Inherent Biases in Spontaneous Cortical Dynamics

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Measurements of spatial and temporal patterns of ongoing (spontaneous) activity in the “resting” (unstimulated) brain provide a valuable insight into the fundamental mechanisms underlying neural information processing. Calculations of information content and signal processing are critically dependent upon the validity of the null assumption — how we define what is “signal” and what is “noise” (Shadlen and Newsome, 1994; Gusnard and Raichle, 2001). One major issue is the level of structure present in spontaneous cortical network activity. While spontaneous neuronal activity may be thought of as “stochastic” in nature, covariations do exist between neighboring neurons and neurons with similar functional tuning (Cox, 1962; Perkel et al., 1967a, 1967b; Ts’o et al., 1986, 1988; Gray et al., 1989; Amzica and Steriade, 1995; Nowak et al., 1995; deCharms and Merzenich, 1996; Leopold et al., 2003). Furthermore, recent papers have elaborated upon this view by suggesting that noise during spontaneous activity appears as a series of random jumps between different population activity patterns that are linked to the underlying cortical structure (e.g., orientation maps in V1; Softky and Koch, 1992, 1993; Arieli et al., 1995; Tsodyks and Sejnowski, 1995; Amit and Brunel, 1997; Tsodyks et al., 1999; Kenet et al., 2003). Here, we propose that such “jumps” are not random, but that there are inherent biases (directionality) in the shift from one population activity pattern to another. We predict that such inherent biases

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would be seen in directional interactions between different response types during spontaneous activity.

To test this prediction, we chose to study interactions between two types of neurons in early visual cortex “oriented” and “luminance-modulated” (LM) neurons using cross-correlation methods. Orientation-selective neurons are commonly encountered in Areas 17 and 18 of the cat (the first and second visual cortical areas), and they are likely to play a role in the initial encoding of object borders and shape (e.g., Hubel and Wiesel, 1969). LM cells respond to large-field modulations of luminance without the presence of orientation cues and are hypothesized to play a role in processing surface brightness information (Rossi et al., 1996; Hung et al., 2001). That orientation-selective (e.g. Malach et al. 1993; Kisvarday et al., 1997; Kenet et al., 2003) and LM selective (Livingstone and Hubel, 1984; Shoham et al., 1997; Tani et al., 2003) neurons have distinct organizations is reasonably well supported. Thus, oriented and LM cells comprise two functional cell types that are distinguishable on physiological, anatomical, and psychophysical bases. We report here that, under spontaneous conditions, a directional, non-random interaction exists between LM cells and oriented cells. Thus, in addition to spatial structure, these data suggest temporal structure in cortical baseline activity.

Methods

Surgery and confirmation of recording sites

All procedures were conducted in accordance with NIH and IACUC guidelines. The surgical, mapping, and experimental methods were previously reported (Hung et al., 2001, 2002). Recordings were obtained from areas 17 and 18 of eight cats under anesthesia (pentothal, 1–2 mg/kg/hr) and paralysis (pancuronium bromide, 100μg/kg/hr). EEG, heart rate, oxygen saturation, expired CO₂, and core temperature were monitored. The location of the 17–18 border was determined by optical imaging of spatiotemporal frequency response and visual field mapping, and by physiological mapping of changes in receptive field size and reversal of receptive field progression across the vertical meridian (Bonhoeffer et al., 1995; Hung et al., 2001). Receptive fields were located between 0 to 10 deg azimuth and 5 to -30 deg elevation.

Receptive field characterization and stimuli

All stimuli were shown in a darkened room (< 1 Cd/m²). After isolation of single-units, receptive fields were mapped and tested for orientation tuning.
Oriented units are defined as those with a 60 deg or narrower orientation tuning width. Luminance-modulated (LM) units are defined by a significant firing rate modulation (Hung et al., 2001, 2002; bootstrap statistics) to a large sinusoidally-modulated uniform light patch (edges at least 2° outside the classical receptive field (RF), 0.5 Hz, 15% p-p contrast at mean 32 Cd/m²). Oriented cells did not respond to full-field luminance modulation. LM cells exhibited both oriented and non-oriented response. Pairs of single units, one LM and one oriented (not LM), were recorded on two separately positioned electrodes in Areas 17 and 18 (mean distance 6.9 mm, range 0.7 to 18.5 mm).

**Stimuli**

The stimulus was then positioned so that the receptive field of the oriented cell overlay the “border” (parallel to the contrast border) and that of the LM cell overlay the “surface” (Figure 5.1, inset bottom). In the “luminance-modulation” condition (Figure 5.1, inset top), the luminance of two brightness fields were sinusoidally counterphased at 0.5 Hz (approx. 8 frames/sec, 16 frames/cyc, 15% peak-to-peak contrast; total luminance was always 32 Cd/m²) across a stationary contrast border (reversing sign). This condition was an effective stimulus for both cells. Responses to this condition were compared to a blank “spontaneous” condition (Figure 5.1, inset middle) in which the luminance was an even gray matching the mean luminance of the luminance-modulated condition. Both conditions contained no motion content. Each stimulus condition was presented continuously (a typical ten-minute recording yielded more than 3,000 spikes for at least one neuron).

**Data analysis**

The synchrony between cell pairs was assessed by cross-correlation histograms (“correlograms”) showing the frequency of occurrence of specific spike timing relationships between pairs of neurons recorded from separate electrodes. Specifically, we focused on the correlograms recorded from two types of cell pairs: between Area 17 oriented cells and Area 17 LM cells (‘17–17’) and between area 17 oriented and Area 18 LM cells (‘17–18’). We recorded a total of 458 correlograms. Correlograms were analyzed for peak position only if they showed significant peak height. Significant correlation was exhibited by 98/113 17–17 and 107/116 17–18 cell pairs during luminance modulation, and by 96/113 17–17 and 99/116 17–18 cell pairs during spontaneous activity. Histograms are shown triggered by the spike of the oriented cell at time 0. Spikes were collected at 0.1 msec resolution. Correlograms consisted of 501 bins of 1.6 msec each, smoothed by a 7-bin median filter. Correlograms were normalized for
FIGURE 5.1 Recordings from LM-oriented pairs. Inset top, The luminance-modulated stimulus. Luminance of the two surfaces was sinusoidally modulated in antiphase across a stationary contrast border at 0.5 Hz (see Methods). Mean luminance remains constant at 32 Cd/m². Inset middle, Stimulus during spontaneous activity, also 32 Cd/m². Inset bottom, The stimulus was positioned such that one surface was centered on the
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Figure 5.1 (Continued) LM cell’s receptive field (RF shown by red box) and the border was positioned at the RF of the oriented cell (green box). (A) Example of a 17–17 pair. Schematic of RF positions is shown at left, relative to the location of the luminance-modulated contrast border (light blue line). At right are correlograms obtained during luminance-modulated (light blue) and Spontaneous (black) conditions. Negative peak position during spontaneous activity indicates a LM-to-oriented direction, and positive peak position indicates an oriented-to-LM direction. Lum: 5014 and 4453 spikes for oriented and LM cells, respectively, 2132 seconds. Spont: 815 and 3872 spikes, 2348 seconds. (B) Example of a 17–18 pair. Lum: 10490 and 3751 spikes, 984 seconds; Spont: 3491 and 1282 spikes, 622 seconds. (C) Average spontaneous correlograms for 17–17 pairs (top row, green) and 17–18 pairs (bottom row, purple) grouped according to distance between RF centers. Gray lines indicate raw correlograms, and black lines indicate correlograms after shuffle subtraction. (D) Population histograms of peak positions for 17–17 (green) and 17–18 (purple) pairs. Arrows indicate mean peak position for each population. Both populations are significantly biased (17–17: $p < 0.001$, 17–18: $p < 0.001$). (E) Peak positions during luminance-modulated versus spontaneous conditions for 17–17 and 17–18 pairs.

Results

**Inherent Bias Between Oriented and LM Cells Based on Peak Position**

Figure 5.1 shows results from pairs isolated from separate electrodes in which one cell (in Area 17, green) was oriented and the other (in Area 18, red) was LM (responsive to large field luminance change). Cells were tested under two stimulus conditions (Figure 5.1 inset). In the “luminance-modulation” condition (Figure 5.1, inset top), luminance contrast was sinusoidally modulated at 0.5 Hz across a stationary contrast border. This stimulus was positioned over the receptive fields (RFs) such that the oriented cell’s RF was at the contrast...
border and the LM cell’s RF was centered on one surface (Figure 5.1, inset bottom). This condition strongly activated both cells. These responses were compared to a spontaneous condition (Figure 5.1, inset middle) in which the luminance was an even gray (no luminance modulation) matching the mean luminance of the luminance-modulation condition. Each stimulus condition was presented continuously for ten minutes, which was typically sufficient time for 3000 spikes to be collected per neuron.

Figures 5.1a and 5.1b show two examples of LM-oriented pairs, the first a 17-17 pair (both cells in Area 17) and the second a 17–18 pair (Area 17 oriented cell, Area 18 LM cell). In both cases, luminance-modulation yielded strong correlation peaks centered near zero (light blue lines). Spontaneous activity resulted in correlograms that were offset from center (black lines), however. Although the spontaneous peaks straddled the zero line, as is typical of cortical correlograms (Nowak et al., 1995; Murthy and Fetz, 1996; Roe and Ts’o, 1999), the bulk of the interactions showed the LM cell firing a few milliseconds before the oriented cell. These spontaneous peak positions are significantly offset from center (p < 0.001) and significantly different from the luminance-modulated peak (Figure 5.1a: luminance peak pos, 3.2 msec ± 1.11 msec; spontaneous peak position, −4.8 msec ± 0.96 msec; Figure 5.1b: luminance peak pos, −6.4 msec ± 2.39 msec; spontaneous peak position, -20.8 msec ± 5.33 msec; bootstrap tests). These shifted peaks show that spontaneous interactions may be directionally biased between oriented and LM cells.

Figures 5.1c and 5.1d show that these LM-to-oriented biases in spike timing exist across the population of 17–17 and 17–18 pairs. Figure 5.1c shows averaged spontaneous correlograms grouped according to receptive field (RF) separation distance at 1–5, 5–20, and 20–35 degrees (receptive fields were non-overlapping). Consistent with previous reports that peak height depends on RF separation, both 17–17 (top row) and 17–18 (bottom row) pairs show a decrease in peak height with RF separation. At all distances, some bias is evident in both 17–17 and 17–18 pairs (compare area left of zero msec with area right of zero msec). The bias in peak position is most evident in the peaks at the shorter RF separations (< 5 deg) which are also the largest peaks. As summarized in Figure 5.1d, under spontaneous conditions peak positions for both 17–17 (green) and 17–18 (dark purple) pairs were significantly biased in the LM-to-oriented direction (17–17: mean −5.2 msec, p < 0.001, n = 96; 17–18: mean −6.2 msec, p < 0.001, n = 99; one-sample t test).

**Comparison between Spontaneous and Evoked Peak Positions**

Traditional correlation analyses of cortical circuitry have focused largely on correlations obtained from evoked activity, neglecting potential differences
between evoked and spontaneous activity. We find, however, that evoked (lumina-
ence-modulation) and spontaneous peak positions do not necessarily coin-
cide and can reveal different facets of the underlying circuitry. Figure 5.1e
shows comparisons between evoked and spontaneous peak positions for 17–17
(green) and 17–18 (purple) pairs. For the population of 17–18 pairs, no differ-
ence was found between evoked and spontaneous peak positions (evoked:
mean -5.3 msec, $p < 0.001$, $n = 107$, one-sample t test; evoked – spont: mean
0.7 msec, $p = 0.6$, $n = 95$, paired t test). For the population of 17–17 pairs, how-
ever, luminance-modulation resulted in a significant positive shift in the peak
positions relative to spontaneous (evoked: mean -2.1 msec, $p > 0.05$, $n = 98$,
one-sample t test; evoked – spont: mean 3.6 msec, $p = 0.01$, $n = 93$). This shift
cannot be simply explained as a decrease of inherent biases and/or strengthen-
ing of common input, as we also observed shifts in the peak away from coinci-
dent activity, in the border-to-LM direction.

INHERENT BIAS BETWEEN ORIENTED AND LM CELLS BASED ON CORRELOGRAM SHAPE

In this section, we aim to further establish that these inherent biases are sig-
nificant by examining two further measures of peak asymmetry. Whereas peak
position is a convenient and simple measure of temporal relationship, it
measures only one aspect of the correlogram and may at times be subject to
noise in the correlogram. To further examine the strength and quality of these
temporal biases, we also quantified the spontaneous correlograms with two
measures that reflect correlogram shape: asymmetries of correlogram area
(correlogram asymmetry, CA) and correlogram slope (peak asymmetry, PA)
(Figure 5.2a) (Alonso and Martinez, 1998). These two measures indicate differ-
ent aspects of temporal asymmetry; whereas CA reflects the total asynchrony,
PA reflects the asymmetry around the peak, which, in ideal circumstances,
can reveal the dominance of monosynaptic relationships versus asymmetric
common input. For example, a CA value of 0 indicates symmetry around zero;
a CA value of 0.5 (-0.5) indicates that 75% of the area is to the right (left) of
zero. With respect to this data set, negative values indicate a bias in the LM-to-
oriented direction, whereas positive values indicate an oriented-to-LM bias.
To avoid the issue of noisy correlograms, the analysis is limited to the larger
peaks (upper 50% of peak sizes).

For LM-oriented cell pairs (Figure 5.2b), CA measurements are predomi-
nantly negative, further confirming the LM-to-oriented bias revealed by peak
position (Figure 5.1). Of the 17–17 pairs (green dots), 70% (31/44) have negative
CA values. Of 17–18 pairs (purple dots), almost all (96%, 47/49) show negative
CA, indicating virtually all of these interactions are in the LM-to-oriented
18-to-17 direction.
**Figure 5.2** Correlograms were asymmetric both with respect to the zero bin (correlogram asymmetry) and with respect to the peak (peak asymmetry). Correlogram asymmetries are consistent with measurements of peak position. (A) Correlogram asymmetry (CA) is defined as \( \frac{R_A - L_A}{R_A + L_A} \), where \( R_A \) and \( L_A \) are the areas of the shuffle-subtracted correlogram between 0 and ±40 msec. Peak asymmetry (PA) is defined as \( \frac{R_T - L_T}{R_T + L_T} \), where \( R_T \) and \( L_T \) are the rise and decay times of the correlogram between 70% height and the shuffle-subtracted baseline. Correlogram in schematic is from example in Fig 1a. (B) Both 17-17 (green dots, \( N=44 \)) and 17-18 (purple squares, \( N = 49 \)) correlograms showed strongly biased CA with PA close to zero, consistent with an offset common input or network state transitions. In comparison, mono-synaptic interactions such as those seen in simple-complex pairs tend to yield more extreme PA values (gray ‘+’ signs, Alonso and Martinez, 1998). Most 17-17 CAs and all but two 17-18 CAs were negative, consistent with measurements of peak position (Fig 1d). CA and PA values for the examples in Figure 5.1a and 5.1b are indicated by hollow dot and hollow square, respectively.
In contrast, PA values are distributed around zero, indicating that even offset peaks show a symmetric profile (symmetric slopes left and right of the peak). Indeed, 68% (17-17: 31/44, 17-18: 32/49) of the correlograms have $|PA|$ values $\leq 0.25$, and all but three (97%) have $|PA| \leq 0.5$, indicating a predominance of negatively shifted symmetrical peaks. For comparison, Alonso and Martinez (1998) tended to find more extreme PA values when recording from mono-synaptic simple-complex pairs (gray “+” signs). One possible interpretation of PA symmetry coupled with CA asymmetry is that LM-oriented pairs receive offset common input (common input modified by differences in the delay to the two cell types).

Discussion

We have shown that appropriate identification of LM versus oriented responses can reveal biases in spontaneous cortical activity. Our results suggest that LM cells in Areas 17 and 18 tend to activate prior to oriented cells in area 17 (Figure 5.3a). We believe that these inherent (spontaneous) biases are likely to be related to either differential timing of common input or asymmetries in the network connections (e.g. mono- or polysynaptic connections between LM and oriented cells and/or asymmetry in common input). These are the first results to show an inherent differential timing between surface versus border networks under spontaneous conditions. We suggest that such biases need to be taken into account when evaluating neuronal interactions under stimulated versus spontaneous ‘control’ conditions.

How Inherent Bias Relates to Vision

These inherent biases suggest that the cortex may be actively processing information, even “at rest”. Computationally, inherent biases in patterns of spontaneous activity may offer an advantage in setting the downstream neuron (e.g. the oriented cell in LM-oriented pairs) closer to an appropriate threshold, rather than at a fixed resting potential (Azouz and Gray, 1999). We speculate that the LM cells may be involved rapid dynamic normalization of response sensitivity across saccades, allowing the appropriate detection of contrast edges (which vary over a 30-fold range in reflectance) despite much wider variations in luminance (up to $10^9$) within the visual field (Gilchrist et al., 1999).

Relationship of Inherent Biases to Cortical Architecture

While our data show only inherent bias between individual pairs of neurons, given what is known about cortical functional architecture, they suggest possible
relationships between clusters of neurons. The existence of orientation-selective networks in visual cortex is fairly well-supported (e.g. Malach et al. 1993; Kisvarday et al. 1997; Kenet et al., 2003). The presence of LM networks is also supported. As demonstrated by optical imaging, surface-responsive regions have been found in Area 18 that are distinct from orientation-selective zones (Tani et al., 2003). Area 17 contains a regular patchwork of clusters tuned to low spatial frequencies (Shoham et al., 1997), and, in monkeys it has been shown that such low spatial frequency preferring zones (blobs) form blob-selective horizontal networks (Livingstone and Hubel 1984; Ts’o and Gilbert 1988). Thus, oriented and LM cells are likely to participate in distinct horizontal networks in early visual areas that subserve border and surface information processing, respectively.

Given these distinct organizations, we view our data in the context of what has been referred to as “network state.” Recent imaging evidence has shown that spontaneous cortical activity (or “network state”) can be similar in structure to that of activated orientation maps, and that this network state
dynamically switches from one state (one orientation map) to another (orientation map) (Figure 5.3b, left, based on Kenet et al., 2003). We speculate that dynamic switching may also occur between different types of functional networks (LM and orientation networks) and, furthermore, that this switching may be directional in nature (Figure 5.3b, right). In this scenario, the simultaneous activation of LM-dominated network activity may be quickly (∼10 msec) followed by orientation-dominated activity. Thus, we suggest the hypothesis that ongoing activity is characterized not only by structured networks but also by directional interactions between surface and border networks.

Summary

The directional nature of these spontaneous interactions indicates that “at rest” there are inherent biases in cortical dynamics and suggest a more structured baseline from which to interpret cortical activity during visual perception. In the case of LM and oriented cells, we speculate that such inherent biases may indicate an underlying network for integrating edge and brightness perception. We suggest that inherent biases may also exist elsewhere in cortical circuitry, and that such inherent biases provide a view of functional circuitry “unadulterated” by the effects of sensory stimulation, attention, or working memory. Further mapping of such biases may provide a useful framework for interpreting evoked activity, both in absolute and relative terms.

Acknowledgements

The authors would like to thank Francine Healy for excellent technical assistance and Jonathan Victor and Jeff Schall for helpful comments on previous versions of this manuscript. Supported by EY11744 and Packard Foundation.

REFERENCES


APPENDICES

Extended Methods

Surgery

Eight cats were anesthetized (pentothal, 1-2 mg/kg/hr), paralyzed (pancuronium bromide, 100 μg/kg/hr) and artificially respirated. Heart rate and EEG were continuously monitored, blood oxygenation was monitored at half-hour intervals, CO₂ was maintained at 4%, and rectal temperature maintained at 38 deg C. Eyes were refracted and fitted with contact lenses to focus upon a tangent screen. Alignment was checked before and after each recording. Proper focusing was determined by an ophthalmoscope and confirmed by the physiological recording of cells with small receptive fields (less than 1 deg width in Area 17). Under aseptic conditions, a 1–2 cm² craniotomy and durotomy were made over Areas 17 and 18 (centered at Horsley-Clark coordinates A-1, L 3). All procedures were conducted in accordance with NIH and IACUC guidelines.

Confirmation of recording sites

Results of our 17/18 border mapping have been previously reported (Hung et al., 2001). Briefly, the location of the Area 17/18 border was determined by optical imaging of spatial-temporal frequency response and by visual field mapping. For mapping by optical imaging, Areas 17 and 18 were differentiated by their spatio-temporal frequency response to horizontal and vertical grating stimuli (Bonhoeffer et al., 1995; Shoham et al., 1997). High spatial frequency stimuli (0.58 cycles/deg, 4 deg/s) and low spatial frequency stimuli (0.14 cycles/deg, 14 deg/s) were used to preferentially activate Areas 17 and 18, respectively. This optically-imaged 17/18 border was subsequently confirmed by physiological mapping, showing changes in receptive field size and reversal of receptive field progression across the vertical meridian (Tusa et al., 1978, 1979). Recorded pairs were generally separated along the rostral-caudal axis, with receptive fields located between 0 to 10 deg azimuth and 5 to –30 deg elevation.

Recording technique

All recordings were made in a darkened room (< 1 Cd/m²). Because of the rarity of luminance-modulated cells (DeYoe and Bartlett, 1980), we always began recordings of oriented-LM pairs (consisting of an oriented cell in Area 17 and an LM cell in Area 17 or 18) by searching for LM units. We located potential LM units by advancing the electrode while listening to an audio monitor for
multi-unit spiking response to a light flash (32 Cd/m\(^2\)) \(3^\circ\times3^\circ\) in size from a handheld light gun. A unit was then isolated based on its waveform (Spike3, Cambridge Electronic Design, Cambridge, UK) and its autocorrelogram checked for contamination from neighboring units. Characterization of the unit as LM was based on the significance of its firing rate modulation under the luminance-modulated stimulus condition, determined by bootstrap tests of the spike train (see *Stimuli* and *Data Analysis*). For recordings from oriented-LM pairs, a second electrode was positioned in Area 17, 0.7-18.5 mm (mean 6.9 mm) away from the first electrode. We deliberately selected for pairs with nonoverlapping receptive fields in which the oriented-LM pair might encode the relationship between a surface and its border, rather than cases where both receptive fields are co-linear and likely to be directly activated by a common border. This was done by selecting for oriented units on the second electrode whose preferred orientation was orthogonal to an imaginary line between its receptive field and the receptive field of the first cell. 80% of the units were isolated from superficial layers (< 1000 \(\mu\)m depth), and the remainder was isolated from deep layers.

**Receptive field characterization**

Classical receptive fields (CRFs) were mapped with a hand-held light gun. We defined CRFs as minimal response fields whose borders were determined by flashing a small patch of light \(1^\circ\times1^\circ\) in size (32 Cd/m\(^2\) against a black background < 1 Cd/m\(^2\)). Oriented receptive fields were mapped manually using a small bar of light of the preferred orientation and optimal length. When the two mapping methods resulted in receptive fields of different sizes, we always erred on the conservative side and used the larger measured CRF. In the oriented-LM pairs we recorded, the oriented unit always had a response to the preferred orientation that was at least twice that to the non-preferred orientation, and the LM unit always exhibited a significant luminance-modulated response (see *Stimuli* and *Data Analysis*). In some cases, the oriented unit exhibited some LM response (tested with no edges in the CRF), or the LM unit exhibited some degree of orientation selectivity. Although oriented units were rarely luminance-modulated (about 10% of the units encountered were luminance-modulated), LM units often exhibited some degree of orientation selectivity. The widths of orientation tuning encountered in LM units spanned the range from very tight (\(<10\) deg) to non-oriented (percentages of cells described as “A”–“D”, “A” sharply oriented (\(<20\) deg width) and “D” non-oriented: 10%, 33%, 22%, and 35%).
FIGURE 5A-1 Orientation tuning specificity versus LM response of LM cells.
(A) Orientation tuning specificity of Area 17 (green dots) and Area 18 (red diamonds) LM cells are plotted versus strength of response to luminance modulation. Tuning specificity was classified into four groups: A (less than 22.5 deg width), B (22.5 to 45 deg width), C (45 to 67.5 deg width), and D (over 67.5 deg width). Response to luminance modulation is given as Modulation Index, which is the contrast ratio corrected for spike count. MIs greater than one result from sinusoidal fitting to the response histogram. Horizontal bars indicate mean MI for each group. 
(B) Percentage of LM cells in each group. Cells include those from an earlier experiment (Hung et al., 2001).
Stimuli

All stimuli were shown on a tangent screen in a darkened room (< 1 Cd/m²) under conditions identical to those previously described (Hung et al., 2001). Two stimulus conditions were tested, a “Luminance-modulation” condition and a “Spontaneous” condition (blank control; see Figure 5.1, top). Each condition was presented continuously for ten minutes. In some cases, the recording was stopped prematurely when more than 3000 spikes had been collected on each channel. Stimuli contained no motion content. In the Luminance-modulation condition, the stimulus had the appearance of a non-moving contrast border between two sinusoidally alternating brightness fields. This stimulus consisted of two adjoining rectangular surfaces (each approximately 5°x8°) whose outline was covered by a non-reflective black mask. The stimulus was positioned and oriented such that the edge between the two surfaces overlay the oriented cell’s receptive field, and one of the two surfaces was centered over the (potential) LM unit’s receptive field. The luminances of the two surfaces were counterphased (crossing sign) sinusoidally around a mean luminance of 32 Cd/m² (approx. 8 frames/sec, 16 frames/cyc, 8-15% peak-to-peak contrast; total luminance was always 32 Cd/m²). The slow sinusoidal modulation was chosen because it was well within the limits of psychophysical measures of filling-in (< 4 Hz), and the slow frame rate allowed us to distinguish phasic (< 15 msec) from tonic LM responses. Although we could clearly distinguish between tonic and phasic responses by the presence of sharp frame-locked bins in the PSTH, subsequent cross-correlation analysis revealed no difference in the results from transient versus tonic LM cells, and so their results are pooled here. In the Spontaneous condition, the cell’s spontaneous activity was recorded during continuous presentation of a static gray stimulus (also 32 Cd/m²) of the same size and location as the Luminance-modulation stimulus.

Data analysis

Characterization of a surface unit as “luminance-modulated” (LM) was based upon the significance of its response to the sinusoidal luminance modulation (determined by bootstrap statistical methods, based on shuffling the spike order of the recorded spike train while preserving the exact inter-spike interval distribution (Hung et al., 2002)). Briefly, significance of the luminance response was measured by fitting the firing-rate response with a sinusoid at the frequency of the stimulus and comparing the strength of the response modulation against those generated by 1000 bootstrap randomizations of the recorded spike train.
FIGURE 5A-2  Significance of Correlogram Asymmetry (A) Comparison of Correlogram Asymmetry versus LM cell response. As suggested by a reviewer, we have plotted the correlogram asymmetry of spontaneous correlograms against the LM cell’s luminance modulation response for 17–17 (green) and 17–18 (purple) pairs. Asymmetry correlates poorly with LM response magnitude, as expected, because LM cells (like oriented cells) respond best at specific stimulus contrasts. At the low stimulus contrasts tested (15% peak-to-peak), many LM cells yielded only moderate responses. (B) Comparison of correlogram asymmetry versus peak height for spontaneous correlograms (shuffle-subtracted). Strong correlogram asymmetry is seen for both 17–17 and 17–18 pairs across the entire range of peak sizes.

For each randomization, the order of the spikes was randomized while preserving the set of inter-spike intervals. We found light-modulated responses in approximately 10% of the cells we encountered. This finding is consistent with the results of DeYoe and Bartlett (1980), considering the stringency of their luxotonic cell criteria compared to our LM cell criteria.
For the paired recordings, we used cross-correlation histograms (‘correlograms’) to show the frequency of occurrence of specific spike timing relationships between pairs of neurons. For oriented-LM pairs, the histograms are shown triggered by the spike of the oriented cell at time 0. For LM-LM pairs, histograms are triggered by the spike of the Area 17 cell. Spikes were collected at 0.1 ms resolution. Correlograms were normalized for total spike count and peak significance was determined by bootstrap statistical methods. Briefly, 10,000 random correlograms were generated from randomizations of the two spike trains (Hung et al., 2002), thereby preserving the profile of the peri-stimulus time histogram (PSTH) of the two spike trains but destroying the specific timing relationships within and between the two spike trains. For randomization under the Spontaneous condition, an artificial cycle trigger was generated at 2-second intervals. Each correlogram consisted of 501 bins of 1.6 msec each, smoothed with a 7-bin median filter. Both raw and shuffle-subtracted correlograms are shown in Figures 5.1c and 5.2c. The other figures show only the shuffle-subtracted correlogram. Only peaks of significant height (Bonferroni-corrected: individual bins at $p < 0.0001$ such that overall $p < 0.05$) were considered. We recorded a total of 644 correlograms. Of these, 98/113 17-17, 107/116 17-18, and 80/93 LM-LM pairs were significant during Luminance-modulation, and 96/113 17-17, 99/116 17-18, and 73/93 LM-LM pairs were significant during spontaneous activity.

Alternative explanations considered

Given that inherent biases were seen for both oriented-LM and LM-LM pairings, we considered other possible explanations for our results. An area-related explanation would predict the same direction of bias (either 17-to-18 or 18-to-17) for all 17–18 interactions regardless of cell type. However, interactions between 17 and 18 are not all biased in the same direction: oriented-LM pairs tended to show an 18-to-17 bias at all distances, while LM-LM pairs showed a 17-to-18 bias for short distances and an 18-to-17 bias at long distances. This also argues that differences in RF size between Areas 17 and 18 (Area 18 RFs larger than Area 17 RFs) do not account for the biases. Neither is RF separation sufficient to explain all of our results: we find that at short distances biases in the peak positions of oriented-LM and LM-LM pairs were in opposite directions (oriented-LM biases were 18-to-17, whereas 0–5 deg LM-LM biases were 17-to-18; compare Figure 5.1c and 5.2c).

Finally, because stimuli were presented continuously for several minutes, we considered whether the spontaneous bias might be due to short-term
experience-dependent plasticity (Fu et al., 2002) resulting from differences in response latencies of LM (surface) and oriented (border) cells during luminance-modulation. Such an explanation would predict that the magnitude of spontaneous bias should depend on whether Luminance-modulation was presented prior to the spontaneous condition, or vice versa. The order of stimulus presentation had no effect upon the spontaneous bias recorded (for all oriented-LM pairs, Luminance condition before spontaneous: peak position mean –6.1 msec, n = 167; Spontaneous condition before luminance: peak position mean –3.7 msec, n = 28; p > 0.3, unpaired t-test). Furthermore, if the spontaneous bias were due to short-term plasticity, then Luminance-modulation bias should be greater than spontaneous bias (assuming that before stimulation the interactions are synchronous, that Luminance modulation induces a short-term bias in spike timing, and that the bias seen during spontaneous conditions occurs during the adaptation decay). However, as shown by the examples in Figure 5.1a,b,e and Figure 5.2e, the magnitude of spontaneous bias was often larger than the magnitude of Luminance-modulation bias, and in many cases the Luminance-modulation and spontaneous biases were in opposite directions. In fact, for 17–17 oriented-LM pairs, Luminance-modulation peak positions were not significantly biased whereas spontaneous peak positions were. Thus, we feel that short-term experience-dependent plasticity does not account for our findings of spontaneous bias.

FIGURE 5A-3 Spontaneous peak positions are centered for LM-LM pairs LM-LM pairs consisting of one cell in area 17 and the other in area 18 were recorded during spontaneous activity. No systematic bias is seen in the population of peak latencies, either in the 17-to-18 direction (right side, area 17 fires first) or the 18-to-17 direction (left side) (peak position mean: 2.5 msec, std error: 3.2 msec, p > 0.05). Thus, not all interactions exhibit bias under spontaneous conditions.
APPENDIX REFERENCES