order to eliminate the self-correction delays. The error rate was extremely low for all control and test subjects across all blocks of trials (>99% accuracy).
8. We delivered TMS with a Cadwell Magneto-electro stimulator 10 (Cadwell Laboratories, Kennewick, WA) through an eight-shaped coil applied to a 5 by 5 grid of scalp positions 1 cm apart over the left sensorimotor cortex. The coil was always held in the same orientation with the handle pointing occipitally and held parallel to the midsagittal line [W. J. Levy, V. E. Amassian, M. Traad, J. Cadwell, *Brain Res.* **510**, 130 (1990)]. Stimulation intensity was 10% above the subject's motor threshold intensity. Motor threshold was defined by the method of limits as the TMS intensity capable of evoking at least five MEPs of 50-μV peak-to-peak amplitude in 10 single trials over the optimal scalp position for activation of each target muscle. The optimal scalp position is the one from which TMS elicits MEPs of maximal amplitude in the target muscles. This technique allows relatively focal stimulation and the generation of restricted topographic maps of cortical motor outputs [L. G. Cohen *et al.*, *Electroencephalogr. Clin. Neurophysiol.* **75**, 350 (1990); P. J. Maccabee *et al.*, *ibid.* **76**, 131 (1990); E. M. Wassermann, L. M. McShane, M. Hallett, L. G. Cohen, *ibid.* **85**, 1 (1992)] that corresponds to the activation of the primary motor cortex, as has been shown by overlay of such maps onto the subject's brain magnetic resonance image [E. M. Wassermann *et al.*, *Soc. Neurosci. Abstr.* **18**, 939 (1992)]. The brain structures stimulated can be inferred from models of the induced electric fields [P. S. Tofts, *Phys. Med. Biol.* **35**, 1119 (1990); B. J. Roth, J. M. Saypol, M. Hallett, L. G. Cohen, *Electroencephalogr. Clin. Neurophysiol.* **81**, 47 (1991); J. M. Saypol, B. J. Roth, L. G. Cohen, M. Hallett, *Ann. Biomed. Eng.* **19**, 317 (1991)]. Electromyographic (EMG) activity was recorded with a Dantec Counterpoint electromyograph (Dantec Medical A/S, Skovlunde, Denmark) with pairs of surface electrodes taped to the skin. Mapping was done with muscles at rest, as verified by EMG monitoring. Motor potentials were printed out on paper for off-line amplitude measurements. Each scalp position was stimulated five times, and we calculated the average amplitude of the MEPs evoked from each scalp position. The cortical output maps were quantified by measurement of the mean amplitude of the five MEPs evoked from the optimal scalp position (peak amplitude) and the number of scalp positions from which TMS evoked MEPs of ≥60% of the peak amplitude. Cortical output maps obtained from the same subject at different times during the experiment were statistically compared by use of a paired *t* test adjusted with the Bonferroni-Dunn correction for multiple comparisons. Response-time data were analyzed with the nonparametric Mann-Whitney test.
9. The nervous system may undergo changes according to patterns of use [M. M. Merzenich, G. H. Recanzone, W. M. Jenkins, K. A. Grajski, *Cold Spring Harbor Symp. Quant. Biol.* **55**, 873 (1990)]. In monkeys, the sensorimotor representation of the preferred hand is more elaborate than that of the nonpreferred hand [R. J. Nudo, W. M. Jenkins, M. M. Merzenich, T. Prejean, R. Grenda, *J. Neurosci.* **12**, 2918 (1992)], and training can result in distortions of body surface and movement representations that lead to behavioral gains [W. M. Jenkins, M. M. Merzenich, G. Recanzone, *Neuropsychologia* **28**, 573 (1990)]. Motor cortical representation of a body part expands after selectively increased activity [J. N. Sanes, J. Wang, J. P. Donoghue, *Cereb. Cortex* **2**, 141 (1992)], and differential stimulation of a restricted skin surface of a finger pad in adult monkeys leads to an enlargement of its somatosensory cortical representation [W. M. Jenkins, M. M. Merzenich, M. T. Ochs, T. Allard, E. Guic-Robles, *J. Neurophysiol.* **63**, 82 (1990)], especially when stimulation has a functional significance [G. Recanzone, W. M. Jenkins, G. T. Hradek, M. M. Merzenich, *J. Neurophysiol.* **67**, 1015 (1992); G. H. Recanzone, M. M. Merzenich, W. M. Jenkins, K. A. Grajski, H. R. Dinse, *ibid.*, p. 1031; G. H. Recanzone, M. M. Merzenich, W. M. Jenkins, *ibid.*, p. 1057; G. H. Recanzone, M. M. Merzenich, C. E. Schreiner, *ibid.*, p. 1071].
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14. Therefore, removal of a target (for example, by amputation or peripheral deafferentation) would result in the takeover of neuronal elements formerly devoted to the network of the removed target by networks targeting neighboring body parts. This would explain the reorganization of the motor outputs targeting muscles proximal to the stump of an amputated limb [L. G. Cohen, S. Bandinelli, T. W. Findley, M. Hallett, *Brain* **114**, 615 (1991)] or an ischemic block [J. P. Brasil-Neto *et al.*, *Neurology* **42**, 1302 (1992); *Brain* **116**, 511 (1993)]. Conversely, increased use of and enhanced sensory feedback from a body part, especially if coupled with functional gain for the subject, may lead to a shift of the balance of intracortical networks toward that body part [A. Pascual-Leone and F. Torres, *Brain* **116**, 39 (1993); A. Pascual-Leone *et al.*, *Ann. Neurol.* **34**, 33 (1993)].
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Neuronal Plasticity That Underlies Improvement in Perceptual Performance

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The electrophysiological properties of sensory neurons in the adult cortex are not immutable but can change in response to alterations of sensory input caused by manipulation of afferent pathways in the nervous system or by manipulation of the sensory environment. Such plasticity creates great potential for flexible processing of sensory information, but the actual effects of neuronal plasticity on perceptual performance are poorly understood. The link between neuronal plasticity and performance was explored here by recording the responses of directionally selective neurons in the visual cortex while rhesus monkeys practiced a familiar task involving discrimination of motion direction. Each animal experienced a short-term improvement in perceptual sensitivity during daily experiments; sensitivity increased by an average of 19 percent over a few hundred trials. The increase in perceptual sensitivity was accompanied by a short-term improvement in neuronal sensitivity that mirrored the perceptual effect both in magnitude and in time course, which suggests that improved psychophysical performance can result directly from increased neuronal sensitivity within a sensory pathway.

Neural circuitry in sensory areas of the cerebral cortex is intricately organized, evoking the impression of an elegantly wired machine that performs stereotyped computations on sensory input. Recent experiments, however, have shown that this circuitry is subject to dramatic plastic changes. Topographic organization can be altered by damage to peripheral afferents or by chronic performance of a sensory task (*1*, *2*). The stimulus-response properties of individual neurons can be modified by pharmacological intervention (*3*), by changes in the behavioral context in which a stimulus is presented (*4*), and by direct manipulation of the sensory environment (*5*). Plasticity thus appears to be a common feature of the adult cortex and may be closely linked to the behavioral ability to respond flexibly to the environment.

We compared neuronal to behavioral plasticity in the context of visual discrimination of motion direction. The monkeys were familiar with this task, having developed asymptotically stable performance over months of training. Within daily sessions, however, the animals often exhibited a steady gain in discriminative ability over the first 300 to 500 trials of a particular task configuration. To search for neural correlates of this phenomenon, we examined the activity of single neurons in two extrastriate visual areas that play a prominent role in motion vision: the middle temporal (MT) and medial superior temporal (MST) visual areas. Neurons in these two areas are typically directionally selective; they respond optimally to motion in a particular

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"preferred" direction and are frequently inhibited by motion in the opposite, or "null," direction. We have recently demonstrated that the electrical activity of neurons in these areas influences judgments of motion direction in the psychophysical task used here (6). This system therefore provides a particularly promising opportunity to identify neuronal correlates of perceptual plasticity.

We trained four monkeys to discriminate between opposite directions of motion in a random dot visual display. In each trial, a percentage of the dots in the display moved coherently in a common direction while the remainder moved in random directions, creating a masking motion noise. The strength of the motion signal was varied from trial to trial by a change in the percentage of dots moving coherently, and the range of stimulus strengths was chosen so as to measure psychophysical and neuronal thresholds for discriminating the direction of motion in the display (7). Each experiment was divided into consecutive blocks of approximately 200 stimulus presentations, and psychophysical and neuronal thresholds were measured in each block. Data from areas MT (155 cells) and MST (73 cells) are presented together because we found no differences between the two areas that were relevant to this study.

The psychophysical data in Fig. 1A show the proportion of correct choices made by the animal as a function of motion strength (dot coherence level) in a single experiment. The neuronal data in Fig. 1B indicate the proportion of correct choices that could be achieved in principle if decisions were based on the responses of the single neuron under study (8). Both the neurometric and psychometric functions shifted leftward in the second block of trials, which indicates an improvement in the discrimination of weak motion signals. The proportional change in threshold represented by this shift (calculated by dividing the threshold in block 2 by the threshold in block 1) was 0.51 for the psychophysical data and 0.47 for the neuronal data. Thus, both psychophysical and neuronal sensitivity increased by a factor of 2 in the second block of trials (sensitivity = 1/threshold).

The distribution of threshold ratios observed in 202 experiments for which we obtained two full blocks of data is illustrated in Fig. 2. The geometric mean of the threshold ratios was 0.84 for the psychophysical data (Fig. 2A) and 0.88 for the neuronal data (Fig. 2B); both effects were significant (paired t test, $P < 0.0001$). On average, psychophysical sensitivity increased by 19.4% and neuronal sensitivity by 13.6%. The change in neuronal sensitivity was not correlated with the change in psychophysical sensitivity on an experiment-by-experiment basis, although the average change was similar.

We conducted an additional 26 experiments with a single monkey that was required to maintain his gaze on a fixation spot during presentation of the visual stimuli; this animal had never been trained on the discrimination task. The neuronal threshold ratios in these experiments are plotted as filled bars in Fig. 2B. These neurons also gained sensitivity during the course of the experiment, and the effect was indistinguishable from that observed in the trained monkeys (9). Thus, the enhancement of neuronal sensitivity appears to be an automatic process that occurs irrespective of the behavioral significance of the stimuli (10). In this respect our data differ from those of Recanzone, Merzenich, and Schreiner, who observed changes in the sensitivity of cortical neurons while monkeys practiced a somatosensory discrimination task but did not observe such changes when the skin surface was passively stimulated (2).

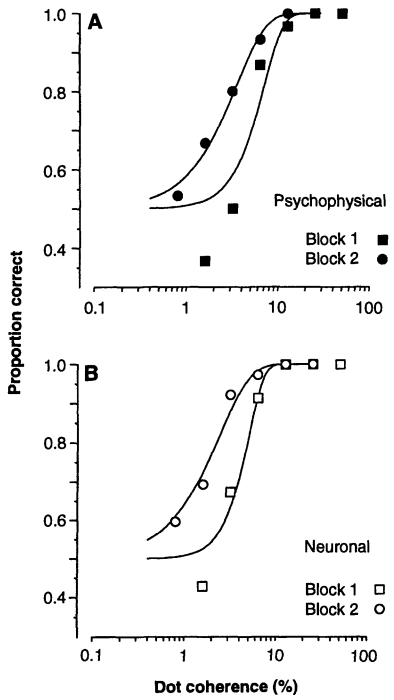

Fig. 1. An example of the effect of stimulus repetition on psychophysical and neuronal performance. Psychophysical performance (**A**) is given as the proportion of correct discriminations made by the monkey as a function of the percentage of coherently moving dots (motion strength). Neuronal performance (**B**) was calculated from the differential responses of the neuron to preferred and null direction motion. For each dot coherence level, we used a method based on signal detection theory to compute the performance expected of an ideal observer who reports the direction of motion in the display on the basis of the responses of the neuron under study (8). The neurons were highly directional for strong motion signals, and the performance expected of the ideal observer was therefore excellent. Weak motion signals elicited roughly equal responses to the two directions of motion, resulting in poor performance by the ideal observer. An experiment consisted of successive blocks of trials, and each block consisted of 150 to 210 stimulus presentations (30 stimulus repetitions—15 in each direction of motion—for each of 5 to 7 dot coherence levels). Sigmoidal functions were fitted to the data, and thresholds were calculated from the fitted curves (14). Threshold is defined as the dot coherence level that supports 82% correct performance.

To compare the time courses of the psychophysical and neuronal effects, we averaged across the entire data set to obtain composite thresholds as a function of time, where time is expressed as consecutive stimulus repetitions during a block of trials. Both psychophysical and neuronal thresholds decreased steadily as a function of stimulus repetition number (Fig. 3). The slopes of regression lines fitted to the two sets of data are not significantly different, which is consistent with the notion that the improvements in neuronal and psychophysical sensitivity occurred at the same rate (11). This temporal correspondence suggests that the improvement in psychophysical performance may be a direct consequence of the improvement in neuronal sensitivity.

To investigate the possible locus of neuronal plasticity, we tested whether im-

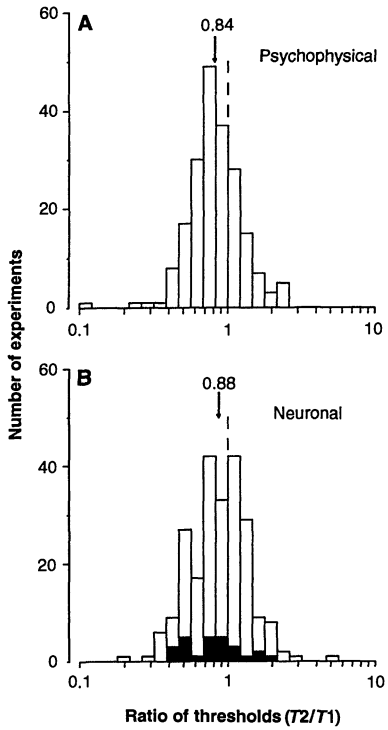

Fig. 2. Frequency histograms describing the ratio of threshold in the second block of trials ($T2$) to threshold in the first block ($T1$) for both psychophysical (**A**) and neuronal (**B**) data. Ratios less than unity indicate an improvement in sensitivity during the experiment, whereas ratios greater than unity indicate the converse. Arrows indicate means of the two distributions.

provement in neuronal sensitivity would "transfer" from a stimulated subregion of the receptive field to a subregion that was not stimulated. If enhanced sensitivity results from plastic changes occurring exclusively within afferent structures with considerably smaller receptive fields (such as the striate cortex) or at specific sets of synapses between small receptive field afferents and MT or MST cells, the increase in sensitivity should not transfer to the unstimulated subregion of the receptive field. If, however, the neuronal plasticity occurs at the level of MT and MST, conditioning at one location in the receptive field should lead to an increase in sensitivity at the other location as well.

Using the experimental design illustrated in Fig. 4, we compared the effect of conditioning stimuli at site 1 on thresholds measured subsequently at both test sites. The effect of the conditioning stimuli on sensitivity at site 1 could be measured directly by comparison of thresholds obtained during the conditioning and test blocks. However, transfer of the effect to site 2 was inferred indirectly, because any attempt to measure a "preconditioning" threshold at site 2 would itself condition the site. To test transfer to site 2, therefore, we compared across all experiments the average postconditioning threshold at site 2 to the average conditioning threshold at site 1. Average thresholds were used because threshold differences between site 1 and site 2 can arise trivially in any single experiment as a result of spatial inhomogeneities in the receptive field. Across experiments, however, receptive field inhomogeneities average out because the conditioning and test subregions were selected randomly in each experiment.

The experimental design is schematized and the main results summarized in Fig. 4B. Compared with initial thresholds measured during the conditioning trials at site 1, average neuronal sensitivity increased by 12.7% at site 1 and by 11.6% at site 2. On average, conditioning of one subregion of the receptive field appeared to enhance sensitivity equally in conditioned and unconditioned regions of the receptive field. These data suggest that the plastic mechanisms reside, at least in part, locally within the superior temporal sulcus. An alternative hypothesis is that the plastic changes result from spatially nonspecific mechanisms located at an earlier level, perhaps involving lateral connections between cells with nonoverlapping receptive fields (*12*).

Humans frequently exhibit long-term improvements in discriminative ability as they learn and practice a particular psychophysical task (*13*). Are the short-term effects demonstrated here related mechanistically to long-term perceptual learning? In principle, perceptual learning could be based on enhanced sensitivity of sensory neurons like that demonstrated here, on more efficient "readout" of information encoded at the sensory level, or on some combination of the two. Comparing the sensitivities of MT and MST neurons before and after training in our direction discrimination task should provide an initial test of these alternatives.

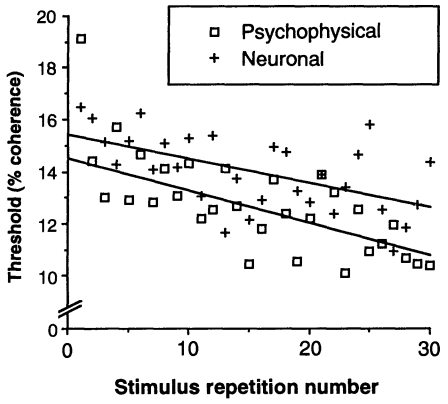

Fig. 3. The dependence of composite threshold on stimulus repetition number over the course of an experiment. Each stimulus was presented 30 times in the experiments included in this analysis. Composite psychophysical data were obtained by summing correct and incorrect responses across experiments for each repetition of each stimulus condition. For example, the proportion of correct choices was calculated across experiments for the first presentation of each dot coherence level (including both the preferred and null directions). The proportion of correct choices was then plotted as a function of stimulus coherence to form a composite psychometric function, and the threshold was computed from fitted functions as described (Fig. 1). This threshold is the psychophysical data point for stimulus repetition number 1. The process was repeated to obtain thresholds for each of the 30 stimulus repetition sequences. To compute composite neuronal thresholds, we generated "decisions" by comparing the physiological responses to preferred and null direction stimuli for each coherence level in each stimulus repetition sequence in an experiment. If the response to the preferred direction was greater, a "correct" decision was scored; if the response to the null direction was greater, an "incorrect" decision was scored. Correct and incorrect decisions were then summed across experiments and expressed as the proportion of correct choices for each coherence level for a given stimulus repetition sequence (as described above for the psychophysical data). The data were plotted to form composite neurometric functions, and thresholds were computed from sigmoidal curves fitted to the composite data. This process was repeated for each of the 30 stimulus repetition sequences to obtain the data illustrated in this figure. The psychophysical data point for stimulus repetition number 1 is an outlier because the monkeys frequently did not know the axis of motion to discriminate until the target light-emitting diodes appeared at the end of the first trial. Performance improved abruptly after the first trial. The first data point was not used, therefore, in the regression analysis of these data.

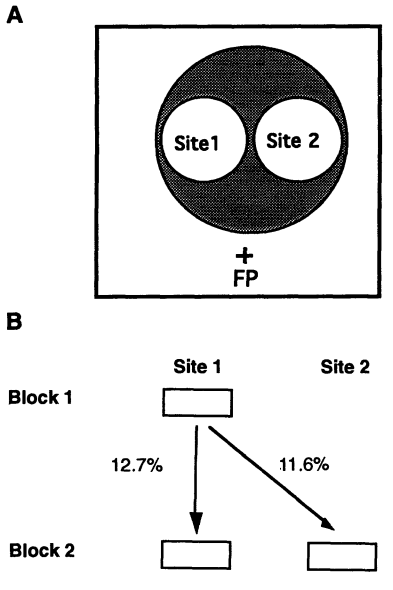

Fig. 4. (**A**) Spatial design of the experiment for studying the locus of neural plasticity. After mapping each cell's receptive field (shaded), we selected two nonoverlapping regions inside the receptive field whose direction properties were qualitatively similar. An initial block of 100 stimuli was presented in one of the two sites; this site was selected randomly at the beginning of the experiment and designated site 1. Then a test block of trials was presented (200 stimuli), with half of the stimuli presented at site 1 and half at site 2; the site of presentation was chosen randomly on each trial. In each block of trials, stimuli were presented at several dot coherence levels to permit measurement of neuronal thresholds. The location of the fixation point for this example experiment is indicated by FP. (**B**) Flow diagram illustrating the sequence of measurements in an experiment. A rectangle represents a block of trials at a given site. An arrow represents a comparison between neuronal thresholds measured in the two blocks connected by the arrow, and the arrow points toward the block having greater sensitivity (lower thresholds). The number accompanying each arrow indicates the increase in sensitivity between the two blocks, averaged across all 36 experiments.

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7. The responses of single neurons were recorded while the monkey performed the direction discrimination task. In each experiment, we placed the stimulus so that it matched the size and location of the neuron's receptive field, and we adjusted the speed of the coherently moving dots to elicit an optimal response from the neuron. The motion signal was presented either in the cell's preferred direction or in the opposite (null) direction. In an individual trial, the monkey was required to fixate a stationary point of light for 2 s while the stimulus was presented. After the viewing period, the monkey indicated his judgment by making a saccadic eye movement to one of two light-emitting diodes corresponding to the two possible directions of motion. Eye movements were measured continuously with the scleral search coil technique [D. A. Robinson, *IEEE Trans. Biomed. Eng.* **10**, 137 (1963)]. The monkey received a liquid reward for a correct choice. Incorrect choices were punished by a brief time-out period. If the monkey broke fixation prematurely, the trial was aborted and the data discarded. Cells were included in our data sample on the basis of direction selectivity—we required that their responses to strong motion in the null direction be consistently smaller than their responses to strong motion in the preferred direction. For most cells, the response in the null direction was equal to or less than the spontaneous firing rate.
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9. The average neuronal threshold ratio in the untrained monkey was 0.79, corresponding to an increase in neuronal sensitivity of 26.4%. The difference in thresholds measured in the first and second blocks of trials was statistically significant (paired t test, $P = 0.005$, df = 25). Although the mean threshold ratio was lower for neurons recorded in the untrained monkey than for those recorded in the trained monkeys, the overall distributions of threshold ratios were not significantly different for the two groups (unpaired t test, $P = 0.15$, df = 226).
10. In general, enhanced discriminative capacity of single neurons can result either from changes in neuronal responsiveness or from a decrease in response variability. An analysis of our data supports the first possibility. We assessed the change in responsiveness by measuring, for each neuron, the slope of the response function relating motion coherence level to firing rate. Slopes were computed separately for the preferred and null direction response functions in each block of trials. These correlation-response functions were fitted well by straight lines for roughly half of the MT neurons [K. H. Britten, M. N. Shadlen, W. T. Newsome, J. A. Movshon, *Visual Neurosci.* **8**, 1157 (1993)], and this analysis was done only on these cells. The slopes of the coherence-response functions for preferred-direction motion were significantly steeper in the second block of trials, which indicated increased responsiveness (paired t test, $P < 0.0002$, df = 151). Across coherence levels, firing rates in response to preferred-direction motion increased by an average of 6.6% in the second block of trials. The slopes of the null direction coherence-response functions were significantly more negative, on average, in the second block of trials (paired t test, $P < 0.0001$, df = 116). Response variance, normalized for firing rate, was unchanged between the first and second blocks of trials.
11. We did an analysis of covariance to determine whether the composite neuronal and psychometric thresholds depended on stimulus repetition number in the same fashion. We used an interaction term between stimulus repetition number and data set (psychophysical or neuronal) to test the null hypothesis that the two data sets were fit as well with the same as with different slopes. The interaction term was not significant ($P = 0.17$).
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Global Form and Singularity: Modeling the Blind Spot's Role in Lateral Geniculate Morphogenesis

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Optic nerve terminals segregate by functional class into distinct layers in the lateral geniculate nucleus, the thalamic relay nucleus of the visual system. In the rhesus monkey, the number of geniculate layers changes abruptly from six posteriorly (central vision) to four anteriorly (peripheral vision). The plane of transition between these patterns passes through small laminar gaps corresponding to the perceptual blind spot caused by the exit of the optic nerve from the eyeball. However, this plane of transition has no apparent functional link to the blind spot. A thermodynamic model of geniculate morphogenesis supports the hypothesis that the blind spot traps the transition in its stereotypic position by introducing a singularity in an otherwise smooth gradient in forces guiding the development of geniculate morphogenesis. This relation suggests that small-scale anomalies may be important in the determination of large-scale patterns in biological structure.

Although brain morphology is subject to considerable individual differences, certain features are constant. For example, there are substantial variations in the size, position, and orientation of the rhesus lateral geniculate nucleus (LGN), the thalamic relay nucleus interposed between the eye and cerebral cortex. However, the internal laminar structure of the LGN maintains an invariant relation with a seemingly unrelated feature, the blind spot caused by the optic nerve exiting the eyeball through the optic disk. Geniculate retinotopy is so precise that the blind spot is represented by small gaps free of relay cells (optic disk gaps). These gaps lie in the plane of transition separating a six-layered posterior region (representing central vision) from a four-layered anterior region (peripheral binocular vision) (*1–3*). This association between the transition and gaps is puzzling: Many psychophysical and anatomical aspects of vision vary dramatically with retinal eccentricity, but the most rapid changes occur at eccentricities well within that of the optic disk. Furthermore, there is no evidence of sudden changes in any perceptual function at the transition and no apparent reason why any such changes should be associated with the blind spot. Here we consider this problem from a developmental viewpoint. We suggest that the blind spot traps the transition at its stereotypic location by introducing a singularity in a gradient controlling laminar development. To evaluate this proposition, we developed a thermodynamic model of geniculate morphogenesis, in which a realistic laminar transition is induced by an anteroposterior gradient in interaction forces between terminals. We then examined the effects of the optic disk gaps on the position of this transition using simulated annealing.

Our simulation was confined to the plane of symmetry of the LGN: a roughly rectangular surface dividing the nucleus into medial and lateral halves. This plane represents the horizontal meridian, so retinotopic organization is described by a single coordinate, eccentricity. Axon terminals from two "retinae" were categorized into six groups according to eye (ipsilateral or contralateral), major functional class (M or P) (*4*), and (for P cells) polarity of receptive-field center (On or Off). The density of retinal cells dropped with eccentricity, paralleling the number of geniculate cells per unit area of visual space (*5*). Because in normal development the formation of layers is induced by the arrival of retinal axons (*6*) and the main functional properties of geniculate relay cells mirror those of their retinal afferents, we considered only the distribu-

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