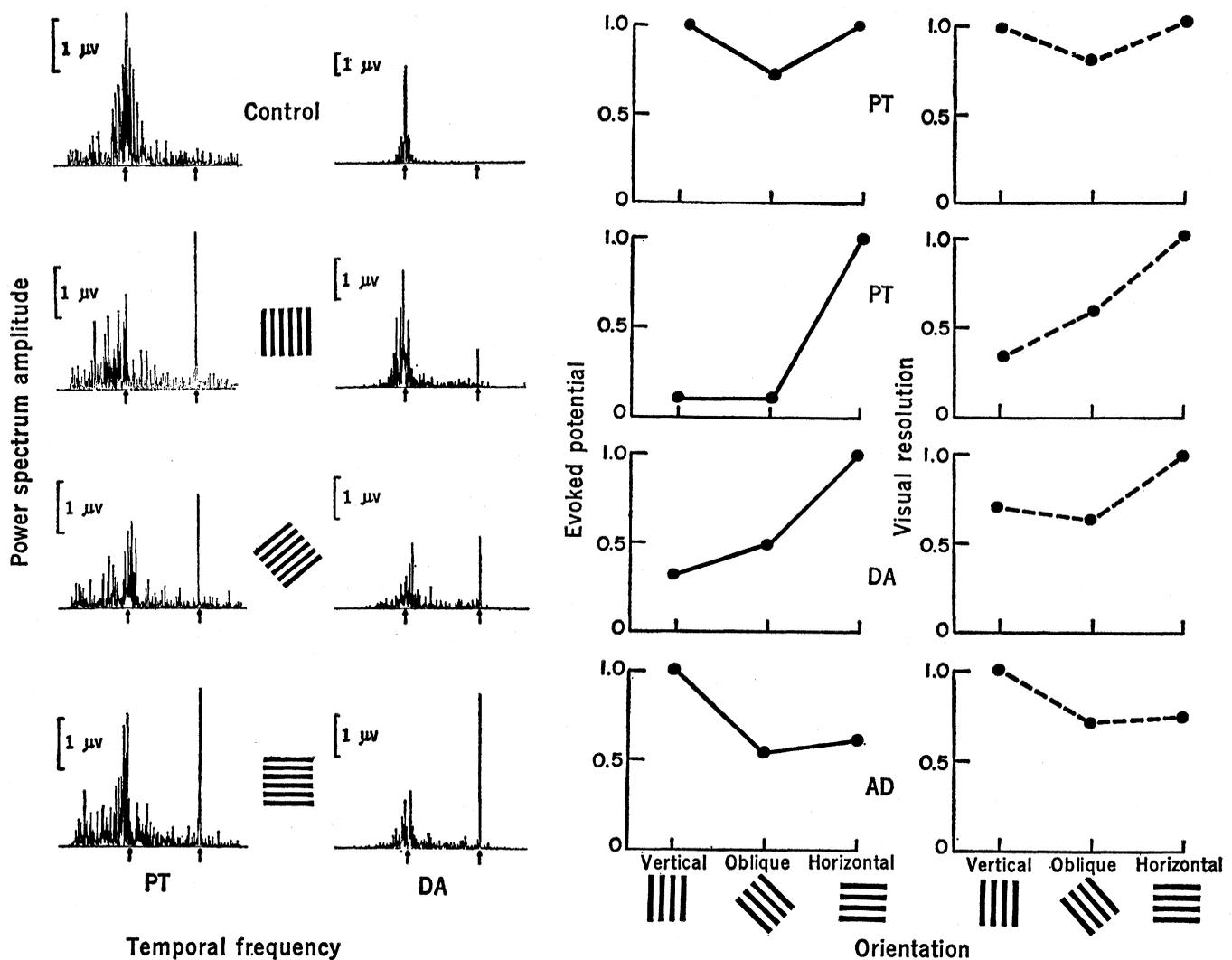


Fig. 1 (left). Power spectra of evoked potential responses. The raw data were recorded on tape, and a computer program was used to analyze the data into Fourier components, which were synthesized into power spectra. The data shown are photocopies of spectra plotted by computer. The column on the left gives results for a nonastigmatic subject (PT), and the one on the right is for a subject (DA) with marked astigmatism that is corrected with ophthalmic lenses. During the control experiment the subjects viewed a blank field. The other responses refer to the target orientation indicated. From left to right, the first arrow of every spectrum is placed at the stimulation frequency (10 hertz) and the second is positioned at the second harmonic of stimulation (twice the first frequency). The calibration insets show the power spectrum amplitude for 1- μ V (root-mean-square) sine wave. Fig. 2 (right). Electrophysiological and psychophysical sensitivities (ordinates) for gratings of horizontal, vertical, and oblique orientations (abscissas). The normalized values are computed by dividing each result by the maximum (11). The data at the top are for the nonastigmatic subject, PT, shown also in Fig. 1. In the results shown just below, subject PT is made artificially astigmatic, which has the effect of blurring vertically oriented detail. The findings for DA are also given in Fig. 1. Subjects DA and AD have substantial astigmatism, which is fully corrected optically. But they have depressed sensitivities for vertical and horizontal orientations, respectively. The orientation-sensitivity profiles show a clear correlation between the psychophysical and electrophysiological data.

dence based on animal studies favors the latter supposition. In deprived kittens, cortical columns do not seem to be "missing," and unusual cells are found which are not encountered in normal animals (3). Finally, experiments with kittens demonstrate that, during the sensitive period, single cortical neurons can selectively modify their responses after short periods of exposure to a particular stimulus (18).

If, in our astigmatic subjects, there were a recruitment of available cells to process detail of a given orientation, one might expect sensitivities greater than normal for that orientation. We find no evidence of such supersensitivity in our results. But normal human resolution approaches the limits imposed by the wave nature of light and the grain of the retina, and it therefore may be difficult or impossible to improve resolution by altering neural connections.

RALPH D. FREEMAN
LARRY N. THIBOS

School of Optometry,
University of California,
Berkeley 94720

References and Notes

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4. R. Shlaer [*Science* **173**, 638 (1971)] found a definite shift in the distribution of disparities that were most effective in stimulating binocularly driven cortical neurons.
5. R. D. Freeman, D. E. Mitchell, M. Millodot, *Science* **175**, 1384 (1972).
6. A detailed account and additional data are given in D. E. Mitchell, R. D. Freeman, M. Millodot, G. Haegerstrom, *Vision Res.*, in press.
7. An interference fringe pattern is formed directly on the retina by imaging two coherent point sources, filtered from a laser beam, in the plane of the eye's pupil. For details, see F. W. Campbell, J. J. Kulikowski, J. Levinson, *J. Physiol.* **187**, 427 (1966); D. E. Mitchell, R. D. Freeman, G. Westheimer, *J. Opt. Soc. Amer.* **57**, 246 (1967); D. G. Green and M. M. Cohen, *Trans. Amer. Acad. Ophthalmol. Otolaryngol.* **75**, 629 (1971).
8. The grating was of high contrast, subtended 5° by 6° and had a spatial frequency of 6 cycles per degree and a luminance of 75 cd/m².
9. For each stimulus presentation of 20 seconds, 1000 data points were analyzed by a Digital Equipment Corporation PDP-8 computer to obtain a power spectrum. The standard error of the evoked potential measurements is less than 10 percent as determined by procedures outlined by J. S. Bendat and A. G. Piersol [*Random Data: Analysis and Measurement Procedures* (Interscience, New York, 1971)]. A detailed description of the data measurement and analytic procedures will be given elsewhere (L. N. Thibos, in preparation). Our techniques are similar to those described by D. Regan [*Evoked Potentials in Psychology, Sensory Physiology, and Clinical Medicine*

(Chapman and Hall, London, 1972)] and N. W. Perry, D. G. Childers, J. C. Falgout [*Science* **177**, 813 (1972)].

10. A detailed description of the basic techniques can be found in F. W. Campbell and D. G. Green, *J. Physiol.* **181**, 576 (1965). The oscilloscope screen had an annular mask that limited the field to 2°. Contrast was 0.65 and screen luminance was 22 cd/m². Five or more determinations were made at each orientation. The standard error of the mean setting is of the order of 1.3 cycles per degree.
11. The normalized values in Fig. 2 are obtained by dividing each value by the maximum. For the evoked potential results, the maximum values, in microvolts (root-mean-square) from PT through AD are 3.14, 2.32, 3.75, and 2.27, respectively. The maximum visual resolution values, in cycles per degree, from PT through AD are 34, 29, 30, and 27.5, respectively.
12. Maffei and Campbell have found that over a wide range of contrast, the amplitude of the evoked potential is greater for vertical and horizontal than for oblique grating orientations [L. Maffei and F. W. Campbell, *Science* **167**, 386 (1970); F. W. Campbell and L. Maffei, *J. Physiol.* **207**, 635 (1970)].
13. M. Millodot and L. A. Riggs, *Arch. Ophthalmol.* **84**, 272 (1970); R. M. Harter and C. T. White, *Vision Res.* **8**, 701 (1968).
14. A likely location for these changes is at the level of cortical binocular cells or beyond [see (12)].
15. Evidently, a complex nervous system cannot develop to functional perfection solely through genetic control. There must be a period of plasticity during which the animal's experience helps to determine the connections of its neural network. Although not established in humans, a critical period of susceptibility to visual deprivation has been shown experimentally in cats and monkeys [D. H. Hubel and T. N. Wiesel, *J. Physiol.* **206**, 419 (1970); G. K. von Noorden, J. E. Dowling, D. C. Ferguson, *Arch. Ophthalmol.* **84**, 206 (1970)]. The case for astigmatically caused deprivation requires the condition to be present during the critical period. The available clinical evidence indicates that in cases of high astigmatism the condition is very likely to be present at birth and remain essentially unaltered into adulthood [S. Duke-Elder, *The Practice of Refraction* (Mosby, St. Louis, 1969), p. 94; M. Hirsch, in *Vision of Children*, M. Hirsch and R. Wick, Eds. (Chilton, Philadelphia, 1963), pp. 145-172; M. Hirsch, in preparation]. Our subjects who show vertical-horizontal orientation differences were optically uncorrected throughout childhood. It is not common to find individuals who have received ophthalmic lens corrections at a very early age. Two subjects we have examined so far, who were corrected at 2 and 3 years of age, respectively, showed no orientation effects in spite of considerable astigmatism.
16. It appears that the effects are permanent since they are present in individuals who have used optimal corrective lenses for a number of years.
17. C. T. Lombroso, F. H. Duffy, R. M. Robb, *Electroencephalogr. Clin. Neurophysiol.* **27**, 238 (1969).
18. J. D. Pettigrew and H. B. Barlow, in preparation.

16 November 1972

Retrograde State Dependent Learning

Abstract. *Sodium pentobarbital administered intravenously after acquisition in a one-trial passive avoidance task results in state dependent (drug dissociated) learning in male albino rats. Findings have methodological implications for drug-based research and theoretical implications for drug discrimination studies. Predictions based on a stimulus generalization hypothesis are not supported, whereas those based on an information storage hypothesis are supported.*

State dependent learning can be demonstrated with a variety of drugs in a wide range of tasks, including one-trial passive avoidance conditioning (1). The basic state dependent learning paradigm utilizes four groups: (i) group D-D is trained in a drugged state (D) and tested for retention in the same drugged state, (ii) group ND-ND is trained in a nondrugged state (ND) and tested for retention in a nondrugged state, (iii) group D-ND is trained in a drugged state and tested in a nondrugged state, and (iv) group ND-D

is trained in a nondrugged state and tested in a drugged state. Groups D-D and ND-ND show transfer of training from acquisition to retention testing, whereas groups D-ND and ND-D do not. Transfer of training occurs only when the drug states are the same in acquisition and test.

Two hypotheses have been advanced to explain state dependent learning (1). (i) The stimulus hypothesis suggests that a drug affects perception of the stimulus complex during the acquisition of a task. Thus, if the drug state during

Table 1. Summary of group comparisons with the use of Scheffe's "S," indicating significant ($P < .05$) and nonsignificant (NS) differences; D, drugged state; ND, nondrugged state; and C, control.

Group	D-D	ND-ND	D-ND	ND-D	C	D-D and ND-ND	D-ND and ND-D	D-ND and ND-D and C
D-D	—	NS	.05	.05	.05	—	.05	.05
ND-ND		—	.05	.05	.05	—	.05	.05
D-ND			—	NS	NS	.05	—	—
ND-D				—	NS	.05	—	—
C					—	.05	.05	—
D-D and ND-ND						—	.05	.05