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# Strobe Rearing Prevents the Convergence of Inputs With Different Response Timings Onto Area 17 Simple Cells

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**Humphrey, Allen L., Alan B. Saul, and Jordan C. Feidler.** Strobe rearing prevents the convergence of inputs with different response timings onto area 17 simple cells. *J. Neurophysiol.* 80: 3005–3020, 1998. The preceding paper showed that the loss of direction selectivity in simple cells induced by strobe rearing reflects the elimination of spatially ordered response timing differences across the receptive field that underlie spatiotemporal (S-T) inseparability. Here we addressed whether these changes reflected an elimination of certain timings or an alteration in how timings were associated in single cells. Timing in receptive fields was measured using stationary bars undergoing sinusoidal luminance modulation at different temporal frequencies (0.5–6 Hz). For each bar position, response phase versus temporal frequency data were fit by a line to obtain two measures: absolute phase and latency. In normal cats, many individual simple cells display a wide range of timings; in layer 4, the mean range for absolute phase and latency was 0.21 cycles and 39 ms, respectively. Strobe rearing compressed the mean timing ranges in single cells, to 0.08 cycles and 31 ms, respectively, and this compression accounted for the loss of inseparability. A similar compression was measured in layer 6 cells. In contrast, the range of timing values across the simple-cell population was relatively normal. Single cells merely sampled narrower than normal regions of the timing space. We sought to understand these cortical changes in terms of how inputs from the lateral geniculate nucleus (LGN) may have been affected by strobe rearing. In normal cats, a wide range of absolute phase and latency values exists among lagged and nonlagged LGN cells, and these thalamic timings account for most of the cortical timings. Also, S-T inseparability in many simple cells can be attributed to the convergence of lagged and/or nonlagged inputs. Strobe rearing did not change the sampling of lagged and nonlagged cells, and the geniculate timings continued to account for most of the cortical timings. However, strobe rearing virtually eliminated cortical receptive fields with mixed lagged and nonlagged timing, and it compressed the timing range in cells dominated by one or the other geniculate type. Thus strobe rearing did not eliminate certain timings in LGN or cortex, but prevented the convergence of different timings on single cells. To account for these results, we propose a developmental model in which strobe stimulation alters the correlational structure of inputs based on their response timing. Only inputs with similar timing become associated on single cortical cells, and this produces S-T separable receptive fields that lack the ability to confer a preferred direction of motion.

## INTRODUCTION

The preceding paper (Humphrey and Saul 1998) showed that strobe rearing causes a loss of direction-selective responses in simple cells of area 17 by altering the space-time structure of their receptive fields. In normal cats, most direction-selective cells display varying degrees of spatiotemporal (S-T) inseparability. The gradual timing shifts across their receptive fields confer a preferred direction of motion (Jagadeesh et al. 1997; McLean et al. 1994; Reid et al. 1991). After strobe rearing, all cells lacking directional tuning had S-T separable receptive fields. The absence of timing gradients in these receptive fields appears to have greatly affected the ability of cells to generate differential responses to opposite directions of motion.

This paper examines in more detail the response timing within receptive fields of strobe-reared cats. The analyses were motivated by our previous studies of timing in the lateral geniculate nucleus (LGN) and area 17 of normal cats. By using stationary counterphasing spots or bars, timing can be characterized in terms of response phase, which in turn reflects two components: absolute phase and latency. Absolute phase reflects where in the stimulus cycle excitation arises in the cell (e.g., increasing or decreasing luminance). This timing component contributes to response phase mainly at low temporal frequencies (<2 Hz) (Saul and Humphrey 1990). Latency reflects conduction delays and integrative processes that occur between the critical stimulus event and the cell's excitatory response. It contributes most to response phase at higher temporal frequencies (>2 Hz). A broad range of absolute phase and latency values is observed in the simple-cell population of cortex (Saul and Humphrey 1992a). Within individual receptive fields, the spatial distribution of these timings determines S-T structure.

We also showed that much of the timing range in area 17 can be accounted for by inputs from lagged and nonlagged relay cells of the LGN (Saul and Humphrey 1992a). The two groups differ in their temporal response properties; lagged cells display absolute phase delays and long latencies relative to nonlagged cells (Saul and Humphrey 1990). In cortex, their characteristic timings are observable in simple cells, particularly in layer 4. Gradual shifts in response timing across S-T inseparable receptive fields there can be accounted for by converging lagged and nonlagged inputs with spatially shifted receptive fields (Saul and Humphrey 1992a). Other inseparable cells may

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exhibit a range of timings that are purely lagged- or nonlagged-like.

Given the importance of different response timings in generating S-T inseparable receptive fields, and the role of geniculate afferents in providing these timings, we wondered whether the strobe-induced elimination of S-T inseparability might reflect a change in timings within cortex and LGN. For example, strobe rearing might affect lagged cells. In normal cats, many of these cells respond poorly to high ( $>6$  Hz) temporal frequencies of visual stimulation (Saul and Humphrey 1990) or to stimuli presented briefly (e.g.,  $<10$  ms duration; unpublished observations). Strobe rearing might interfere with the development of lagged cells or with their ability to form connections in cortex. Alternatively, the different LGN cell types might develop normally but fail to converge on common cortical cells. Still another possibility is that strobe rearing might change the timing properties of all geniculate and cortical cells, producing timing distributions markedly different from normal.

We addressed these possibilities as follows. First, proceeding from the previous study (Humphrey and Saul 1998) that showed strobe-induced elimination of timing differences in simple-cell receptive fields, we documented the degree of timing compression. This showed that there was a marked compression in the range of latency and absolute phase values in individual receptive fields. Second, we asked whether this timing compression reflected a reduction in the range of timings in the cortical population, perhaps with a loss of lagged-like responses. We will show that the population range was unaltered, and lagged- and nonlagged-like timings were still present. Third, we examined strobe-reared LGN and found a normal range of cell types and timings there. Fourth, we examined how lagged- and nonlagged-like timings were distributed in individual simple cells. We will show that, unlike normal cats where many simple cells show evidence of converging lagged and nonlagged inputs, such convergence is virtually absent after strobe rearing. The segregation of lagged and nonlagged timings onto different cortical cells reflected a broader action of strobe rearing, which was to reduce the timing range in virtually all simple cells.

These results show that strobe rearing did not substantially affect the range of timings in LGN and cortex. Despite this range, however, individual simple cells became linked only to inputs with very similar timing, and this resulted in S-T separable, nondirection-selective receptive fields. To account for this, we propose a developmental model in which strobe rearing alters S-T receptive-field structure by changing the pattern of inputs to cortical cells based on their response timing.

Portions of this study have been presented previously in abstract form (Humphrey et al. 1997; Humphrey and Saul 1995).

## METHODS

Cortical data were obtained using the strobe-reared and normal cats described in the preceding paper (Humphrey and Saul 1998). LGN data were obtained in four strobe-reared and five normal cats.

## Response timing

Methods for studying response timing in LGN and cortex are described elsewhere (Humphrey and Saul 1998; Saul and Humphrey 1990, 1992a). Briefly, line-weighting functions were obtained for LGN and simple cells, respectively, by sinusoidally modulating the luminance of a stationary stimulus. For simple cells, we used an elongated, optimally oriented, narrow bar placed at 8 or 16 positions in the receptive field, and modulated the luminance at 5–7 temporal frequencies. For each bar position/temporal frequency pair, the first harmonic response amplitude and temporal phase were measured from peristimulus time histograms (PSTHs) obtained from multiple trials. For LGN cells, similar measures were obtained using a small spot always centered on, and of the same size as, the hand plotted receptive-field center. The use of spots in LGN and bars in cortex did not preclude a valid comparison of timing in the two regions, because timing in LGN cells measured with spots is very similar to that obtained with narrow bars (unpublished observations; Wolfe and Palmer 1998).

Response phase was expressed in cycles, with 0.0 cycles corresponding to a response that coincided with the maximum stimulus luminance, and 0.5 cycles reflecting a response in register with the minimum luminance. A response that led the stimulus had a phase value between  $-0.25$  and 0 cycles or between 0.25 and 0.5 cycles. Responses with phase lags had values in the other quarter-cycles (i.e., 0.0–0.25 cycles or 0.5–0.75 cycles). For sufficiently low temporal frequencies, ON responses had phase values between  $-0.25$  and 0.25 cycles, and OFF responses fell into the interval between 0.25 and 0.75 cycles.

For each stimulus position in a receptive field, summary measures of timing were obtained as follows. We plotted response phase versus stimulus temporal frequency and fit the points by a line (e.g., Fig. 1B). The intercept of each line reflects *absolute phase*, the response phase extrapolated to 0 Hz. Absolute phase was normalized for ON and OFF responses by collapsing values into a half cycle, that is, between  $-0.25$  and  $+0.25$  cycles relative to the maximum (for ON responses) or minimum (for OFF responses) luminance (Saul and Humphrey 1990). Note that the absolute phase axis is circular, with  $-0.25$  and 0.25 cycles being the same timing. For example, an ON nonlagged response of  $-0.25$  cycles occurs at the same point in the luminance cycles as an OFF lagged response of 0.25 cycles. The second timing measure was *latency*; expressed in milliseconds, it is the slope of the regression line. Together, the two timing components provided signatures that allowed us to compare timings in LGN and cortex of normal and strobe-reared animals, and infer geniculocortical convergence patterns in the two rearing groups.

Fits to the phase data were weighted by the reciprocals of the standard errors of the response phase means and by the square roots of the mean response amplitudes at each temporal frequency. Stimulus positions were rejected if fits yielded standard errors of absolute phase or latency  $>0.03$  cycles or 15 ms, respectively. Such positions tended to be located near the edges of the receptive field or at the border between ON and OFF zones, and they usually exhibited the weakest amplitudes. Positions with unreliable timing are not included in the analyses below.

In addition to quantifying timing at each stimulus position, for simple cells we measured the range of timings within individual receptive fields, using cells that had three or more positions with reliable timing. The latency range was taken as the difference between the maximum and minimum latencies in the receptive field. For absolute phase range, we used the normalized phase values described above. Theoretically, a receptive field can be comprised of different positions having absolute phase leads and lags that, together, span up to 0.5 cycles. Our measure of absolute phase range, then, was a value that encompassed all of the timings

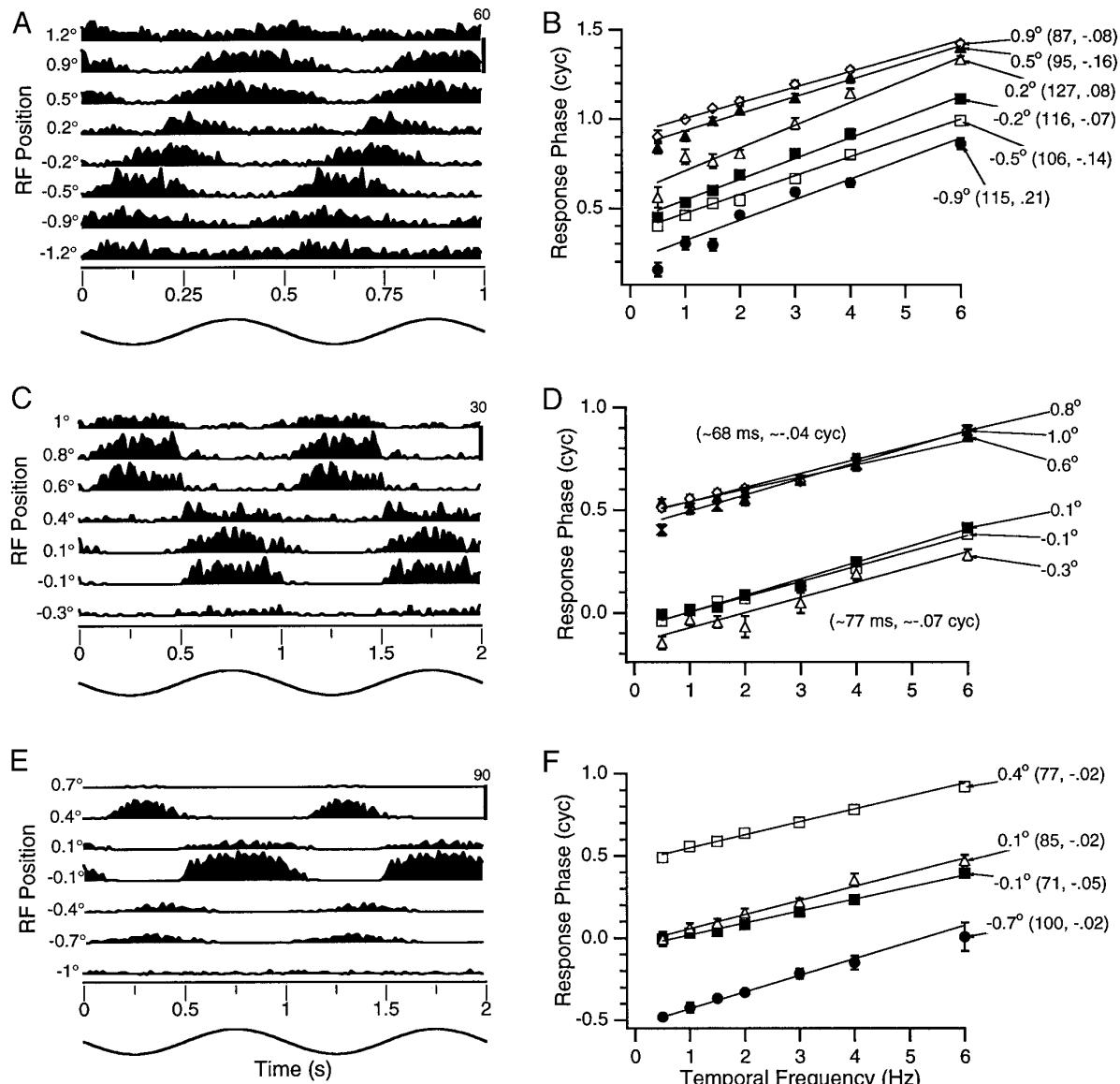


FIG. 1. Response timing measurements in 3 simple cells. *A*, *C*, and *E*: line-weighting functions revealing the spatiotemporal (S-T) structure of each receptive field. Each peristimulus time histogram (PSTH) was derived from responses to a stationary bar undergoing sinusoidal luminance modulation at different positions and at a fixed temporal frequency. Luminance profile is indicated beneath each set of PSTHs; 2 cycles are illustrated, for clarity. Vertical scale bar and response scaling (in impulses/s) are shown in the *top right* of each plot. The receptive fields had, respectively, 3, 2, and 3 ON and OFF zones. Directional (DI) and Inseparability (II) Indexes (Humphrey and Saul 1998) for the cells were, respectively: 0.79 and 0.89; 0.07 and 0.07; and 0.12 and 0.01. *B*, *D*, and *F*: mean  $\pm$  SE fundamental response phase is plotted as a function of stimulus temporal frequency for each receptive-field position on the left that yielded acceptably reliable timing. Each set of points was fit by a line to estimate latency (slope, in ms) and absolute phase (intercept, in cycles), the values of which are indicated in parentheses. Values for receptive-field position reflect rounding.

in the receptive field and minimized the distance around the circumference of the absolute phase axis.

#### Identifying cells

Simple cells were identified as previously described (Humphrey and Saul 1998). Cells in the LGN were identified as X or Y based on previously published criteria. In order of importance these were linearity of summation to counterphasing sinewave gratings (Enroth-Cugell and Robson 1966), latency to electrical stimulation of the optic chiasm, and receptive-field center size (Humphrey and

Weller 1988a). Cells were also identified as lagged, nonlagged, or partially lagged by their responses to square-wave luminance-modulated spots centered in the receptive field (Humphrey and Weller 1988a; Mastronarde 1987a).

#### Statistics

Most comparisons between means were based on the *t*-test (Winer 1962). When nonparametric statistics were required, the tests used (Siegel 1956) are indicated in the text.

## RESULTS

*Examples of response timing in simple cells*

Figure 1 illustrates response timings in three representative simple cells from normal and strobe-reared cats. For each cell, a set of PSTHs obtained at one of several tested temporal frequencies shows the S-T structure of the receptive field (Fig. 1, A, C, and E). For each stimulus position we plotted the fundamental response temporal phase versus stimulus temporal frequency and fit the points with a line. Figure 1, B, D, and F, shows data for stimulus positions with reliable timings. Latency and absolute phase values derived from these fits are indicated in parentheses.

The figure illustrates three points. First, for most positions, phase values were quite reliable, as indicated by the low standard errors of phase (e.g., Fig. 1B). Second, data at these positions were adequately fit by a straight line, thus providing reliable measures of absolute phase and latency. Third, there were clear differences between cells in how timing was organized across the receptive field. The direction-selective cell in Fig. 1A, from a normal cat, had a receptive field characterized at most temporal frequencies by small ( $\leq 0.25$  cycles) shifts in response phase between adjacent positions (Fig. 1B). For each position, the phase versus temporal frequency plots revealed the component timings underlying the response phase values. For example, position  $0.5^\circ$  had a latency of 95 ms and an absolute phase lead of  $-0.16$  cycles. Position  $0.2^\circ$  displayed a somewhat longer latency (127 ms) and an absolute phase lag ( $+0.08$  cycles). These and other timings were spatially organized to produce S-T inseparability.

The other two cells (Fig. 1, C and E), respectively from a normal and strobe-reared cat, were not direction selective. Each had a separable receptive field characterized by virtually identical timing within each zone. For example, all receptive-field positions in Fig. 1C had short latencies ( $\sim 72$  ms) and small absolute phase leads (approximately  $-0.06$  cycles; Fig. 1D).

*Range of timings in cortical receptive fields: single cell versus population data*

The differences between cells in Fig. 1 that were or were not direction selective epitomize the key effect of strobe rearing: it produced a compression in the range of response timings in individual receptive fields. For example, the inseparable field in A, from a normal cat, resulted from latency and absolute phase values that spanned a range of 40 ms and 0.35 cycles, respectively. In contrast, the range for the separable field in E, from a strobe-reared cat, was narrower: 29 ms and 0.03 cycles.

Table 1 summarizes the timing ranges observed among individual cells in the two rearing groups. Layer 4 receptive fields in normal cats displayed absolute phase values that extended over 0.205 cycles, on average. The mean range of latencies was 39 ms. In contrast, layer 4 cells in strobe-reared cats displayed a significantly narrower range of absolute phase values (0.079 cycles;  $P < 0.001$ ). Their average latency range (31 ms) was lower but not significantly different from normal. Interestingly, the nonsignificant reduction

in mean latency reflected the inclusion of three cells that remained direction selective and S-T inseparable. Without them the mean latency range was 28 ms, significantly ( $P < 0.05$ ) lower than normal; the absolute phase range also remained lower (0.070 cycles). Overall, then, strobe rearing reduced the timing range in layer 4 receptive fields, with absolute phase showing the greatest reduction.

Layer 6 cells are normally less S-T inseparable than layer 4 cells (Humphrey and Saul 1998; Murthy et al. 1998), and this was reflected in their narrower mean range of absolute phase and latency: 0.122 cycles and 32 ms (Table 1). Strobe rearing significantly reduced both of these ranges, to 0.068 cycles and 23 ms, respectively ( $P \leq 0.035$ , Mann-Whitney  $U$  test). This reduction accords with the strobe-induced decrease in the Inseparability Indexes of layer 6 cells reported in the companion paper (Humphrey and Saul 1998).

Comparing only cells that were not direction selective, all of which had separable receptive fields, we found no differences between normal and strobe-reared cats in individual cell timing ranges (Table 1). For both groups, the latency range was  $\sim 29$  ms, and the absolute phase range was  $\sim 0.08$  cycles.

Given the strobe-induced compression in timing range within single receptive fields, one might expect a corresponding reduction in the timing range of the cortical population. However, this was not the case. Figure 2 plots the latency and absolute phase values for all receptive-field positions tested in the two rearing groups. Normal cats displayed absolute phase values that were distributed fully across the negative and positive quarter cycles (Fig. 2A;  $-0.12 \pm 0.009$  cycles, mean  $\pm$  SE). The distribution of latencies also was quite wide, extending from about 55 to 200 ms ( $97 \pm 1$  ms). Figure 2B reveals that strobe-reared cats displayed a range of timings as wide as that in normal animals. The mean latency ( $96 \pm 1$  ms) was essentially identical to normal. However, the mean absolute phase ( $-0.07$  cycles) was shifted slightly toward zero and the distribution was narrowed (SE, 0.008 cycles). This can be appreciated in the scatter plot as a greater than normal frequency of values between  $-0.10$  and  $0.05$  cycles. The change in the absolute phase distribution was statistically significant ( $P < 0.001$ ) and was observed separately in layers 4 and 6. We have previously shown that absolute phase values near zero tend to reflect sustained responses, compared with values of approximately  $\pm 0.25$ , which reflect transient responses (Saul and Humphrey 1990). Strobe rearing thus appears to have increased the frequency of positions generating sustained visual responses. We will address the potential impact of this shift below. For now, the important point from Fig. 2 is that a full range of timing was present in the population of strobe-reared simple cells.

The analysis of response timing is continued in Fig. 3, which graphically shows how strobe rearing compressed the range of absolute phase values in single layer 4 cells but did not affect the population range. Data from 31 cells in each rearing group are shown. Tick marks along each horizontal bar plot the absolute phase values measured in a receptive field. Directional Indexes (DI) are indicated to the right of the bars. The key point is that most of the direction-selective cells in normal layer 4 displayed values that spanned large

TABLE 1. Range of response timings in individual receptive fields

	All Cells				Non-DS Cells	
	Layer 4		Layer 6		All layers	
	Latency, ms	Absolute phase, cycles	Latency, ms	Absolute phase, cycles	Latency, ms	Absolute phase, cycles
Normal	39 ± 22 (31) [3–115]	0.205 ± 0.102 (31) [0.037–0.382]	32 ± 15 (9) [12–58]	0.122 ± 0.062 (9) [0.043–0.215]	29 ± 17 (8) [10–58]	0.085 ± 0.032 (8) [0.040–0.140]
Strobe	31 ± 18 (31) [1–96]	0.079 ± 0.051 (31) [0.014–0.241]	23 ± 14 (21) [1–55]	0.068 ± 0.039 (21) [0.003–0.167]	28 ± 16 (51) [1–81]	0.074 ± 0.051 (51) [0.0–0.220]
Significance	NS	P < 0.001	P = 0.035	P = 0.013	NS	NS

Values are means ± SD with number of cells in parentheses and minimum and maximum values of timing ranges in brackets. The layer 4 group includes a few cells localized to the layer 3/4 border region and layer 5A; layer 6 group includes some cells located in layer 5B (see Fig. 8). Nondirection-selective cells had DIs <0.33. Comparisons are based on cells displaying at least 3 positions with acceptably reliable timing, with the exception of 2 cells from strobe-reared cats with very small receptive fields that were each completely tested by 2 bar positions. Statistical comparisons reflect Mann-Whitney *U* test for samples <10; otherwise a *t*-test was used. NS, not significant.

portions of the absolute phase axis (Fig. 3A). In comparison, values for most single cells in strobe-reared cats spanned a much more limited range. In effect, narrow regions of the phase axis were sampled by different cells.

We noted above that strobe rearing produced a slight shift in the distribution of absolute phase values, with a greater than normal frequency occurring around −0.05 cycles. Figure 3B also reveals a tendency for absolute phase values to fall near this phase region. Might the compression in phase range among layer 4 receptive fields simply reflect a change in the underlying distribution of phase values? That is, if the range of absolute phase values in any single receptive field were to reflect mainly the frequency of timings available in the cortical population, then the greater frequency near −0.05 cycles in strobe-reared cats might account for the compressed phase range in receptive fields. We will show that a strobe-induced change in the frequency of certain timings could contribute to the compression in at most a minor way, but other factors must play a critical role.

Figure 4, A and D, shows the distribution of absolute phase values for the cells in Fig. 3 expressed in terms of sampling probability. The strobe distribution peaked closer to −0.05 cycles than the normal one and was somewhat narrower. Figure 4, B and E, plots joint probability distributions, which show to what extent pairs of absolute phase values were observed in single cells. For these plots, all combinations of pairs in each receptive field were considered. The contours reflect the frequency of finding a given pair of values associated in a cell. In normal cats (B) the joint distribution was moderately wide, with a reasonable probability of finding negative and positive phase values in a cell. For strobe-reared cats (E), the joint distribution was much narrower, with phase values being similar in single receptive fields, and very few pairings of positive with negative values. This partly reflects relatively fewer absolute phases near 0.15 cycles (D). However, the distribution in D does not account for the compressive effect of strobe rearing on individual cell timing ranges, as revealed next.

Figure 4, C and F, illustrates distributions of conditional probability: given that a cell has some position with absolute phase value  $\varphi$ , what is the probability that it has another position with absolute phase value  $\psi$ ? Here,  $\varphi$  and  $\psi$  are

points on the vertical and horizontal axes, respectively. These probabilities were obtained by dividing the joint probabilities in B and E, respectively, by the marginal probabilities in A and D. The distribution for normal cats (C) showed strong associations between differing absolute phase values (e.g., +0.15 and −0.15 cycles). In contrast, the strobe distribution (F) was restricted to the diagonal; only similar values were associated. Another way to view these plots is to ask whether, in a cell that had one absolute phase value of, for example, 0.1 cycles, another position was likely to have a value of −0.1 or 0.1 cycles. For normal cells, either value was likely. For cells in strobe-reared cats, only the 0.1 cycles pairing was likely, despite the lower underlying probability (D) of such absolute phase values.

These analyses indicate that the strobe-induced compression in absolute phase range among simple cells primarily reflects factors other than, or in addition to, the slight narrowing in the underlying frequency distribution of absolute phase values. We will argue below that strobe stimulation evokes a process that restricts the range of inputs to an individual cell based on the similarity of the input timings. As a foundation for this proposal, we next consider some specific sources of inputs to simple cells, the potential effect of strobe rearing on them, and their likely contribution to cortical timings in normal and strobe-reared cats.

#### Alterations in geniculocortical relationships?

The fact that strobe rearing greatly narrowed the range of timings in single receptive fields suggests that it altered cells' inputs. The LGN is a major source of inputs to cortex, and the afferent timings may be relayed to cortical cells either directly (Reid and Alonso 1995; Tanaka 1983) or indirectly via other cortical neurons. The present finding that a wide range of timings was present across the cortical population following strobe rearing (Fig. 2) thus led us to two hypotheses: 1) the LGN was relatively normal after strobe rearing, and 2) the rearing impacted how geniculate inputs with different timings became linked to individual cortical cells. In the following sections, we pursue these hypotheses. We first show that strobe-reared LGN was normal. We then return to cortex to show that different geniculate timing types became segregated onto different cortical cells.

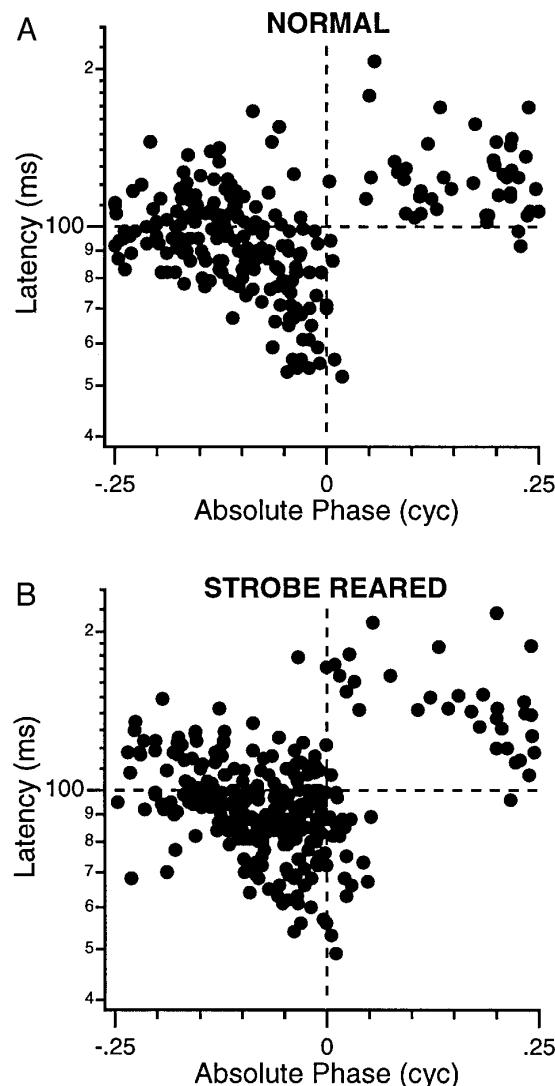


FIG. 2. Distributions of latency and absolute phase for 229 receptive-field positions in 46 cells from normal cats (A), and 303 positions in 84 cells from strobe-reared cats (B). Absolute phase values are normalized to a half cycle (see METHODS). Dashed lines are cutoff values for distinguishing lagged and nonlagged cells in the lateral geniculate nucleus (LGN). Strobe rearing did not affect the range of timings but increased the frequency of absolute phase values near 0 (see text). Note that in normal cats, the absolute phase distribution is similar to that which we reported previously for normal cats (Saul and Humphrey 1992a), but the mean latency is ~20 ms greater than the earlier sample. The upward shift in latency may reflect the slightly lower mean luminance used in the present study (i.e., 15 vs. 25 cd/m<sup>2</sup>).

#### Cell types and response timings in the LGN

We recorded from 52 cells in the geniculate A-laminae of strobe-reared cats. Most receptive fields were within 10° of the area centralis. The physiological class of all but two units could be easily identified. The exceptions were one cell with mixed X and Y properties and one that was suppressed by bright and dark stimuli. Mixed cells exist in normal cats (Wilson et al. 1976); whether the suppressed cell reflects an effect of strobe rearing is unclear based on our small sample. What was clear, however, was that X and Y cells of the lagged and nonlagged types could be sampled

at normal frequencies. As in normal cats (Humphrey and Saul 1992; Saul and Humphrey 1990) most (87%) of the cells recorded at these central retinal eccentricities were X type, with 31, 64, and 5% being lagged ( $X_L$ ), nonlagged ( $X_N$ ) and partially lagged ( $X_{PL}$ ), respectively. The remainder were Y cells, all but two of which were nonlagged.

Figure 5 illustrates responses from four typical cells recorded in strobe-reared cats. Each PSTH was generated by placing a spot in the cell's receptive-field center and flashing it off and on using the four-part luminance cycle indicated below the lower histograms. These examples are ON-center cells; thus we analyzed responses to the onset of the bright spot, the third quadrant in the cycle. Figure 5, A and B, is from an  $X_N$  and  $Y_N$  cell; each responded to spot onset with a brisk transient discharge followed by variably sustained firing, and then a rapid firing decay at spot offset. Figure 5, C and D, shows responses of two  $X_L$  cells; each displayed a strong inhibitory dip in discharge (arrows) at spot onset that delayed the subsequent excitatory response by ~50–90 ms relative to that of the nonlagged cells. At spot offset each  $X_L$  cell generated a brief “anomalous offset discharge” (asterisks) that was followed by a slow decay in firing. The response profiles of these and nearly all other cells were indistinguishable from lagged and nonlagged responses in normal cats (Humphrey and Weller 1988a; Mastronarde 1987a).

The minimum criteria for distinguishing lagged and nonlagged cells quantitatively are latencies to half-maximal (*halfrise*) and half-minimal (*halffall*) discharge at spot onset and offset, respectively. Figure 6A (and Table 2) shows the distribution of these measures for cells in normal cats. Half-rise and halffall latencies of ~65 ms (dashed lines) were cutoffs for distinguishing lagged and nonlagged cells. A few X cells were identified as partially lagged ( $X_{PL}$ ) due to having mixed latencies (e.g., long halfrise but short halffall). Overall, this distribution is very similar to that reported by Mastronarde (1987a) and Humphrey and Weller (1988a). In strobe-reared cats the latencies to flashing spots were nearly identical to those in normals (Fig. 6B). There were no differences between rearing groups in mean halfrise or halffall latency for lagged and nonlagged cells (Table 2), or in their cutoff latencies.

We also measured latency and absolute phase from responses to sinewave-modulated spots. In normal cats (Fig. 7A) a wide range of values was observed, which reflects variation across the lagged and nonlagged populations. Nearly all  $X_N$  and  $Y_N$  cells, identified as such using flashing spots, had latencies <100 ms and absolute phase leads; most  $X_L$  and  $Y_L$  cells had latencies >100 ms and absolute phase lags. These distributions are similar to those previously reported (Saul and Humphrey 1990). Strobe rearing had no obvious effect on these timing distributions (Fig. 7B). Although there were slightly fewer nonlagged cells with large phase leads, paralleling the slight reduction in these timings in cortex (Fig. 2B), there were no significant rearing-associated differences in absolute phase or latency, either across the geniculate population or within cell groups (Table 2).

**OTHER RESPONSE PROPERTIES.** We noted previously (Humphrey and Saul 1998) that strobe rearing did not alter the

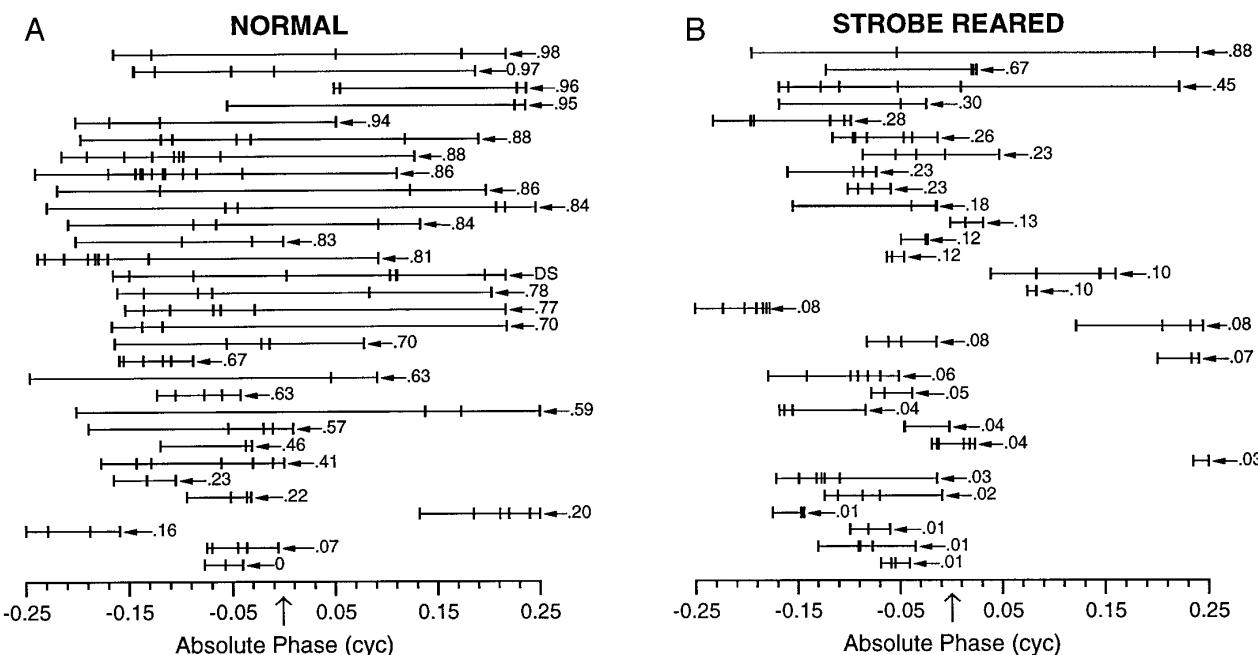


FIG. 3. Absolute phases observed in individual layer 4 cells. Tick marks along each bar indicate phase values measured at different receptive-field positions. As noted in METHODS, the phase axis is circular, being connected at  $\pm 0.25$  cycles, but for clarity it is presented here as linear. The DI is indicated to the right of each bar. Bars are organized from bottom to top according to increasing direction selectivity. Arrows on abscissae indicate 0 absolute phase. A: in normal cats, there was a clear trend toward greater absolute phase range with increasing direction selectivity ( $r = 0.66, P < 0.001$ , Pearson correlation). Also, most direction-selective cells displayed absolute phase leads and lags. The cell labeled "DS" was highly selective during hand plotting, but its tuning was not quantified. B: in strobe-reared cats most cells were not direction selective; individual simple cells displayed much narrower absolute phase ranges that sampled phase leads or lags but rarely both. Only cells having 3 or more positions with reliable timing are included in the figure, with 2 exceptions (see Table 1 legend).

spatial or temporal tuning of simple cells in area 17. Likewise, within each geniculate cell class, we found no rearing effect on optimal spatial and temporal frequency or spatial and temporal resolution. There was no effect on receptive-field dimensions, and cells were normal in peak and average firing rates and in latency to optic chiasm stimulation.

Strobe rearing thus had no apparent effect on the development of cells in the A-laminae. Although we did not distinguish between relay neurons and interneurons, it is likely that all lagged and most nonlagged cells projected to visual cortex, as in normal cats (Humphrey and Weller 1988a,b; Mastronarde 1987a). Further, comparison of Figs. 2 and 7 indicates that the geniculate timings could account for many of the cortical timings in strobe-reared, as in normal, cats. Cortical positions with absolute phase leads and latencies  $<100$  ms likely reflect nonlagged inputs, whereas positions with absolute phase lags and latencies  $>100$  ms reflect lagged inputs. In both rearing groups, the slightly longer latencies observed in cortex, compared with LGN, could reflect cortical integration and the relaying of geniculate timings through other cortical neurons. Note that in both groups many cortical positions displayed timing that was neither lagged- nor nonlagged-like. Most of these "unclassifiable" positions had long latencies and absolute phase leads. They might reflect nonlagged timings whose latencies are increased intracortically via the above mechanisms. They might also reflect inputs that are subject to synaptic depression (Abbott et al. 1997; Chance et al. 1998), which, theoret-

ically, would advance response timing in a cortical cell relative to its inputs, and increase latency.

#### Effects of strobe rearing on the convergence of geniculate-like timings in individual simple cells

Having determined that strobe rearing did not affect lagged and nonlagged LGN cells, we pursued the hypothesis that it interfered with the linking of their timings in cortical cells. Indeed, Fig. 3 suggests that this was the case. In normal layer 4, the range of absolute phase values in many direction-selective receptive fields reflected phase leads and lags (Fig. 3A). After strobe rearing receptive fields displayed either phase leads or lags, but rarely both (Fig. 3B). The main exceptions were the few direction-selective cells, which displayed both types of timings. To further address the linkage hypothesis, we classified cortical cells based on their geniculate-like timings, using both absolute phase and latency to identify timing type.

Simple cells were classified as predominantly nonlagged, predominantly lagged, or mixed as in a previous study (Saul and Humphrey 1992a). Predominantly lagged or nonlagged cells had  $\geq 50\%$  of their positions identified as lagged-like or nonlagged-like, respectively, and  $<20\%$  of the opposite type. Cells were deemed mixed if  $>20\%$  of their positions were lagged-like and  $>20\%$  nonlagged-like. Most cells also had one or more position with admissible but unclassifiable timing (e.g., Fig. 2). These positions were taken into account

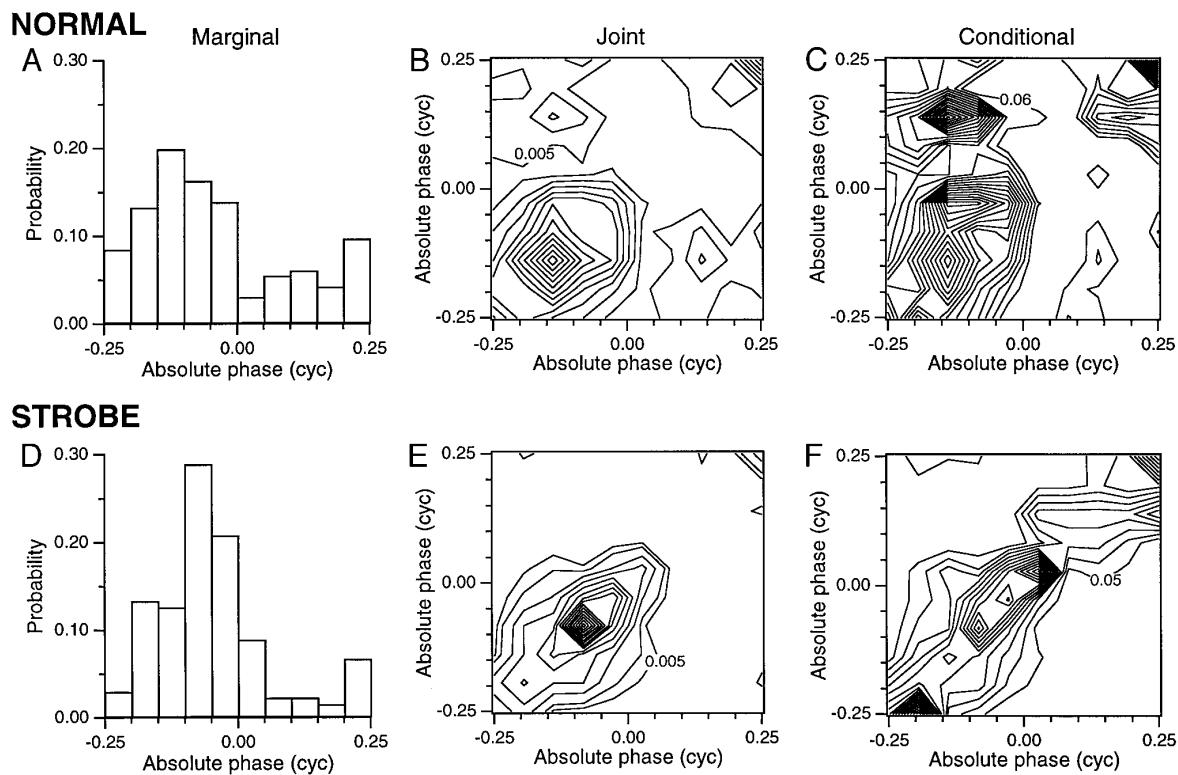


FIG. 4. Probability distributions of absolute phase values for the layer 4 cells in Fig. 3. A and D: histograms show the probability of sampling various absolute phase values in the 2 rearing groups. Strobe rearing slightly shifted the mean value and reduced the variation in the distribution. B and E: contour lines plot the joint probability distribution: the frequency with which pairs of absolute phase values were associated in single cells. Compared with normal cats, strobe-reared animals displayed a narrow range of pairings. C and F: contour lines plot conditional probability distributions, the probability that a cell displays a particular absolute phase value (x-axis) given that it has another value (y-axis). In normal cats, associations between different values were common. After strobe rearing, only similar values tended to be associated, independent of the underlying sampling distribution. This suggests a strobe-associated process that limits inputs to a cortical cell based on their timing. Contour lines plot probabilities from 0.005 to 0.064 in B, 0.06 to 0.367 in C, 0.005 to 0.147 in E, and 0.05 to 0.888 in F, with the lowest contour in each plot identified by its value.

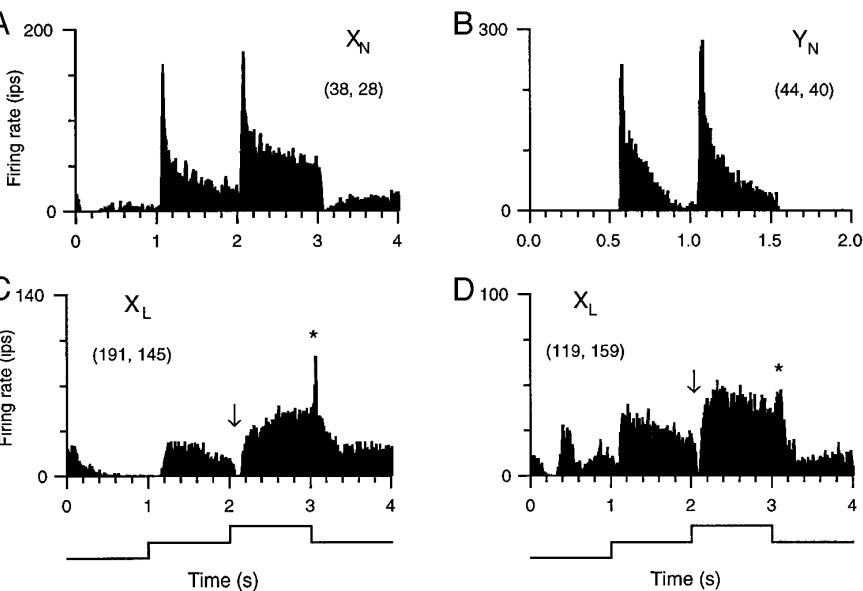


FIG. 5. Average responses to flashing spots of 4 ON-center LGN cells in strobe-reared cats. Spot luminance, indicated by the step profiles at bottom, was modulated over a 4-part cycle to include luminances below, equal to, above, and equal to the surrounding screen luminance. Contrast was  $\sim 0.5$ . Latency (in ms) of each cell to half-maximal (halfrise) and half-minimal (halffall) discharge at spot onset and offset, respectively, are indicated in parentheses. A and B: responses of an  $X_N$  and  $Y_N$  cell. C and D: responses of 2  $X_L$  cells. Arrows and asterisks mark inhibitory dips and anomalous offset discharges, respectively. These profiles are indistinguishable from lagged and nonlagged responses in normal cats.

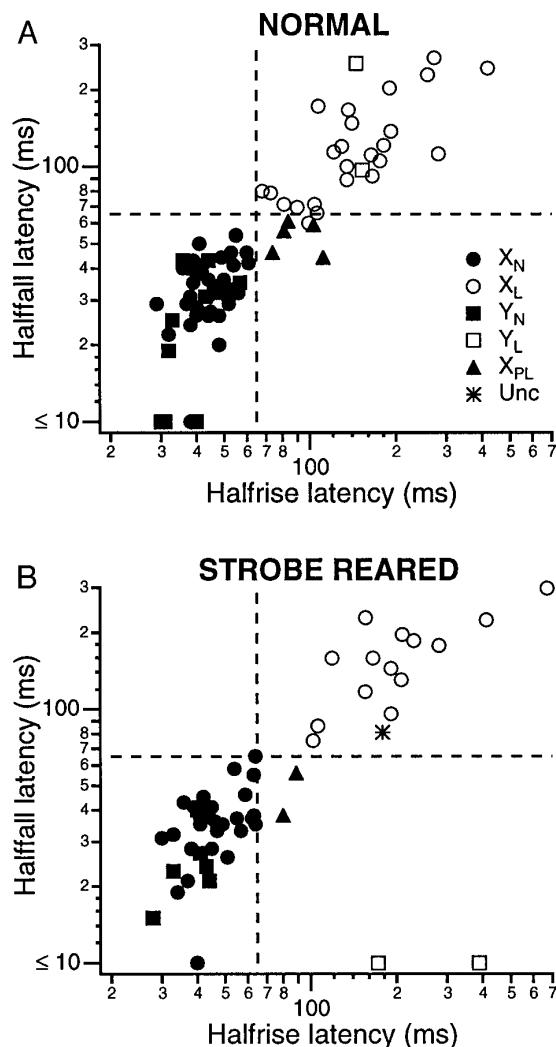


FIG. 6. Distributions of halfrise and halffall latencies for each class of LGN cells in normal (A) and strobe-reared (B) cats. Cells indicated by “ $\leq 10$ ” had halffall latencies that could not be measured due to responses having decayed to baseline before spot offset. Summary statistics for cells in the 3 major classes ( $X_N$ ,  $X_L$ , and  $Y_N$ ) are indicated in Table 2. Latency distributions were unaffected by strobe rearing.

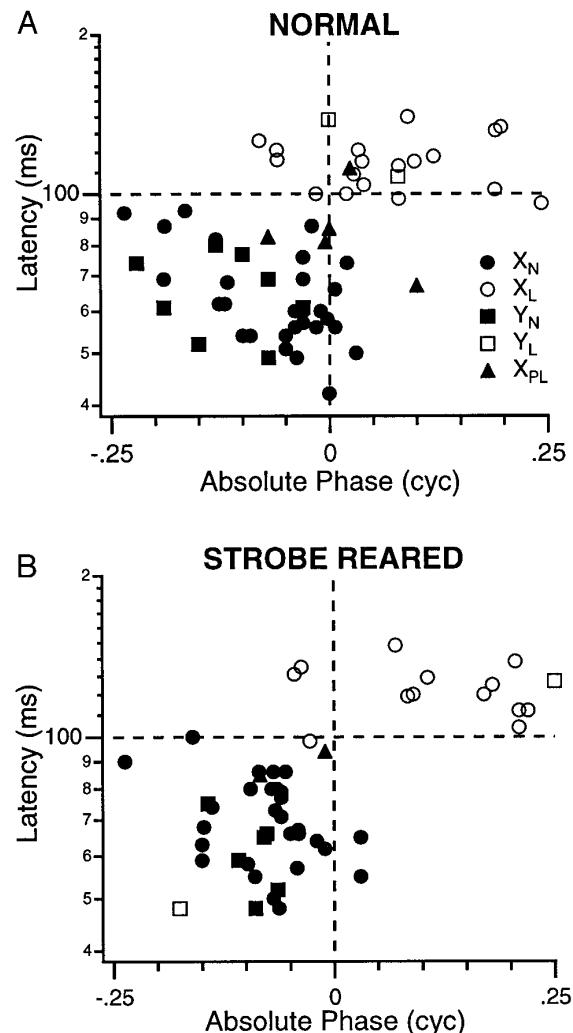


FIG. 7. Distributions of latency and absolute phase for LGN cells in normal (A) and strobe-reared (B) cats. Summary statistics are indicated in Table 2 for the major classes. Strobe rearing had no significant effect on the timing values of any cell class.

TABLE 2. Response timing properties of LGN cells

Cell Type	Halfrise, ms	Halffall, ms	Absolute Phase, cycles	Latency, ms
$X_N$				
Normal	46 $\pm$ 7 (38)	33 $\pm$ 9 (38)	-0.064 $\pm$ 0.071 (28)	64 $\pm$ 14 (28)
Strobe	48 $\pm$ 10 (28)	36 $\pm$ 11 (28)	-0.076 $\pm$ 0.058 (28)	70 $\pm$ 13 (28)
$Y_N$				
Normal	39 $\pm$ 8 (10)	27 $\pm$ 14 (10)	-0.120 $\pm$ 0.065 (8)	65 $\pm$ 11 (8)
Strobe	38 $\pm$ 6 (6)	25 $\pm$ 8 (6)	-0.093 $\pm$ 0.028 (6)	61 $\pm$ 10 (6)
$X_L$				
Normal	174 $\pm$ 108 (25)	135 $\pm$ 74 (25)	0.075 $\pm$ 0.095 (19)	113 $\pm$ 13 (19)
Strobe	229 $\pm$ 151 (14)	163 $\pm$ 62 (14)	0.110 $\pm$ 0.090 (13)	112 $\pm$ 14 (13)

Values are means  $\pm$  SD with number of cells in parentheses. Halfrise and halffall were measured using flashing spots. Absolute phase and latency were derived from responses to counterphasing spots. Lagged Y and partially lagged X cells are not included because too few were sampled to provide meaningful comparisons. There were no significant differences between normal and strobe-reared cats on any of the timing measures. LGN, lateral geniculate nucleus;  $X_N$ , nonlagged X cell;  $Y_N$ , nonlagged Y cell;  $X_L$ , lagged X cell.

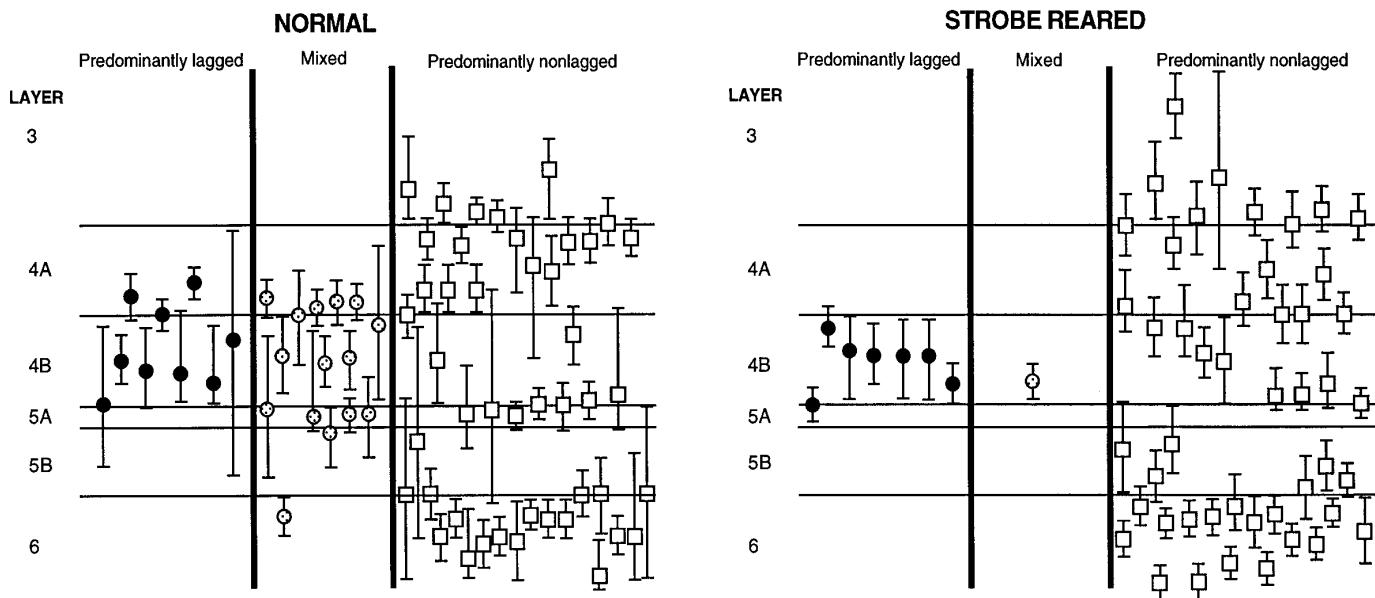


FIG. 8. Laminar locations of cells in each of the 3 cortical cell timing categories, for each rearing group (see text for description). Error bars indicate our subjective assessment of the maximum error in assigning recording locations. On average, receptive fields in the normal (*A*) and strobe-reared (*B*) cats, respectively, had 5.4 and 4.4 positions with acceptable timing; the means were not significantly different ( $P > 0.05$ , *t*-test). Number of cells: normal, 69; strobe-reared, 54. The laminar distributions of response timing categories were unaffected by strobe rearing. In particular, lagged-like timing was generally restricted to lower layer 4. However, mixed cells were virtually absent after strobe rearing.

in calculating percentages of timing types. However, any cell with  $>50\%$  of its positions deemed unclassifiable was excluded from the comparison. Using these criteria, on average 80% of the receptive-field positions in cells from both rearing groups displayed classifiable timing. Figure 8 shows the numbers of cells in the three categories for each rearing group. Although this is a rather coarse categorization, it is a convenient way of considering how the afferent timings were distributed in cortical cells. We will show that strobe rearing not only eliminated the convergence of lagged- and nonlagged-like timing, but it constricted the range of timings among cells dominated by one or the other afferent type.

**NORMAL CATS.** The sample from normal cats consisted of 31 cells from a previous study (Fig. 15 of Saul and Humphrey 1992a) and 38 new cells. Of these, 9 cells (13%) were predominantly lagged, 45 (65%) were predominantly nonlagged, and 15 (22%) were mixed (Fig. 8*A*). An example of a predominantly nonlagged cell that was not direction selective is illustrated in Fig. 1*C*. Six of the seven positions tested had admissible timing, and all were nonlagged-like, having latencies  $<100$  ms and absolute phase leads. As noted above, the narrow range of timings produced an S-T separable receptive field.

Another cell from a normal cat is shown in Fig. 1*A*; it exhibited mixed timing. Two positions ( $+0.5^\circ$  and  $+0.9^\circ$ ) were nonlagged-like, two ( $-0.9^\circ$  and  $+0.2^\circ$ ) were lagged-like, and two were unclassifiable. As noted above, these timings produced an inseparable receptive field that was direction selective.

**STROBE-READED CATS.** Of 54 cells in strobe-reared cats, 7 (13%) were predominantly lagged, 46 (85%) were predominantly nonlagged, and 1 (2%) was mixed (Fig. 8*B*). Strobe

rearing thus had no effect on the sampling of predominantly lagged cells but led to a slight increase in the frequency of predominantly nonlagged cells (i.e., 65 to 85%) and a marked decrease in mixed cells (22 to 2%).

An example of a predominantly nonlagged cell is illustrated in Fig. 1*E*. The mean latency of the four positions with admissible timing was 83 ms, with little variation (Fig. 1*F*). Similarly for absolute phase, variation around the mean of  $-0.029$  cycles was low. These homogeneous timings underlay the S-T separable receptive field and lack of direction selectivity.

Figure 9*A* illustrates an S-T separable receptive field that was predominantly lagged and not direction selective. It had a small receptive field that was completely tested by four stimulus positions, three of which provided reliable lagged-like responses (Fig. 9*B*). Again, the positions had very similar timing: mean latency and absolute phase were 166 ms and 0.016 cycles, respectively.

These two examples were typical of strobe-reared simple cells. Most of the separable receptive fields could be accounted for largely by positions with nonlagged- or lagged-like timings. Additionally, there often was one or more unclassifiable position that displayed an absolute phase similar to the other positions. This resulted in uniform timing across the receptive field. Importantly, compared with normal cats, receptive fields with mixed timing were rare. Only one had clearly mixed timing, and it was S-T inseparable and directionally tuned (not illustrated).

The strobe-induced timing compression in receptive fields thus reflected a nearly complete loss of convergent lagged- and nonlagged-like timings that characterize mixed cells. However, the compression extended beyond mixed cells and also impacted predominantly lagged and nonlagged cells. In

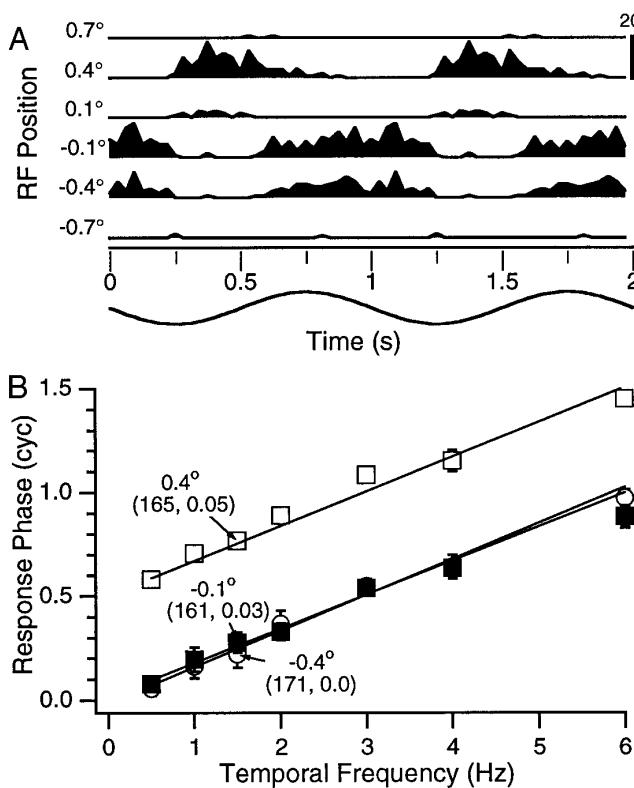


FIG. 9. Example of a simple cell with predominantly lagged timing recorded in layer 4 of a strobe-reared cat. A: S-T map obtained using counterphasing bars undergoing sinusoidal luminance modulation at 1 Hz. B: response phase vs. temporal frequency data for 3 positions were fit by lines to measure latency and absolute phase, the values of which are indicated in parentheses. The cell's DI and II were 0.13 and 0.0, respectively. Conventions are as in Fig. 1.

layer 4 of normal cats, cells in these latter two groups displayed an absolute phase range of  $0.166 \pm 0.091$  cycles (mean  $\pm$  SD,  $n = 18$ ; sample taken from cells recorded in present study). Strobe rearing reduced the mean range to  $0.075 \pm 0.043$  cycles ( $n = 26$ ), a value significantly lower than normal ( $P < 0.02$ ). In layers 5B and 6 of normal cats, where virtually all cells were predominantly nonlagged, strobe rearing reduced the mean absolute phase range from  $0.122 \pm 0.043$  cycles ( $n = 9$ ) to  $0.068 \pm 0.003$  cycles ( $n = 21$ ;  $P = 0.013$ , Mann-Whitney  $U$  test). Thus the timing compression affected most cells, independent of their timing category.

We should note that the lower frequency of cells with lagged-like timing in Fig. 8B, relative to 8A, does not imply that strobe rearing substantially reduced the occurrence of such timings in cortex. Among all cells in layer 4, where most lagged timings were found, 19% of timings were lagged-like in strobe-reared cats, compared with 25% in normals. The frequency of lagged timings relative to other timing types was not significantly different between the two rearing groups ( $P > 0.3$ ,  $\chi^2$  test).

#### Laminar locations of timing types

We previously showed that simple cells with lagged- and/or nonlagged-like timing have characteristic laminar distri-

butions in area 17 (Saul and Humphrey 1992a). Figure 8A shows the distribution for our expanded normal sample. Simple cells with predominantly nonlagged timing were concentrated in two zones: lower layer 3 through the 4/5 border zone, and layer 6. Their distribution corresponds well to the laminar terminations of nonlagged afferents (Humphrey et al. 1985). In contrast, cells with significant amounts of lagged-like timing (i.e., predominantly lagged or mixed) were largely restricted to the region extending from lower layer 4A through the 4/5 border zone, including layer 5A. We previously (Saul and Humphrey 1992a) summarized evidence that these locations correspond to the likely termination zones of lagged afferents.

Figure 8B shows that strobe rearing had little effect on the laminar distributions. Predominantly nonlagged cells were found mainly in and adjacent to layers 4 and 6. Cells with lagged timing were restricted to lower layer 4. These results, along with the LGN data above, suggest that not only did lagged and nonlagged cells develop appropriately during strobe rearing, but their laminar targets in cortex were grossly normal.

#### DISCUSSION

In the companion paper (Humphrey and Saul 1998) we showed that the loss of direction selectivity in simple cells resulting from strobe rearing reflects the elimination of S-T inseparable receptive-field structure. The response timings measured here provide a complementary view of these receptive fields and reveal a strobe-induced compression in the range of latency and absolute phase values in individual cells. Despite the compression, a wide range of timings was observed in the cortical population. Further, lagged and nonlagged cells appeared to be normal, and their different response timings could account for most of the cortical timings, as in normal cats (Saul and Humphrey 1992a). The strobe-induced deficit, therefore, is a failure to link inputs with different response timing onto individual cortical cells. Only inputs with similar timing become linked, and this produces S-T separable receptive fields.

In the following sections, we review the circuitry that appears to underlie response timings in LGN, and consider the implications of their normal development despite strobe rearing. Next we review evidence that the LGN contributes to cortical timings in normal cats, and consider geniculocortical timing relationships following strobe rearing. Finally, we propose a model to account for the strobe-induced changes in receptive-field structure and direction selectivity.

#### Strobe rearing and LGN development

Strobe rearing had no major effect on neurons in the A-laminae of the LGN. Lagged and nonlagged X- and Y-cells were sampled in normal frequencies, and their temporal and spatial response properties were normal. Thus geniculate, and presumably retinal, circuits appear to have developed appropriately despite the altered temporal pattern of stimulation. Physiological and anatomic evidence indicates that lagged and nonlagged responses are produced by different circuits. Lagged cells receive their excitatory drive from

retinal cells that have nonlagged-like discharge profiles (Mastronarde 1987a; Mastronarde et al. 1991). Lagged cells also appear to receive input from intrageniculate inhibitory neurons (Humphrey and Weller 1988b), retinal activation of which appears to trigger rapid, feed-forward inhibition of the lagged cells (Mastronarde 1987b) that is mediated by GABA<sub>A</sub> receptors (Heggelund and Hartveit 1990). The inhibition accounts for the profound dip in discharge and delayed halfrise latency to flashing spots (Fig. 5C) (Heggelund and Hartveit 1990), and likely underlies the absolute phase lag measured using sinewave stimuli (Saul and Humphrey 1990). In addition, the long latencies of lagged cells and their sensitivity to inhibition may reflect a reliance on N-methyl-D-aspartate (NMDA) receptor-mediated retinal activation that is greater than among nonlagged cells (Hartveit and Heggelund 1990; Heggelund and Hartveit 1990; Kwon et al. 1991). The retinal input to nonlagged cells appears to be tied less, or not at all, to feed-forward inhibition, which results in geniculate excitation that largely mimics the temporal pattern of the retinal input (Mastronarde 1987a,b). Again, the development of these different circuits seems unaffected by the strobe paradigm. This suggests that, unlike the cortex, circuit formation in the LGN proceeds independent of the temporal properties of the afferent signal, provided that some amount of signal is present (Dubin et al. 1986). This developmental resiliency parallels the relatively limited effect of monocular lid suture on LGN development. Although that paradigm produces some reduction in Y-cell sampling (Sherman et al. 1972) and changes in some retino-geniculate arbors (Garraghty and Sur 1993), the LGN is relatively less affected than cortex (Sherman and Spear 1982).

In cortex, strobe-reared cats were remarkably similar to normals in the laminar locations of cells with lagged- or nonlagged-like timing (Fig. 8). We infer that strobe rearing did not grossly affect these geniculocortical projections. It remains to be determined whether it influenced the precise patterns of arborization, numbers of synapses, or other features associated with the afferents.

#### Sources of cortical timings in layer 4

Our working assumption is that lagged and nonlagged cells provide the timings that underlie S-T inseparable receptive-field structure and direction selectivity in cat area 17. Here we briefly review evidence from normal animals that supports this assumption. We next consider some alternative models for the origin of cortical timings. Finally, we consider the strobe rearing results from a geniculocortical perspective. We will focus on layer 4 because the relationship between S-T structure and direction selectivity is clearest there.

Multiple lines of evidence from normal cats indicate an important role for lagged and nonlagged afferents in determining cortical response timing. 1) About 40% of X cells, the dominant input to area 17, are lagged while the rest are nonlagged (Humphrey and Weller 1988b), so both groups must have a substantial impact on cortex. 2) Lagged- and nonlagged-like timings are readily identifiable in simple-cell receptive fields (Saul and Humphrey 1992a; and present

data); these timings can most simply be accounted for by inputs from the LGN. 3) Cells with the most S-T inseparable receptive fields are found in layer 4 (Humphrey and Saul 1998; Murthy et al. 1998), where the two afferent groups appear to converge. Some inseparable receptive fields there result from spatially interdigitating zones of lagged- and nonlagged-like timing. Others may achieve inseparability via a range of, for example, nonlagged-like timings. 4) Many cortical cells are direction selective at low temporal frequencies and lose their selectivity at ~4 Hz (Saul and Humphrey 1992b). This pattern is predicted by the changing temporal phase relationships between lagged and nonlagged cells with increasing temporal frequency (Saul and Humphrey 1990). 5) Cortical cooling, designed to suppress intracortical interactions, fails to reduce direction selectivity in layer 4 cells, as measured from membrane potential fluctuations (Ferster et al. 1996). This result suggests that the geniculocortical inputs convey timing information sufficient to generate directional tuning.

Although these findings support a geniculate origin for the cortical timings, they do not indicate at what stage the timings are combined to influence S-T structure. Direct geniculocortical convergence onto layer 4 cells is highly likely given that nearly all such cells receive monosynaptic input from the LGN (Bullier and Henry 1979; Ferster and Lindstrom 1983; Martin and Whitteridge 1984). Indirect convergence via other cortical cells undoubtedly also plays a role. For example, an S-T inseparable simple cell could be created by inputs from two separable cells in approximate spatiotemporal quadrature. One input could be dominated by lagged timing and the other by nonlagged timing. Various combinations of excitatory and/or inhibitory intracortical interactions are possible. Recent work has shown that intracortical inhibition also contributes to inseparability. For some layer 4 simple cells, blocking GABA<sub>A</sub>-mediated inhibition by iontophoretic application of bicuculline concomitantly reduces S-T inseparability and direction selectivity (Murthy and Humphrey 1998). Thus a variety of geniculocortical and intracortical interactions likely play a role in producing direction selectivity. Importantly, our studies indicate that the LGN is the primary source of the response timings that underlie these interactions. We assume that the timings are distributed through, and further modified by, intracortical networks, and combined in different ways to produce S-T inseparable structure and direction selectivity.

Other models of cortical direction selectivity assume that all relevant mechanisms are intracortical. Two recent models (Maex and Orban 1996; Suarez et al. 1995) have suggested how temporal delays may be created in cortex, with the former explicitly addressing S-T inseparability. Maex and Orban (1996) propose that inseparability arises via corticocortical feedback from simple cells with spatially offset receptive fields. The required temporal delays are produced via excitatory inputs mediated by NMDA receptors. (All LGN inputs are assumed to be nonlagged and identical in timing.) Additionally, direction selectivity is enhanced by inhibitory inputs whose preferred direction is opposite to that of the target cell.

We note that some types of corticocortical connections employed in the Maex and Orban (1996) model would not be incompatible with our suggestions on the cortical net-

works that relay geniculate signals. Again, the main difference between the models is the primary source of the timings: LGN versus cortex. The advantage of the geniculocortical model is that it is based on known timing differences among LGN relay cells. Its simplicity rests on the reasonable assumption that these timings are relayed through cortical networks to produce different S-T structures. Further, long timing delays (e.g., 250–1,000 ms) that are necessary to produce direction tuning at low temporal frequencies (e.g., 1–0.25 Hz) are readily accounted for in terms of known response phase differences between lagged and nonlagged cells at low temporal frequencies (Saul and Humphrey 1990, 1992b). Although, theoretically, long timing delays may be created intracortically, there is little experimental evidence that the postulated mechanisms (e.g., NMDA receptors, GABA<sub>B</sub> receptors) can produce the required delays. The synaptic depression model (Chance et al. 1998) only produces phase leads and hence cannot account for the phase lags measured in many simple cells (Humphrey and Saul 1998; Saul and Humphrey 1992a). Creating directional tuning at higher temporal frequencies (e.g., 5 Hz) requires shorter (e.g., 50 ms) delays, and intracortical mechanisms could produce them. Once again, however, the timings are already available in the nonlagged geniculate population.

Turning to strobe data, the rearing paradigm did not affect the range of timings in the cortical or geniculate populations. Lagged- and nonlagged-like timings were readily observed in strobe-reared cortex and displayed normal laminar distributions. It is likely, therefore, that the LGN continued to serve as the primary source of the cortical timings. Nevertheless, we did observe a narrowing in the distribution of absolute phase values in cortex, with a greater than normal frequency of values near zero (Figs. 3B and 4B). We previously showed (Saul and Humphrey 1990) that absolute phase values near zero generally reflect sustained responses, whereas values farther from zero reflect greater response transience. Strobe rearing thus appears to have increased the frequency of sustained responses to sinewave stimuli. At present, we cannot explain this change.

The major action of strobe rearing was to constrict the range of timings in individual simple cells. From a geniculocortical perspective, this reflected a virtually complete loss of receptive fields with mixed (i.e., lagged and nonlagged) timing (Fig. 8B). Even among predominantly lagged or nonlagged cells, the range of timings was narrower than normal. The result was a widespread elimination of S-T inseparability that was particularly profound in layer 4, where most cells are normally inseparable. These data suggest that strobe stimulation restricted inputs (geniculocortical and intracortical) to individual simple cells based on their timings. Below, we propose a mechanism to account for this change.

#### *Directional mechanisms in layer 6*

Our data provide few insights into directional mechanisms in layer 6 or the loss of directional tuning there following strobe rearing. We have shown in normal cats that “first-order” S-T maps derived from responses to counterphasing gratings (Murthy et al. 1998) or bars (Humphrey and Saul

1998) reveal little S-T inseparability among direction-selective layer 6 cells. Strobe rearing further reduced the weak inseparability (Humphrey and Saul 1998), which suggests that first-order structure contributes to directional tuning. However, the contribution must be small because it grossly underpredicts direction selectivity (Murthy et al. 1998). Some direction-selective simple cells with first-order separable receptive fields display second-order space-time inseparability that is revealed using two bars flashed sequentially across space. The space-time interactions can account well for cells’ directional tuning (Baker and Boulton 1994; Emerson and Citron 1989). Importantly, the nature of the interactions suggests that, like layer 4 cells, inputs to the neurons arise from sources having different receptive-field locations and timing delays (Emerson 1997). The nature and source of these timings remain to be elucidated. However, a prediction from our study is that strobe rearing also produces a compression in the range of timings there. It should be possible to infer such a compression from analysis of second-order S-T maps.

#### *Model to account for the effects of strobe rearing*

Here we propose a mechanism for how strobe rearing changes receptive-field structure. We assume that, during development, inputs with different response timings form connections with a common cortical cell via a competitive, self-organizing process that strengthens synaptic connections of well-correlated inputs. Such a Hebb-type process has been shown to account for the development of receptive-field spatial structure and orientation selectivity (Miller 1990, 1994; von der Malsburg 1973). We (Feidler et al. 1997) and others (Wimbauer et al. 1997a,b) recently showed that lagged and nonlagged afferents, activated by normal illumination, could be associated using Hebb-type rules to produce S-T inseparability and direction selectivity.

We hypothesize that a competitive self-organizing process also governs development of geniculocortical connections during strobe rearing, but the strobe stimulus changes the correlational structure of the inputs so as to restrict the range of input timings that become associated. We illustrate this using a simple model. Our goal here is to convey the essential features and assumptions associated with the hypothesis rather than to elaborate a full model.

The model is illustrated in Fig. 10 using a geniculocortical circuit consisting of two ON-center LGN units [lagged (L) and nonlagged (NL)] that project to a simple cell (not shown). The two receptive fields are displaced and a quarter cycle apart relative to a vertical, drifting sinewave grating (Fig. 10A); that is, they are in spatial quadrature. The unit responses also are in temporal quadrature (Fig. 10B), a valid assumption given that lagged and nonlagged cells respond, on average, a quarter cycle apart at low temporal frequencies (Saul and Humphrey 1990). Figure 10, C and D, illustrates the stimulus under continuous illumination; the luminance profile is plotted over time as the stimulus passes through the center of each receptive field in the two directions. Two cycles are shown for clarity. Figure 10, E and F, indicates the response of each unit to the stimulation. In the leftward, preferred direction, the units respond synchronously (i.e.,

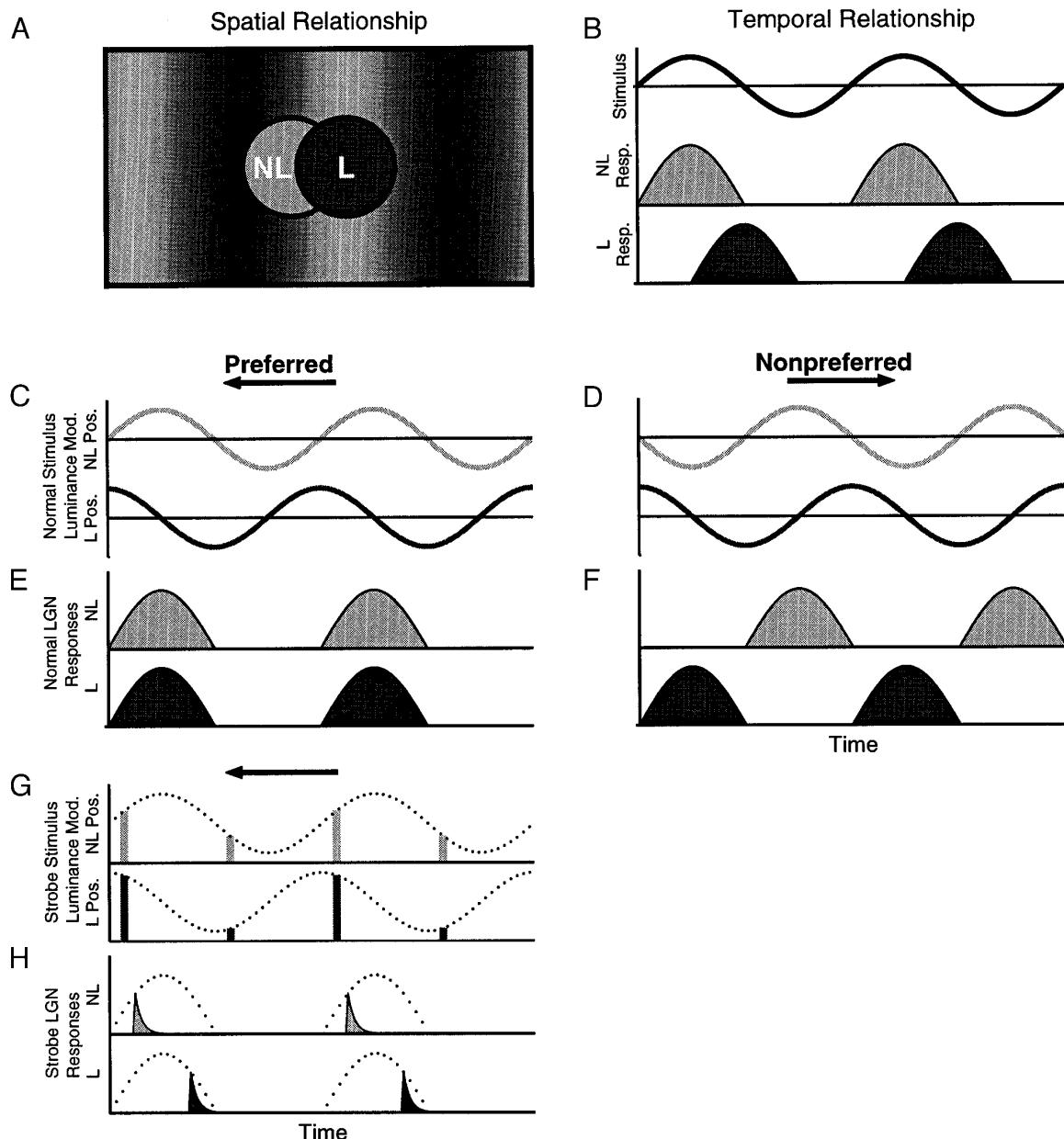


FIG. 10. Model illustrating the hypothesized effect of strobe stimulation on geniculate responses. *A*: receptive fields of an ON-center lagged and nonlagged unit displaced from each other by  $\frac{1}{4}$  cycle relative to a sinewave grating. Both units project to a simple cell (not shown). *B*: LGN unit responses to a sinusoidally modulated spot in their receptive fields; they are in temporal quadrature. *C* and *D*: luminance profiles of the grating in the center of each receptive field as a function of time, for opposite directions of motion. *E* and *F*: temporal relationships of geniculate responses evoked during *continuous* illumination. For leftward motion the lagged and nonlagged units respond synchronously (i.e., are well correlated) over  $\frac{1}{2}$  of the cycle, which enhances their association in cortex. For rightward motion the responses are uncorrelated. *G*: during *stroboscopic* illumination the leftward moving grating profile is unchanged (···) but is illuminated only briefly by the strobe flash (vertical bars). *H*: LGN units are activated synchronously by the strobe but respond with different latencies and more transiently than normal (cf., ···). This separates the 2 responses in time, lowering their correlations and preventing them from both becoming associated with the cortical cell.

are correlated) over approximately one-half of the stimulus cycle. The responses would sum to produce a robust discharge in the cortical cell, and their synaptic connections would strengthen. Rightward motion elicits nonoverlapping (i.e., uncorrelated) responses, which might be expected to dissociate the inputs. However, the poorer postsynaptic response in the rightward direction prevents this dissociation

(Feidler et al. 1997). During continuous illumination, then, the lagged and nonlagged units should associate in cortex to generate an S-T inseparable, directionally tuned receptive field.

Figure 10, *G* and *H*, shows that stroboscopic illumination should affect this Hebb-type process by producing poorly correlated responses in the LGN units even to the "pre-

ferred" direction of motion. We hypothesize that this reflects three factors. First, although the grating drifts continuously (dotted curves in *G*), as above, it is only illuminated at intervals by the brief (10  $\mu$ s) strobe flash (vertical bars in *G*). This forces all units to synchronously sample the stimulus at discrete points in time. Second, each brief flash evokes responses of short duration in all cells; these responses, illustrated by the narrow discharge profiles in *H* are much shorter than under continuous illumination (cf., dotted curves in *H*). Third, lagged and nonlagged cells respond with different latencies (*H*) due to their normally developing timing differences. Together, these factors will reduce the temporal overlap of discharges in the two afferents, diminishing the probability that they both will be associated with the cortical cell. Under strobe illumination, then, only inputs with very similar timings will become associated, and this will produce an S-T separable receptive field that is not direction selective.

Whereas this simple example uses two inputs in temporal quadrature, it is likely that during strobe rearing there is a range of timings in the geniculocortical population. Even within the lagged and nonlagged groups a range of timings likely exists, analogous to that seen normally (Saul and Humphrey 1990). Strobe stimulation therefore should not only prevent the association of lagged with nonlagged inputs, but reduce the probability of convergence among, for example, nonlagged inputs with different timing.

The same principles would restrict the range of input timing from other cortical cells, thus precluding the development of S-T inseparable receptive fields by intracortical interactions. For example, an inseparable receptive field could be produced by combining two separable fields, one dominated by nonlagged timings and the other by lagged timings, that are in spatiotemporal quadrature. Strobe rearing should prevent the linking of the two inputs by decorrelating their responses in a manner analogous to that in Fig. 10.

We recently obtained support for the geniculocortical aspect of this model (Humphrey et al. 1997). In normally developing kittens, 8-Hz stroboscopic illumination of drifting stimuli was shown to entrain visual responses of LGN cells and to evoke short-duration discharges. Further, the latencies of lagged and nonlagged cells differed in response to the strobe stimulus, and little temporal overlap was seen in their response histograms. Latency differences were observed within each group as well. These preliminary data thus strongly support the three assumptions of the model. We are pursuing the model in additional experiments.

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## REFERENCES

- ABBOTT, L. F., VARELA, J. A., SEN, K., AND NELSON, S. B. Synaptic depression and cortical gain control. *Science* 275: 220–224, 1997.
- BAKER, C. L., JR. AND BOULTON, J. C. Neurobiological mechanisms of cortical direction selectivity. In: *Computational Vision Based on Neurobiology: SPIE Proceedings*, 2054, edited by T. B. Lawton. Bellingham, Washington: SPIE, 1994, p. 104–123.
- BULLIER, J. AND HENRY, G. H. Laminar distribution of first-order neurons and afferent terminals in cat striate cortex. *J. Neurophysiol.* 42: 1271–1281, 1979.
- CHANCE, F. S., NELSON, S. B., AND ABBOTT, L. F. Synaptic depression and the temporal response characteristics of V1 cells. *J. Neurosci.* 18: 4785–4799, 1998.
- DUBIN, M. W., STARK, L. A., AND ARCHER, S. M. A role for action-potential activity in the development of neuronal connections in the kitten retinogeniculate pathway. *J. Neurosci.* 6: 1021–1036, 1986.
- EMERSON, R. C. Quadrature subunits in directionally selective simple cells: spatiotemporal interactions. *Vis. Neurosci.* 14: 357–371, 1997.
- EMERSON, R. C. AND CITRON, M. C. Linear and nonlinear mechanisms of motion in single neurons of the cat's visual cortex. In: *Proceedings of the IEEE International Conference on Systems, Man and Cybernetics*, edited by D. L. Kleinman. Cambridge, MA: IEEE, 1989, p. 448–453.
- ENROTH-CUGELL, C. AND ROBSON, J. G. The contrast sensitivity of retinal ganglion cells of the cat. *J. Physiol. (Lond.)* 187: 517–552, 1966.
- FEIDLER, J. C., SAUL, A. B., MURTHY, A., AND HUMPHREY, A. L. Hebbian learning and the development of direction selectivity: the role of geniculocal response timings. *Network: Comput. Neural Syst.* 8: 195–214, 1997.
- FERSTER, D., CHUNG, S., AND WHEAT, H. Orientation selectivity of thalamic input to simple cells of cat visual cortex. *Nature* 380: 249–252, 1996.
- FERSTER, D. AND LINDSTROM, S. An intracellular analysis of geniculocortical connectivity in area 17 of the cat. *J. Physiol. (Lond.)* 342: 181–215, 1983.
- GARRAGHTY, P. E. AND SUR, M. Competitive interactions influencing the development of retinal axonal arbors in cat lateral geniculate nucleus. *Physiol. Rev.* 73: 529–545, 1993.
- HARTVEIT, E. AND HEGGELUND, P. Neurotransmitter receptors mediating retinal input to cells in the cat lateral geniculate nucleus. II. Non-lagged cells. *J. Neurophysiol.* 63: 1361–1372, 1990.
- HEGGELUND, P. AND HARTVEIT, E. Neurotransmitter receptors mediating retinal input to cells in the cat lateral geniculate nucleus. I. Lagged cells. *J. Neurophysiol.* 63: 1347–1360, 1990.
- HUMPHREY, A. L., FEIDLER, J. C., AND SAUL, A. B. Hebbian mechanisms may explain altered S-T receptive-field structure in simple cells induced by strobe rearing. *Soc. Neurosci. Abstr.* 23: 453, 1997.
- HUMPHREY, A. L. AND SAUL, A. B. The action of brainstem reticular afferents on lagged and non-lagged cells in the cat lateral geniculate nucleus. *J. Neurophysiol.* 68: 673–691, 1992.
- HUMPHREY, A. L. AND SAUL, A. B. Strobe rearing alters the spatiotemporal structure of simple cell receptive fields in cat area 17. *Soc. Neurosci. Abstr.* 21: 1648, 1995.
- HUMPHREY, A. L. AND SAUL, A. B. Loss of direction selectivity in cortical area 17 following strobe rearing reflects changes in spatiotemporal receptive-field structure. *J. Neurophysiol.* 80: 2991–3004, 1998.
- HUMPHREY, A. L., SUR, M., UHLRICH, D. J., AND SHERMAN, S. M. Projection patterns of individual X- and Y-cells axon from the lateral geniculate nucleus to cortical area 17 in the cat. *J. Comp. Neurol.* 233: 159–189, 1985.
- HUMPHREY, A. L. AND WELLER, R. E. Functionally distinct groups of X-cells in the lateral geniculate nucleus of the cat. *J. Comp. Neurol.* 268: 429–447, 1988a.
- HUMPHREY, A. L. AND WELLER, R. E. Structural correlates of functionally distinct X-cells in the lateral geniculate nucleus of the cat. *J. Comp. Neurol.* 268: 448–468, 1988b.
- JAGADEESH, B., WHEAT, H. S., KONTSEVICH, L. L., TYLER, C. W., AND FERSTER, D. Direction selectivity of synaptic potentials in simple cells of the cat visual cortex. *J. Neurophysiol.* 78: 2772–2789, 1997.
- KWON, Y. H., ESGUERRA, M., AND SUR, M. NMDA and non-NMDA receptors mediate visual responses of neurons in the cat's lateral geniculate nucleus. *J. Neurophysiol.* 66: 414–428, 1991.
- MAEX, R. AND ORBAN, G. A. Model circuit of spiking neurons generating directional selectivity in simple cells. *J. Neurophysiol.* 75: 1515–1545, 1996.
- MARTIN, K. A. C. AND WHITTERIDGE, D. Form, function and intracortical projections of spiny neurones in the striate visual cortex of the cat. *J. Physiol. (Lond.)* 353: 463–504, 1984.
- MASTRONARDE, D. N. Two classes of single-input X-cells in cat lateral

- geniculate nucleus. I. Receptive-field properties and classification of cells. *J. Neurophysiol.* 57: 357–380, 1987a.
- MASTRONARDE, D. N. Two classes of single-input X-cells in cat lateral geniculate nucleus. II. Retinal inputs and the generation of receptive-field properties. *J. Neurophysiol.* 57: 381–413, 1987b.
- MASTRONARDE, D. N., HUMPHREY, A. L., AND SAUL, A. B. Lagged Y cells in the cat lateral geniculate nucleus. *Vis. Neurosci.* 7: 191–200, 1991.
- MCLEAN, J., RAAB, S., AND PALMER, L. A. Contribution of linear mechanisms to the specification of local motion by simple cells in areas 17 and 18 of the cat. *Vis. Neurosci.* 11: 271–294, 1994.
- MILLER, K. D. Correlation-based models of neural development. In: *Neuroscience and Connectionist Theory*, edited by M. A. Gluck and D. E. Rumelhart. Hillsdale, NJ: Erlbaum, 1990, p. 267–353.
- MILLER, K. D. A model for the development of simple cell receptive fields and the ordered arrangement of orientation columns through activity-dependent competition between ON- and OFF-center inputs. *J. Neurosci.* 14: 409–441, 1994.
- MURTHY, A. AND HUMPHREY, A. L. Inhibitory contributions to spatiotemporal receptive-field structure and direction selectivity in simple cells of cat area 17. *J. Neurophysiol.* In press.
- MURTHY, A., HUMPHREY, A. L., SAUL, A. B., AND FEIDLER, J. C. Laminar differences in the spatiotemporal structure of simple cell receptive fields in cat area 17. *Vis. Neurosci.* 15: 239–256, 1998.
- REID, R. C. AND ALONSO, J. M. Specificity of monosynaptic connections from thalamus to visual cortex. *Nature* 378: 281–284, 1995.
- REID, R. C., SOODAK, R. E., AND SHAPLEY, R. M. Directional selectivity and spatiotemporal structure of receptive fields of simple cells in cat striate cortex. *J. Neurophysiol.* 66: 505–529, 1991.
- SAUL, A. B. AND HUMPHREY, A. L. Spatial and temporal response properties of lagged and nonlagged cells in the cat lateral geniculate nucleus. *J. Neurophysiol.* 64: 206–224, 1990.
- SAUL, A. B. AND HUMPHREY, A. L. Evidence of input from lagged cells in the lateral geniculate nucleus to simple cells in cortical area 17 of the cat. *J. Neurophysiol.* 68: 1190–1207, 1992a.
- SAUL, A. B. AND HUMPHREY, A. L. Temporal frequency tuning of direction selectivity in cat visual cortex. *Vis. Neurosci.* 8: 365–372, 1992b.
- SHERMAN, S. M., HOFFMANN, K.-P., AND STONE, J. Loss of a specific cell type from the dorsal lateral geniculate nucleus in visually deprived cats. *J. Neurophysiol.* 35: 532–541, 1972.
- SHERMAN, S. M. AND SPEAR, P. D. Organization of visual pathways in normal and visually deprived cats. *Physiol. Rev.* 62: 738–855, 1982.
- SIEGEL, S. *Nonparametric Statistics for the Behavioral Sciences*. New York: McGraw-Hill, 1956.
- SUAREZ, H., KOCH, C., AND DOUGLAS, R. Modeling direction selectivity of simple cells in striate visual cortex within the framework of the canonical microcircuit. *J. Neurosci.* 15: 6700–6719, 1995.
- TANAKA, K. Cross-correlation analysis of geniculostriate neuronal relationships in cats. *J. Neurophysiol.* 49: 1303–1318, 1983.
- VON DER MALSBURG, C. Self-organisation of orientation sensitive cells in the striate cortex. *Kybernetik* 14: 85–100, 1973.
- WILSON, P. D., ROWE, M. H., AND STONE, J. Properties of relay cells in the cat's lateral geniculate nucleus: a comparison of W-cells with X- and Y-cells. *J. Neurophysiol.* 39: 1193–1209, 1976.
- WIMBAUER, S., WENISCH, O. G., MILLER, K. D., AND VAN HEMMEN, J. L. Development of spatiotemporal receptive fields of simple cells. I. Model formulation. *Biol. Cybern.* 77: 453–461, 1997.
- WIMBAUER, S., WENISCH, O. G., VAN HEMMEN, J. L., AND MILLER, K. D. Development of spatiotemporal receptive fields of simple cells. II. Simulation and analysis. *Biol. Cybern.* 77: 463–477, 1997.
- WINER, B. J. *Statistical Principles in Experimental Design* (2nd ed.). New York: McGraw-Hill, 1962.
- WOLFE, J. AND PALMER, L. A. Temporal diversity in the lateral geniculate nucleus. *Vis. Neurosci.* 15: 653–675, 1998.