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12. Several modifications were made to the bone marrow transplant protocol reported earlier (*4*) in an attempt to obtain multilineage engraftment. First, SCID recipient mice were used rather than athymic *bg/nu/xid* mice because normal human T cells and human leukemic cells migrate to the murine thymus (*6, 7*). The SCID mice were bred and maintained under defined flora conditions at the Ontario Cancer Institute. Second, the bone marrow cell dose was increased to 2×10^7 to 4×10^7 cells. Third, cytokines were delivered by alternate daily intraperitoneal (IP) injection rather than osmotic minipump to permit the delivery of higher doses over a longer time. The quantities of growth factors given IP to each mouse on alternate days were PIXY321, 8 μg; MGF, 20 μg; and EPO, 20 U. PIXY321 at 0.8 μg was ineffective. Fourth, recipient SCID mice were sublethally irradiated with 400 cGy before transplantation. This radiation dose permits immune reconstitution of SCID mice with syngeneic bone marrow and at the same time nontransplanted mice survive provided they are maintained in a pathogen-free environment (*27*).
13. DNA (5 μg) was digested with Eco R1 and hybridized with a human chromosome 17–specific α-satellite probe (p17H8). To quantitate the amount of human cells present in these tissues, the intensity of the 2.7-kb band was compared to human/mouse DNA mixtures (0.1, 1.0, 10, and 50% human) by described procedures (*4, 7*). Multiple exposures of the autoradiographs were taken to ensure sensitivity to 0.01% human DNA.
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16. Bone marrow cells from transplanted mice (2×10^5) were plated in methylcellulose cultures (*5*). Briefly, the cultures contained tested lots of human plasma and hu-IL-3 (10 U/ml), hu-GM-CSF (1 U/ml), PIXY321 (5 ng/ml), MGF (50 ng/ml), and hu-EPO (2 U/ml). The specificity of the assay was confirmed by plating human and mouse mixtures and by PCR on individual colonies using primers specific for the human dystrophin gene (*5*). Morphological criteria and histological staining were used to identify colonies derived from colony-forming unit granulocyte-macrophage (CFU-GM), burst-forming unit erythroid (BFU-E), and colony-forming unit granulocyte-macrophage-erythroid-megakaryocyte-eosinophils (CFU-GEMM) progenitors. Blast colony-forming progenitors were detected after 21 days of culture and their identity was confirmed by histological analysis.
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Form-Cue Invariant Motion Processing in Primate Visual Cortex

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The direction and rate at which an object moves are normally not correlated with the manifold physical cues (for example, brightness and texture) that enable it to be seen. As befits its goals, human perception of visual motion largely evades this diversity of cues for image form; direction and rate of motion are perceived (with few exceptions) in a fashion that does not depend on the physical characteristics of the object. The middle temporal visual area of the primate cerebral cortex contains many neurons that respond selectively to motion in a particular direction and is an integral part of the neural substrate for perception of motion. When stimulated with moving patterns characterized by one of three very diverse cues for form, many middle temporal neurons exhibited similar directional tuning. This lack of sensitivity for figural cue characteristics may allow the uniform perception of motion of objects having a broad spectrum of physical cues.

OBJECTS IN OUR VISUAL WORLD commonly differ physically, such as in brightness, texture, or distance from an observer. This variation generally bears little relation to the ways in which an object can move through space. Optimal detection of visual motion thus demands that the underlying neural apparatus disregard physical diversity among the cues that define moving objects. In this report I present neurophysiological evidence that motion-sensitive neurons in the middle temporal area (MT) of monkey visual cortex meet this demand by expressing form-cue invariance (*1*) in their selectivity for direction of motion.

Moving stimuli fall into two broad classes on the basis of the spatial characteristics of the defining figural cue. The first and most typical class consists of moving stimuli that are either brighter or darker than their surroundings. Adopting the terminology of Cavanagh and Mather (*2*), I refer to this as first-order motion (*3*). Consider, alternatively, the motion percept elicited by a traveling wave of flickering leaves arising from movements of a predator through a forest canopy. This complex but biologically significant temporal texture (*4*) is but one instance of a second class of visual motion that is clearly perceived despite the absence of any unique pattern of luminance traceable over space and time. More precisely, moving stimuli of this second class (i) are discriminable only by means other than luminance contrast (for example, spatial or temporal texture, stereoscopic disparity) and (ii) have a spatial luminance profile that varies during motion. Such stimuli have been labeled second-order motion (*2*).

The descriptive differences between these two classes of motion underscore important functional differences with respect to the mechanisms necessary for their detection. Owing to a pattern of luminance that is correlated over space and time, first-order motion can be detected in conventional spatiotemporal frequency or energy models for motion detection (*5, 6*). The computations utilized by these models may also underlie motion detection at early stages in the primate visual system, and there is abundant psychophysical (*5, 7*) and physiological (*8*) evidence in support of this possibility. Traditional motion models cannot account for detection of second-order motion (*9*). However, despite the substantial differences be-

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tween the physical properties of these two classes of stimuli and the presumed mechanisms for their detection, the percept of motion [for central vision (*10*)] has a quality that is form-cue invariant (*11, 12*). This perceptual invariance hints of a common neural substrate; it seems likely that motion-sensitive neurons at an early stage in the primate visual system are capable of encoding both first- and second-order motion. Neurons in cortical visual area MT (*13*) are specialized for motion detection, as evidenced by their directional selectivity for conventional first-order stimuli (such as bars and gratings defined by luminance contrast) (*14, 15*). As a first test of the hypothesis that this neural substrate for motion perception exhibits form-cue invariance, I examined the possibility that the functions of MT also include detection of second-order motion.

I recorded from 111 isolated neurons in extrastriate area MT of three rhesus monkeys and tested each cell for responses to second-order motion (*16*). Directional selectivity was assessed with the movement-without-correlation stimulus, a second-order stimulus described by Sperling (*17*) (Fig. 1). This type of stimulus, which has been used in a number of psychophysical studies of motion perception (*10–12, 18*), is visible by a kind of contrast best described as flicker or temporal texture. It has the appearance of a rectangle of twinkling dots that drifts smoothly across a background of identical but static texture. The average luminance of this stimulus does not differ from the background, nor is the spatial foreground pattern consistent over time (*19*). Most cells in the sample were also tested for directional selectivity with a conventional first-order stimulus. The latter consisted of a moving, solid luminous bar that was identical in all other respects (size, position, speed, background texture, and so on) to the second-order stimulus.

In agreement with earlier reports (*14, 15*), nearly all cells (82 of 83, 99%) were selective (*20*) for the direction of first-order motion. However, 87% (97 of 111) of the sampled MT neurons also responded selectively to the direction of motion of the second-order stimulus. Ten percent (11 of 111) responded to second-order motion but were not selective for direction, and the remaining cells (3 of 111) were completely unresponsive to this stimulus. Data from a cell typical of those selective for direction of second-order motion are shown in Fig. 2A. Casual inspection of the responses reveals pronounced directional selectivity for second-order motion. Responses were characteristically weaker than those obtained with first-order motion stimuli, but there was marked similarity between the patterns of directional selectivity elicited by the two stimulus types. By contrast, the cell in Fig. 2B was selective for the direction of first-order motion but exhibited no clear directional selectivity for second-order motion.

First- and second-order direction tuning data were subjected to quantitative analyses in order to better evaluate relative effects of these stimuli (*21*). One informative comparison was obtained by computation of the angular difference between the preferred directions of motion seen with first- and second-order stimuli. The mean of the sample distribution for these difference measures (Fig. 3) did not differ from zero [angular mean, 6.2°; $P < 0.0001$, V test of circular uniformity (*22*)]. Although there were some clear examples of neurons with widely disparate preferred directions, most cells were like that shown in Fig. 2A, having similar preferences (65% were within ±45°) for the two stimulus types (*23*).

Other indices of the relative effects of first- and second-order stimuli include comparisons of direction-tuning bandwidth, direction bias, and response magnitude. Direction tuning bandwidths did not differ for the two conditions (Mann-Whitney U). Comparison of directionality indices (1 − opposite response/preferred response), however, reveals a greater tendency toward bidirection-

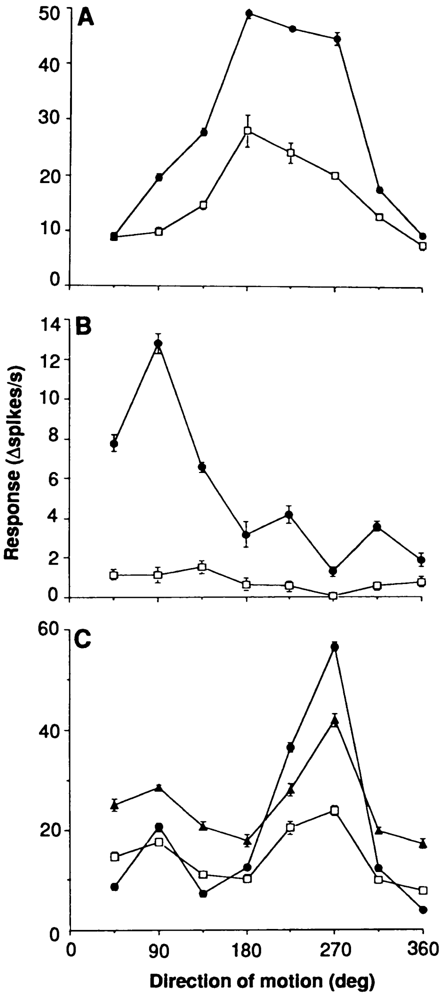

Fig. 2. Direction tuning of three MT neurons tested with first- and second-order motion. (**A**) A cell representing the form-cue invariant (*1*) class of MT neurons, responding with similar selectivity to first- (luminance, ●) and second-order (temporal texture, □) stimuli. (**B**) A cell selective for direction of first-order motion (●) but with no significant preference for second-order direction (□). (**C**) A cell exhibiting similar directional selectivity for first-order (luminance, ●) and two types of second-order (temporal texture, □; and spatial texture, ▲) motion. Error bars indicate SEM. Data were obtained with bar stimuli moved in each of eight different directions for five trials each in pseudo-random sequence. Sweeps were centered on the receptive field of each cell. Stimulus width, length, and speed were chosen to be optimal.

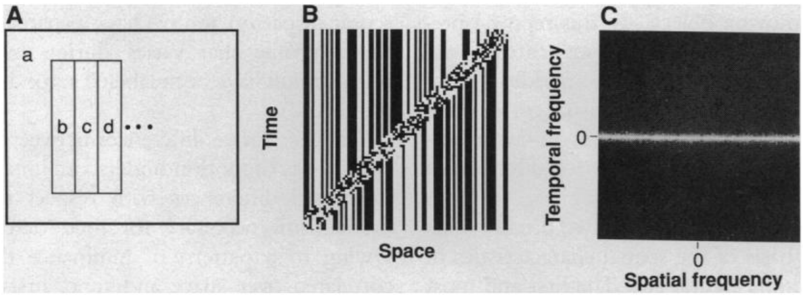

Fig. 1. (**A**) Schematic depiction of second-order movement-without-correlation stimulus, originally described by Sperling (*17*). Background (a) is a static two-dimensional random dot pattern. On each temporal frame, spatially consecutive bar-shaped regions of the pattern (b, c, d, . . .) are replaced with different uncorrelated random patterns of equal density and equal mean luminance. The resultant percept is that of a twinkling bar drifting smoothly to the right. (**B**) Space-time plot of the stimulus illustrated in (A). Luminant energy is plotted as a function of time and one spatial dimension (the axis of motion). The rightward-moving stimulus appears as a diagonal band of spatiotemporal noise. The background pattern is randomly varying in space and constant in time, before (below diagonal) and after (above diagonal) the passage of the stimulus. (**C**) Spatiotemporal Fourier amplitude spectrum of (B) (normalized cube-root scaling). The spatial frequency spectrum is broadband because of the spatially random background. Absent, however, is any evidence of spatiotemporal frequency interaction (for example, diagonal lines), which could be used to identify stimulus direction and speed. For this reason, Chubb and Sperling (*9*) have referred to such stimuli as non-Fourier motion.

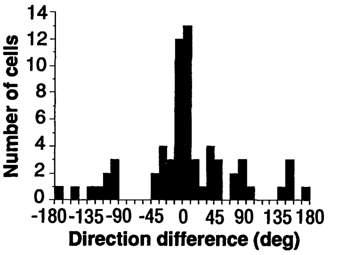

Fig. 3. Quantitative comparison of first- and second-order direction tuning in MT. The histogram shows the distribution of angular differences between the preferred directions (*21*) seen with first- (luminance) and second-order (temporal texture) motion stimuli. The sample mean did not differ from zero [angular mean, 6.2°; $P < 0.0001$, $n = 65$, V test of circular uniformity (*22*)]. Most cells (65%) exhibited similar (±45°) preferred directions of motion for the two stimulus types (*23*). The sample includes neurons tested systematically with both stimulus types and found directionally selective for each.

ality for second-order (median, 0.475) compared to first-order motion (median, 0.680; $P < 0.005$, Mann-Whitney U). Responses to the optimal direction of second-order motion (median, 5.09 spikes per second) were also weaker than those to first-order motion (median, 11.80 spikes per second; $P < 0.001$, Mann-Whitney U). The greater bidirectionality and weaker neural responses associated with second-order stimuli parallel differences in perceptual salience (second-order clearly being less salient than first-order) and may underlie these differences. In support of this possibility, we have recently observed similar effects by simply reducing the contrast of first-order stimuli (hence making them less salient) (*24*).

Only two of the many potential cues for figure-ground segregation were used in this first experiment. To provide support for the generality of form-cue invariance, I conducted a second experiment, in which a smaller sample of MT neurons ($n = 20$) was tested for directional selectivity with a stimulus set that included a third cue in addition to the two cues used in the first experiment. This third cue, another variety of second-order motion, consisted of a moving foreground discriminable solely by spatial texture. Both foreground and background were composed of random dot patterns, but foreground dots were slightly larger. The average foreground luminance was identical to background luminance, and the foreground texture pattern changed randomly while the foreground moved. The random background pattern was also dynamic to eliminate temporal cues between foreground and background. Data from a cell exhibiting similar selectivity for direction across all three cues are shown in Fig. 2C. Across the sample, the average angular difference in preferred direction for each pairing of the three cues did not differ from zero [$P < 0.0005$, V test of circular uniformity (*22*)], and no more than 30% of the differences (for any pairing) were outside the range of ±45° (*23*).

Thus, many MT neurons act as generalized motion detectors capable of using both first- and second-order cues to establish spatiotemporal correspondence. The significance of these results lies in the fact that such neurons are capable of encoding direction despite radically different physical stimulus conditions and thereby exhibit the same qualitative form-cue invariance that is manifested perceptually. Information about the defining characteristics of image features is sacrificed, the consequence of which is uniform sensitivity to motion across the spectrum of cues that characterize our visual world. In view of the computational advantage afforded by form-cue invariant motion processing, some MT neurons will probably be found to express form-cue invariance in the broadest sense: encoding motion of objects defined by other perceivable cues as well, such as stereoscopic disparity and color. In support of this possibility, several recent experiments (*25*) have shown that movement of stimuli defined solely by chromatic contrast is sufficient to activate many MT neurons.

What might be the origin of form-cue invariant directional selectivity in MT? The sensitivity of MT neurons to first-order motion is adequately accounted for by the luminance contrast sensitivity of cells at earlier stages. Chubb and Sperling (*9*) have noted that one can apply the essential features of spatiotemporal frequency models for motion detection to second-order motion by adding appropriate filters at the input stage—a flicker or spatial texture detector, for example. Although researchers have little information about how this might be implemented, one possibility is that the sensitivity of neurons in primary visual cortex (V1) to image contours is also invariant over different cues for form (*26*).

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20. Response amplitude was computed as the mean spike rate (spikes per second) within the period of stimulus presentation. A cell was considered directionally selective if response varied significantly [$P < 0.05$, analysis of variance (ANOVA)] with direction of motion.
21. Quantitative analysis was facilitated by fitting smooth functions to the direction-tuning data with an iterative, least squared residuals algorithm. As in my study of MT direction tuning (*15*), the Gaussian model provided an excellent fit to nearly all tuning data, offering relatively unbiased estimates of the preferred direction and tuning bandwidth.
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