inwardly rectifying K^+ current. Rod horizontal cells are larger with a flatter soma composed of three to five broad, radiating parts. Rod horizontal cells have a passive resistance of 6 to 10 Gohm. They have a simpler mixture of voltage-activated currents and lack both the voltage-dependent Na^+ current and the inward rectifier.
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Blockade of "NMDA" Receptors Disrupts Experience-Dependent Plasticity of Kitten Striate Cortex

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Intracortical infusion of the "*N*-methyl-D-aspartate" (NMDA) receptor blocker D,L-2-amino-5-phosphonovaleric acid (APV) renders kitten striate cortex resistant to the effects of monocular deprivation. In addition, 1 week of continuous APV treatment (50 nanomoles per hour) produces a striking loss of orientation selectivity in area 17. These data support the hypothesis that crucial variables for the expression of activity-dependent synaptic modifications are a critical level of postsynaptic activation and calcium entry through ion channels linked to NMDA receptors.

AT THE TIME OF FIRST EYE OPENING in the newborn cat, most cells in kitten striate cortex are responsive to visual stimulation through either eye (*1*). During a critical period of development (the second and third months after birth in cats) these binocular connections are readily modified by visual experience (*2*). For example, a week of monocular deprivation during the critical period leaves few neurons in visual cortex responsive to stimulation of the deprived eye. This decrease in synaptic efficacy has been attributed to competition between the afferents from the two eyes, and it appears that the activation of cortical neurons is one necessary condition for such modifications to occur (*3*). However, the postsynaptic depolarization required for experience-dependent modification apparently differs from the activation threshold of Na^+-dependent soma spikes: the "modification threshold" is reached only if there is sufficient cooperativity between retinal and nonretinal inputs to cortical cells (*4*). It has been proposed that this cooperativity is required for the activation of postsynaptic Ca^{2+} conductances and that the resulting Ca^{2+} fluxes serve as a trigger for synaptic modifications (*5*).

The "*N*-methyl-D-aspartate" (NMDA) receptor could evaluate cooperativity between converging afferents of different origin and gate Ca^{2+} conductances accordingly (*6*). Activation of this receptor by the endogenous ligand, presumably an excitatory amino acid neurotransmitter, opens a channel that is permeable to Ca^{2+} ions, but only if the membrane is concurrently depolarized sufficiently to eliminate a voltage-dependent block of the channel by Mg^{2+} ions (*7–10*). That NMDA-mediated processes might be crucial for ocular dominance plasticity is indicated by the fact that NMDA receptors exist in the membranes of cortical neurons (*11*) and the fact that NMDA receptor activation is involved in the induction of activity-dependent long-term changes of synaptic transmission both in the hippocampus (*12*) and in the visual cortex (*13*).

To determine whether NMDA receptors are involved in developmental plasticity we continuously applied the selective NMDA receptor blocker D,L-2-amino-5-phosphonovaleric acid (APV) (*14*) to the striate cortex of kittens as they were monocularly deprived. Animals (age 4 to 5 weeks) were fitted with osmotic minipumps connected to 27-gauge cannulae inserted 2 mm below the cortical surface near the area centralis representation of area 17 (Table 1). These pumps delivered either 5 or 50 mM APV to the striate cortex of the left hemisphere at a rate of 1 μl (50 nmol) per hour for 1 week. The opposite hemisphere either received an infusion of saline or was left undisturbed, and served as control. At the same time, one eye was deprived of vision by monocular lid suture. After 7 days, the animals were prepared for a standard neurophysiological assay of ocular dominance and orientation selectivity (*15*). Recordings were taken from both hemispheres at a distance of between 3 and 6 mm from the infusion site. Assuming an approximately exponential dilution of the drug with increasing distance, we estimate that the concentrations of APV during the infusion were between 10^{-4} and $10^{-6}M$ at the cortical loci sampled (*16*).

Two kittens were reared in complete darkness before minipump implantation and monocular exposure to light (Table 1). In these animals infusion of 50 mM APV had three consequences (Fig. 1, A and B). (i) The ocular dominance profile in the treated hemispheres appeared to be completely unaffected by the monocular experience, as evidenced by the absence of an ocular dominance shift. (ii) In the drug-treated cortex there was a virtually complete absence of neurons with normal orientation selectivity. Most neurons had large receptive fields and responded to nonoriented visual stimuli presented to either eye. (iii) The neurons in the experimental hemispheres were less respon-

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sive to light stimuli than those recorded on the control sides (Fig. 2, A and B). Thus, APV treatment had apparently prevented all experience-dependent modifications.

The effects of APV infusion on ocular dominance plasticity were similar in kittens that were normally reared before the monocular deprivation (Table 1). The 7 days of monocular deprivation produced little shift of ocular dominance in the cortex infused with 50 m*M* APV, contrasting sharply with the ocular dominance shift toward the open eye in the control hemispheres (Fig. 1, C and D). However, APV infusion had also interfered with orientation selectivity in these kittens, leading to despecification that was nearly as severe as in the dark-reared kittens. This was unexpected since at 4 weeks of age—the time of minipump implantation—light-reared kittens have already developed nearly normal orientation selectivity (*17*). This suggests that the drug treatment affects not only the acquisition but also the maintenance of neuronal selectivity and responsiveness during the critical period.

In five light-reared, monocularly deprived kittens, 5 m*M* APV was infused instead of the 50 m*M* solution (Table 1). As in the other experiments, many of the neurons were binocular and either aspecific or only broadly tuned for stimulus orientation (Fig. 1, E and F). However, a substantial fraction displayed a strong preference for stimulation of the nondeprived eye and were orientation-selective. These results indicate that the APV effects are dose-specific, and they suggest that the processes that lead to ocular dominance changes and to the loss of orientation selectivity are similarly susceptible to APV treatment. In fact, when all of the hemispheres are considered together (Table 2), a clear linear relation emerges between ocularity changes and preservation of receptive field specificity (Fig. 1G).

As a test for the pharmacological specificity of the observed APV effects, we infused the visual cortex of two kittens with 50 m*M* solution of the pharmacologically inactive stereoisomer L-APV (*18*). In these kittens the effects of monocular deprivation were indistinguishable from those obtained in kittens infused with saline. Therefore, the effects of D,L-APV are not simply due to an unspecific toxic action.

Because experience-dependent modifications of cortical circuitry appear to require that cortical neurons respond to retinal signals (*3*), it is crucial to determine to what

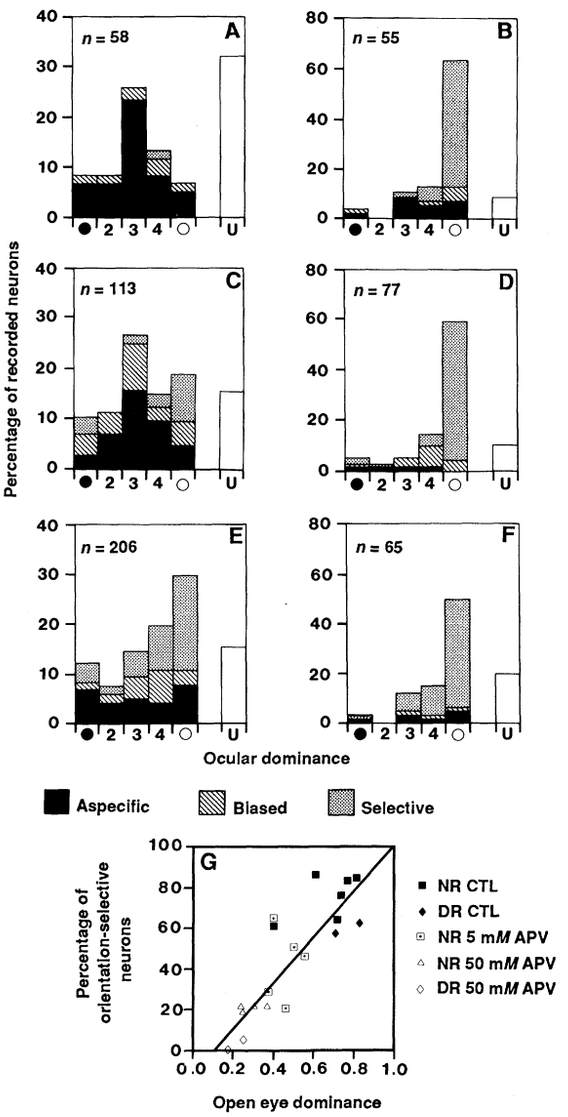

Fig. 1. Ocular dominance (OD) and orientation selectivity data from the striate cortex in monocularly deprived kittens. In each histogram, the open circle indicates the monocular open eye group; the filled circle, the monocular closed eye group; 3, the strictly binocular group; filled bars indicate the percentage of cells in each OD group that were aspecific for stimulus orientation; cross-hatched bars, cells that showed a weak bias toward some orientation; and stippled bars, neurons that were selective for stimulus orientation (*15*). U indicates the percentage of neurons that were unmappable or visually unresponsive. (**A** and **B**) Results from two kittens that were dark-reared prior to the drug infusion and monocular exposure to light: (A) hemispheres treated with 50 m*M* APV, (B) control hemispheres. (**C** through **F**) Results from nine kittens that were reared normally before the drug infusion and monocular deprivation (MD): (C) data from four hemispheres treated with 50 m*M* APV; (D) data from the three control hemispheres; (E) data from five hemispheres treated with 5 m*M* APV; (F) data from three control hemispheres. (**G**) Scatter plot of the percentage of orientation-selective neurons as a function of the open eye dominance for each of the 19 hemispheres assayed. Open eye dominance is the number of cells in OD group 5 plus 0.5 times the number of cells in group 4 divided by the total number of classifiable cells (group 5, by convention, is the monocular group dominated by the open eye). Percentage orientation selective was 100 times the number of selective neurons in each hemisphere divided by the total number of classifiable cells. NR CTL, data from control recordings in six kittens normally reared before the MD; DR CTL, data from control recordings in two dark-reared kittens; NR 5 m*M* APV, data from five hemispheres infused with 5 m*M* APV during the MD; NR 50 m*M* APV, data from the hemispheres of four normally reared kittens that were infused with 50 m*M* APV; DR 50 m*M* APV, data from APV-treated hemispheres of the two dark-reared kittens (Table 1). The regression line was calculated from these data points (slope = 111.7 ± 31.7, $P < 0.05$).

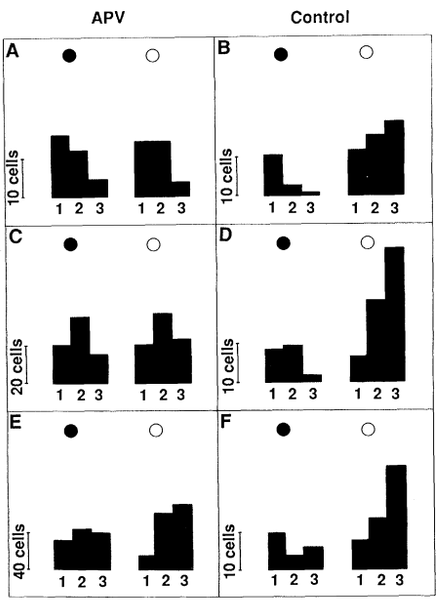

Fig. 2. Response qualities of the cells. Data in (**A**) through (**F**) correspond to populations of neurons from the same animals as (A) through (F) in Fig. 1. The filled and open circles denote the groups of cells activated by the deprived and nondeprived eye, respectively. Responses were classified as follows: 1, response of highly variable and generally low strength and not apparent in every trial; 2, response of medium strength and some variability, but easily detectable with conventional hand-mapping; 3, highly reliable, brisk response, present in every trial.

extent APV disrupts excitatory transmission. Therefore, we investigated the effects of iontophoretically applied APV on the neuronal responses elicited by NMDA, glutamate, and visual stimulation (*19*). Forty striate cortical neurons were studied in two kittens, and the results were generally in agreement with those recently reported by Tsumoto *et al.* (*20*). APV completely antagonized the effects of NMDA and incompletely, and to a variable extent, also antagonized those of glutamate. In most cases, but not all, APV also attenuated spontaneous activity and responses to light. However, even at phoresis currents 20 times as great as those necessary to block NMDA actions (up to 200 nA), APV never abolished light responses completely nor did it alter direction or orientation selectivity. These iontophoretic findings are consistent with a second type of control experiment. In this case we recorded from the striate cortex of a monocularly deprived adult cat, with a minipump cannula assembly still in place, on the seventh day of 50 m*M* APV infusion. Again, most neurons responded to visual stimuli and displayed apparently normal orientation selectivity. As a final control for overt APV effects, we also recorded from the cortex of two kittens on the seventh day of 50 m*M* APV infusion while the minipumps were still in place. With regard to ocular dominance, receptive field selectivity, and response quality, the results obtained under the influence of continuous APV infusion were indistinguishable from those of experiments in which we had removed the implants prior to data collection.

Taken together, the results of these control experiments indicate that neurons in the cortical regions sampled respond to light under the influence of APV and suggest that the decrease of orientation selectivity and response vigor observed in kittens after 7 days of continuous APV infusion is not attributable solely to the presence of APV during the recording. It appears as if prolonged APV treatment caused a reduction of neuronal transmission or excitability that persisted after cessation of APV administration. Finally, the data indicate that long-term APV treatment affected neuronal functions much more in the developing than in the mature cortex, causing despecification of receptive fields in the former but not in the latter.

Our results suggest that activation of visual cortical NMDA receptors is required for both the modification and the maintenance of the neuronal response properties that depend on visual experience. Since the NMDA-dependent conductance changes occur only when the postsynaptic membrane is sufficiently depolarized, our data provide an explanation for the evidence that a critical level of postsynaptic activation is necessary for the normal expression of experience-dependent synaptic changes in visual cortex. Because the NMDA-dependent channel is permeable to Ca^{2+} ions (*7*), our results also support the hypothesis that a decisive postsynaptic variable for the occurrence of long-term modifications may be the activation of dendritic Ca^{2+} conductances (*5, 21*).

Because the NMDA receptor causes conductance changes only if presynaptic activity is contingent with sufficient postsynaptic activation, it could be a substrate for the cooperative interactions crucial in experience-dependent pruning of synaptic connections during development. This may be a general mechanism for activity-dependent control of neuronal plasticity that is not confined to critical periods of development, since the NMDA mechanism is involved in use-dependent long-term potentiation of synaptic transmission in the hippocampus (*12*) and the visual cortex of adult rats (*22*) and also plays a role in certain forms of learning in the adult brain (*23*).

Table 1. The rearing conditions for each of the kittens used in this study. Indicated are the type of rearing before the implantation of minipumps (N, normally raised; D, raised in the dark); the age at the time of implantation with minipumps and lid suture (in each case, the left hemisphere received the APV infusion); which eye was deprived (L, left eye, ipsilateral to the APV-treated hemisphere; R, right eye, ipsilateral to the control hemisphere); the concentration of APV in the minipump; and the number of neurons recorded in each hemisphere ("APV, number recorded in APV-treated cortex, "CTL, number recorded in control cortex).

Kitten	Rearing	Age at implant (postnatal day)	Deprived eye	APV dosage (m*M*)	Control infusion	"APV	"CTL
1	D	P38	R	50	Saline	30	25
2	D	P39	L	50	Saline	28	30
3	N	P31	R	50	Saline	28	30
4	N	P31	R	50	Saline	29	28
5	N	P28	R	50		28	
6	N	P30	L	50	Saline	28	19
7	N	P26	R	5	None	78	16
8	N	P30	R	5	None	35	30
9	N	P27	R	5		39	
10	N	P33	R	5	Saline	28	19
11	N	P30	R	5		26	

Table 2. Quantitative indices of ocular dominance and orientation selectivity (mean ± SEM) for the hemispheres studied in each of the three groups indicated. Only animals that were normally reared before the minipump implant and monocular deprivation are included. See legend to Fig. 1 for definition of open eye dominance. Binocularity is defined as the total number of cells in groups 2 to 4 divided by the total number of classifiable cells. Orientation selectivity is defined as the number of orientation-selective neurons divided by the total number of classifiable neurons. A neuron was classified as "selective" if nonpreferred stimulus orientations elicited no response.

Index	Control (n = 5)	5 m*M* APV (n = 5)	50 m*M* APV (n = 4)
Open eye dominance	0.74 ± 0.04	0.46 ± 0.03*	0.29 ± 0.03*
Binocularity	0.29 ± 0.04	0.52 ± 0.04*	0.66 ± 0.06*
Orientation selectivity	0.78 ± 0.04	0.43 ± 0.08*	0.21 ± 0.06*

*Denotes a significant difference from control at $P < 0.04$ with a two-tailed Mann-Whitney U-test with Bonferroni correction for multiple comparisons.

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to stimulation of the nondeprived eye fall into group 5; and neurons equally responsive to stimulation of either eye fall into group 3. Cells in groups 2 and 4 are binocular but their responses are dominated by either the deprived or the open eye, respectively. In addition, each neuron was assessed qualitatively for orientation selectivity. "Selective" neurons were defined operationally as those that did not respond to a nonpreferred orientation; "biased" neurons responded to all orientations, but the response to the nonpreferred orientation was detectably weaker than the response to the preferred orientation; "aspecific" neurons responded to all orientations without any clear preference. See also W. Singer, *Exp. Brain Res.* **47**, 209 (1982).

16. In one control experiment we infused tritiated APV for 5 days and then determined the diffusion gradient by densitometric analysis of autoradiographs with standard tritium sources for calibration. In agreement with previous reports (*24*), this revealed an approximately exponential decay of drug concentration with increasing distance from the injection site.

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Conduction Velocity Variations Minimize Conduction Time Differences Among Retinal Ganglion Cell Axons

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The visual system is able to accurately represent the spatiotemporal relations among the elements of a changing visual scene as the image moves across the retinal surface. This precise spatiotemporal mapping occurs despite great variability in retinal position and conduction velocity even among retinal ganglion cells of the same physiological class—a variability that would seem to reduce the precision with which spatiotemporal information can be transmitted to central visual areas. There was a strong negative relation between the intraretinal and extraretinal conduction time for axons of individual ganglion cells of the X-cell class. The effect of this relation was to produce a nearly constant total transmission time between the soma of a retinal X cell and its central target site. Thus, the variation in the conduction velocities of retinal ganglion cell axons may ensure that, regardless of the constraints imposed by retinal topography, a precise spatiotemporal central representation of the retinal image is maintained.

OUR VISUAL SYSTEM ENABLES US TO perceive both the spatial and temporal aspects of a constantly changing visual world. The temporal relationships between the elements of a moving retinal image, therefore, must be preserved in the central structures responsible for visual perception. These relationships are maintained despite a number of sources of variability that can obscure the timing between retinal ganglion cell signals in the pathway from the retina to central visual areas. Two primary factors influence the time that it takes the signal from a retinal ganglion cell to reach its central target—the cell's axonal conduction velocity and position in the retina. The axons of retinal ganglion cells comprise two segments. These axons are unmyelinated as they course across the retina from the cell soma to the optic disk; at the optic disk they are invested with myelin and leave the retina to form the optic nerve. Conduction velocity is quite slow in the intraretinal, unmyelinated segment of the axon and increases considerably in the myelinated extraretinal segment. In the cat, there are a number of classes of ganglion cells (*1–4*) but, even within a single physiological class, there is a wide range of axonal conduction velocities both within the retina and in the optic nerve and tract (*4–6*). Because of the slow intraretinal conduction velocities of these cells, the distance between a ganglion cell and the optic disk greatly influences the time required for the signal from that cell to travel across the surface of the retina. Intraretinal conduction time is also a function of the position of a retinal ganglion cell relative to the area centralis. Conduction velocity within the retina is a function of axon caliber (*7*), which increases with retinal eccentricity (distance from the area centralis). These sources of variability lead to an apparent paradox. How is the visual system able to encode spatiotemporal information, the precise direction of movement of an object, for instance, when variations in axonal conduction velocity, and differences in retinal location, can apparently obscure the temporal relationships among ganglion cell signals in the pathway from the retina to the central visual areas of the brain?

To answer this question, we have analyzed the conduction characteristics of a sample of retinal ganglion cell axons from the cat in vivo. All of these data were obtained from retinal X cells, the ganglion cells in the cat that have, among other physiological characteristics, small receptive fields, predominantly linear spatial summation of visual stimuli, and a sustained response to standing contrast (*8, 9*). After we had investigated their physiological properties with an intraretinal microelectrode, these cells were intracellularly injected with horseradish peroxidase (HRP) and were found to have the morphological characteristics ascribed to the anatomically recog-

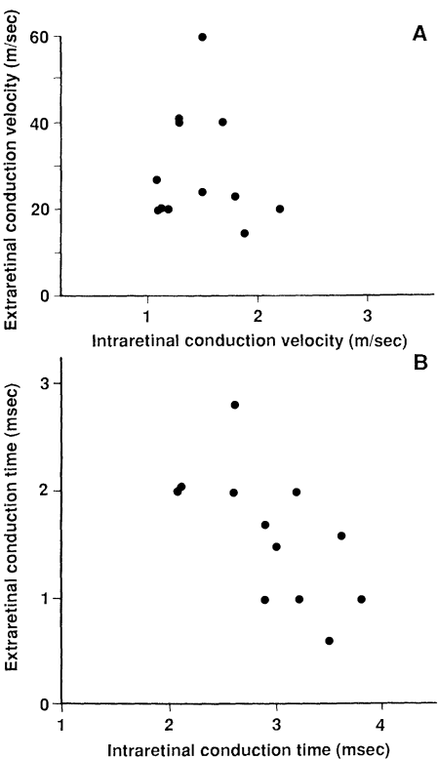

Fig. 1. (**A**) Conduction velocity across the retinal surface (intraretinal conduction velocity) plotted as a function of conduction velocity within the optic nerve and tract (extraretinal conduction velocity) for twelve retinal X-cell axons. There was no obvious relation between these two measures. (**B**) The relation between intraretinal conduction time and extraretinal conduction time for the same X-cell axons as in (A). There is a negative relation ($r = -0.62$, $P < 0.013$) between the time that it takes an action potential to travel across the surface of the retina and the time in which that same signal travels through the optic tract.

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