Peaked Encoding of Relative Luminance in Macaque Areas V1 and V2

Xinmiao Peng and David C. Van Essen

Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, Missouri

Submitted 4 2004; accepted in final form 31 October 2004

Peng, Xinmiao and David C. Van Essen. Peaked encoding of relative luminance in macaque areas V1 and V2. J Neurophysiol 93: 1620–1632, 2005: First published November 3, 2004; doi:10.1152/jn.00793.2004. It is widely presumed that throughout the primate visual pathway neurons encode the relative luminance of objects (at a given light adaptation level) using two classes of monotonic function, one positively and the other negatively sloped. Based on computational considerations, we hypothesized that early visual cortex also contains neurons preferring intermediate relative luminance values. We tested this hypothesis by recording from single neurons in areas V1 and V2 of alert, fixating macaque monkeys during presentation of a large, spatially uniform patch oscillating slowly in luminance and surrounded by a static texture background. A substantial subset of neurons responsive to such low spatial frequency luminance stimuli in both areas exhibited prominent and statistically reliable response peaks to intermediate rather than minimal or maximal luminance values. When presented with static patches of different luminance but of the same spatial configuration, most neurons tested retained a preference for intermediate relative luminance. Control experiments using luminance modulation at multiple low temporal frequencies or reduced amplitude indicate that in the slow luminance-oscillating paradigm, responses were more strongly modulated by the luminance level than the rate of luminance change. These results strongly support our hypothesis and reveal a striking cortical transformation of luminance-related information that may contribute to the perception of surface brightness and lightness. In addition, we tested many luminance-sensitive neurons with large chromatic patches oscillating slowly in luminance. Many cells, including the gray-prefering neurons, exhibited strong color preferences, suggesting a role of luminance-sensitive cells in encoding information in three-dimensional color space.

INTRODUCTION

Luminance, the density of light energy absorbed by retinal photoreceptors, is an essential dimension of visual information. It is obviously important for neurophysiologists to understand how each stage of the visual system encodes various aspects of luminance-related information. This includes absolute luminance, spatial contrast in luminance (relative to a background or surround), and temporal contrast in luminance (relative to the recent average luminance). Luminance provides a basic cue to brightness and lightness, two important and related surface attributes that can be influenced by many global as well as local visual cues (Adelson 1993; Knill and Kersten 1991; Lotto et al. 1999; Purves et al. 1999; Williams et al. 1998). Given that in natural vision, luminance often varies slowly in space and in time (except during eye movements or object motion), it is particularly important to understand how low spatial and temporal frequency luminance information is encoded and transformed at successive stages of the visual hierarchy. However, our knowledge about the neuronal representation of luminance at low spatial and temporal frequencies (herein referred as luminance) is far from complete, especially for visual cortex.

At subcortical levels, primate retinal ganglion cells and lateral geniculate nucleus neurons have an unbalanced center-surround antagonistic receptive field structure (Croner and Kaplan 1995; Irvin et al. 1993), allowing them to convey low spatial frequency luminance as well as high spatial frequency contrast information. When these cells are presented with step increases in luminance of a large spatially uniform patch covering both the center and surround (i.e., of low spatial frequency), the responses either increase progressively (on-center cells) or decrease progressively (off-center cells) as a function of luminance level (Creutzfeldt et al. 1986; Sakmann and Creutzfeldt 1969; Virsu and Lee 1983). These results, along with the hyperbolic contrast tuning curves of early cortical neurons probed with sinusoidal gratings (Albrecht and Hamilton 1982; Levitt et al. 1996) have contributed to the widespread assumption that throughout the primate visual pathway low spatial frequency luminance information is encoded by a purely monotonic encoding strategy in which progressively brighter or darker stimuli evoke progressively stronger responses (Fig. 1A).

In the monotonic encoding strategy, intermediate luminance values (gray) elicit at most moderate firing from individual neurons and a low aggregate firing rate from the population. This constitutes a qualitatively different representation, with lower signal-to-noise ratio, than for low and high luminance values (dark and bright). Natural images, on the other hand, are typically dominated by intermediate luminance values (Laughlin 1981), which may warrant an alternate processing strategy to effectively represent many subtle shades of gray. Accordingly, we hypothesize that visual cortex includes luminance-sensitive neurons with peaked luminance encoding functions that explicitly represent intermediate values of relative luminance (bold curves in Fig. 1B).

At the cortical level, studies using large spatially uniform stimuli suggest that only a subset of neurons encode low spatial frequency luminance information (Bartlett and Doty 1974; Kinoshita and Komatsu 2001; Komatsu et al. 1996; Maguire and Baizer 1982; Rossi et al. 1996). Although it has been asserted that luminance encoding by V1 neurons is purely monotonic, the available evidence is not compelling (see discussion).

The present study used a combination of approaches to systematically examine luminance encoding at low spatial and temporal frequencies by V1 and V2 neurons. In one paradigm, we used a slowly and continuously varying (oscillating) luminance (bold curves in Fig. 1B).

Peng, Xinmiao and David C. Van Essen. Peaked encoding of relative luminance in macaque areas V1 and V2. J Neurophysiol 93: 1620–1632, 2005: First published November 3, 2004; doi:10.1152/jn.00793.2004. It is widely presumed that throughout the primate visual pathway neurons encode the relative luminance of objects (at a given light adaptation level) using two classes of monotonic function, one positively and the other negatively sloped. Based on computational considerations, we hypothesized that early visual cortex also contains neurons preferring intermediate relative luminance values. We tested this hypothesis by recording from single neurons in areas V1 and V2 of alert, fixating macaque monkeys during presentation of a large, spatially uniform patch oscillating slowly in luminance and surrounded by a static texture background. A substantial subset of neurons responsive to such low spatial frequency luminance stimuli in both areas exhibited prominent and statistically reliable response peaks to intermediate rather than minimal or maximal luminance values. When presented with static patches of different luminance but of the same spatial configuration, most neurons tested retained a preference for intermediate relative luminance. Control experiments using luminance modulation at multiple low temporal frequencies or reduced amplitude indicate that in the slow luminance-oscillating paradigm, responses were more strongly modulated by the luminance level than the rate of luminance change. These results strongly support our hypothesis and reveal a striking cortical transformation of luminance-related information that may contribute to the perception of surface brightness and lightness. In addition, we tested many luminance-sensitive neurons with large chromatic patches oscillating slowly in luminance. Many cells, including the gray-prefering neurons, exhibited strong color preferences, suggesting a role of luminance-sensitive cells in encoding information in three-dimensional color space.

INTRODUCTION

Luminance, the density of light energy absorbed by retinal photoreceptors, is an essential dimension of visual information. It is obviously important for neurophysiologists to understand how each stage of the visual system encodes various aspects of luminance-related information. This includes absolute luminance, spatial contrast in luminance (relative to a background or surround), and temporal contrast in luminance (relative to the recent average luminance). Luminance provides a basic cue to brightness and lightness, two important and related surface attributes that can be influenced by many global as well as local visual cues (Adelson 1993; Knill and Kersten 1991; Lotto et al. 1999; Purves et al. 1999; Williams et al. 1998). Given that in natural vision, luminance often varies slowly in space and in time (except during eye movements or object motion), it is particularly important to understand how low spatial and temporal frequency luminance information is encoded and transformed at successive stages of the visual hierarchy. However, our knowledge about the neuronal representation of luminance at low spatial and temporal frequencies (herein referred as luminance) is far from complete, especially for visual cortex.

At subcortical levels, primate retinal ganglion cells and lateral geniculate nucleus neurons have an unbalanced center-surround antagonistic receptive field structure (Croner and Kaplan 1995; Irvin et al. 1993), allowing them to convey low spatial frequency luminance as well as high spatial frequency contrast information. When these cells are presented with step increases in luminance of a large spatially uniform patch covering both the center and surround (i.e., of low spatial frequency), the responses either increase progressively (on-center cells) or decrease progressively (off-center cells) as a function of luminance level (Creutzfeldt et al. 1986; Sakmann and Creutzfeldt 1969; Virsu and Lee 1983). These results, along with the hyperbolic contrast tuning curves of early cortical neurons probed with sinusoidal gratings (Albrecht and Hamilton 1982; Levitt et al. 1996) have contributed to the widespread assumption that throughout the primate visual pathway low spatial frequency luminance information is encoded by a purely monotonic encoding strategy in which progressively brighter or darker stimuli evoke progressively stronger responses (Fig. 1A).

In the monotonic encoding strategy, intermediate luminance values (gray) elicit at most moderate firing from individual neurons and a low aggregate firing rate from the population. This constitutes a qualitatively different representation, with lower signal-to-noise ratio, than for low and high luminance values (dark and bright). Natural images, on the other hand, are typically dominated by intermediate luminance values (Laughlin 1981), which may warrant an alternate processing strategy to effectively represent many subtle shades of gray. Accordingly, we hypothesize that visual cortex includes luminance-sensitive neurons with peaked luminance encoding functions that explicitly represent intermediate values of relative luminance (bold curves in Fig. 1B).

At the cortical level, studies using large spatially uniform stimuli suggest that only a subset of neurons encode low spatial frequency luminance information (Bartlett and Doty 1974; Kinoshita and Komatsu 2001; Komatsu et al. 1996; Maguire and Baizer 1982; Rossi et al. 1996). Although it has been asserted that luminance encoding by V1 neurons is purely monotonic, the available evidence is not compelling (see discussion).

The present study used a combination of approaches to systematically examine luminance encoding at low spatial and temporal frequencies by V1 and V2 neurons. In one paradigm, we used a slowly and continuously varying (oscillating) luminance (bold curves in Fig. 1B).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
monitored by standard scleral search eyecoil implanted before training. Before recording, a craniotomy of 5 mm in diameter was made through an acrylic patch mounted on the skull, and a stainless chamber with a screw-on cap was cemented to the acrylic. All surgical procedures were conducted in accordance with National Institutes of Health guideline and reviewed and approved in advance by Washington University Animal Studies Committee.

Visual stimuli

Stimuli were generated by an SGI Indy computer and presented on a 17-in, 72-Hz color CRT monitor placed in a dark room 57 cm in front of the animal, with screen dimensions subtending 32 × 24° in visual angle. When measured by a Chroma Meter (CS100A, Minolta), the maximal luminance (at RGB fraction 1.0) of the two monitors used (full screen) was 62 cd/m² (146 cells) and 77 cd/m² (108 cells), respectively. With dithering enabled and after gamma correction, the luminance of the uniform screen varied linearly with RGB fraction over the range from 0.03 to 1.0 (correlation coefficient: 0.9998, P < 0.0001). At lower RGB values, the relationship was more nonlinear owing to nonlinear phosphor output and to light scatter (~0.3 cd/m²) from the texture background surrounding the stimulus (see following text). Accordingly, we further calibrated stimulus luminance with texture background present, converted all RGB fractions to luminance fractions (normalized to maximal luminance), and used the luminance fraction in analyzing and illustrating our results.

Test stimuli were large uniform squares more than five times the size of the classical receptive field (usually 8–10 times, 8 ~ 12° on a side) surrounded by a static “checkerboard” texture background, which was composed of small squares 1/8 the width of the stimulus patch (Fig. 1C). In each trial, the luminance of individual background squares was selected randomly from a uniform distribution across the full luminance range. This ensured a wide range of local contrasts along the borders for patches of all luminance values. The luminance patch either oscillated sinusoidally in luminance (slow oscillating paradigm) or made step changes in luminance (static patch paradigm). In the oscillating test, the mean luminance of both the background and the initial stimulus patch was half-maximal (luminance fraction: 0.5). The temporal configuration is shown in Fig. 1D. In each trial, the texture background appeared 0.3 s after fixation point onset on a uniform gray at mean luminance. The large uniform stimulus emerged 0.7 s later and began oscillating sinusoidally in luminance for 5 s, covering the full luminance range available in 44 steps (RGB fraction between 0 and 1, corresponding to luminance fractions between 0.004 and 1). The temporal frequency of luminance oscillation was usually 0.4 Hz (2 cycles/5 s). For some neurons, oscillations of 0.2 Hz (1 cycle/5 s) and 1 Hz (5 cycles/5 s) were also interleaved. The initial phase of the oscillation was randomly selected to be 0 (increasing) or π (decreasing). Stimuli of each phase were typically repeated 20 times (minimum 10).

In the static patch paradigm, the spatial configuration remained the same as in the oscillating paradigm. Patches of six luminance levels were presented, evenly distributed on a logarithmic scale for the RGB fraction: 0.001, 0.005, 0.02, 0.08, 0.32, and 1; the corresponding luminance fractions were: 0.004, 0.006, 0.013, 0.072, 0.32, and 1.0. The steps in log(luminance fraction) were nonuniform for the lowest three levels due to nonlinearities described in the preceding text. The stimuli lasted 1.4 s with transient onsets and offsets and were pseudorandomly interleaved for 60 trials (Fig. 1E). Each luminance level was preceded by one of the other luminance levels or by the texture background (mean luminance fraction: 0.5). Each stimulus condition was repeated six times.

In the chromatic paradigm (Fig. 1F), a large black patch (luminance fraction: 0.004) and the texture surround appeared 0.3 s after the fixation onset. After another 0.6 s, the gun value of the red (chromaticity values: x = 0.62, y = 0.35), green (x = 0.29, y = 0.60), or blue (x = 0.14, y = 0.60) phosphor oscillated slowly and sinusoidally over.

METH ODS

Physiological preparation

Two male Macaca mulatta were trained to fixate on a small dot within a fixation window of radius 0.4–0.6° for 6 s. Eye position was

FIG. 1. Encoding strategies and stimulus configuration. A: a pure Monotonic Encoding strategy. B: peaked luminance tuning included (Bold curves). C: spatial configuration of the stimuli. D: oscillating paradigm. In each trial, fixation onset was at time 0, uniform texture background onset was at 0.3 s; the luminance patch onset was at 1.0 s; and the oscillation lasted 5 s (solid curve: phase 0; dashed curve: phase π). E: static paradigm. In each trial, luminance changed every 1.4 s. F: chromatic paradigm. In each trial, the intensity of 1 or 2 phosphors (1 color) oscillated successively for 3 cycles, each lasting 1.7 s.
5.1 s (initial phase: 1.5, gun value: 0, see the dashed curve in Fig. 9, B, D, F, and H) for three cycles. In each trial, the intensity oscillations of the three hues were randomly ordered. For some neurons, oscillations of magenta (red plus blue guns, x = 0.29, y = 0.15), cyan (green plus blue guns, x = 0.21, y = 0.30) were also included. The maximal luminance of white (L_{max}) for these experiments was 77 cd/m^2. The maximal luminance for red, green blue, magenta, and cyan was 18, 52, 7, 25, and 59 cd/m^2, respectively, corresponding to 0.23, 0.68, 0.09, 0.32, and 0.77 as fractions of L_{max}. Each stimulus was repeated 40 times.

**Recording and data analysis**

Well-isolated single units in areas V1 and V2 were recorded extracellularly with tungsten electrodes (1–5 MΩ) in daily sessions. The search stimuli were Cartesian or non-Cartesian gratings of a range of spatial frequencies and colors. The receptive field (eccentricity: 2–5°) was mapped quantitatively using oriented small bars. For units not driven by the standard mapping stimuli, we directly tested for responsiveness using a large uniform oscillating patch. Orientation tuning, and sometimes tunings for spatial frequency, color and size were determined prior to the main experiment.

Randomization tests were performed to determine the significance of response modulation driven by the oscillating stimulus. The test statistic was the sum of the power of the stimulus fundamental frequency and second harmonic, normalized to the total area under the power spectrum of the peristimulus time histogram (PSTH). The null hypothesis was that all frequency components in the response were equally weighted. If the measured value fell in the upper 5% of a distribution generated by randomly shuffling interspike intervals during 5 s and recalculating the test statistic 10^5 times, the response was considered significant. When the fundamental frequency alone was used for the test statistic, significance persisted for all but two (157/159) V1 and one (97/98) V2 neurons, and the exceptions all had considered significant. When the fundamental frequency alone was considered significant for decreasing luminance relative to the corresponding luminance value when it is increasing; +1 signifies a complete bias for increasing luminance; and 0 indicates no directional bias. To determine the statistical reliability of a test statistic (preferred luminance, direction index), we drew 10^5 bootstrap samples (40 trials randomly selected with replacement) and calculated the test statistic. When 95% values of the bootstrap distribution were above or below a certain value, we considered the test statistic as significantly higher or lower than that value, respectively.

In the chromatic paradigm, the color selectivity index was defined as 1 − R_{color}/R_{gray}. Where R_{color} and R_{gray} refer to the maximal response to the preferred and nonpreferred color, respectively. The color to gray index was defined as sign*(1 − R_{color}/R_{gray})sign, where R_{color} and R_{gray} refer to the maximal response in the chromatic and achromatic experiments, respectively. Sign refers to the sign of (R_{color} − R_{gray}).

**RESULTS**

We recorded responses from single units in areas V1 and V2 in two alert, fixating rhesus monkeys. In the slow oscillating test, the stimulus (Fig. 1, C and D) was a large spatially uniform square that oscillated sinusoidally in luminance (0.4 Hz) for 5 s, embedded in a static texture background (Fig. 1D). The slow oscillations allowed us to continuously sample a wide range of luminance values at low spatial frequency, and the texture background ensured a clear patch figure at all luminance values tested (see DISCUSSION). In an initial qualitative
assessment, about one-third of the neurons encountered responded to large patches that oscillated slowly in luminance and were then tested quantitatively. The large majority of these (159 V1 and 98 V2 neurons) showed significant stimulus-driven modulation (randomization analysis, see METHODS) and will be referred to as luminance-sensitive neurons in the results presented in the following text.

Diversity of luminance-modulated responses: examples

We encountered several distinct types of response modulated by low spatial frequency luminance as illustrated by the three example cells shown in Fig. 2. The top panels show responses of a V1 neuron that fired maximally at an intermediate (gray) luminance level, as indicated by the PSTHs in Fig. 2A and the response profile by collapsing responses to stimuli of both initial phases to a single cycle in B. The dashed curve in Fig. 2B shows the collapsed response profile after latency compensation with fixed response delays (40 ms). The clear preference for an intermediate luminance value (peak responses at luminance fraction 0.24) supports our hypothesis that early visual cortex includes neurons that respond best to gray instead of black or white at a given adaptation level.

Most cells fired substantially only to luminance values within fairly small ranges. Many of these cells also responded selectively to the direction of luminance change. For example, the V2 neuron in Fig. 2C responded well at a low-intermediate luminance level (preferred a luminance fraction value of 0.04) but only when it was increasing. Relatively few cells showed broad tuning, and most of these responded best to high luminance values (Fig. 2D, preferred luminance fraction: 0.83).

Distributions of preferred luminance: gray-preferring neurons

To analyze the population data, we compensated the collapsed response profile of each cell with typical response delays for V1 (40 ms) and V2 (50 ms) neurons (dashed curves in Fig. 2, B–D) and determined the luminance fraction at which each neuron responded maximally (see METHODS). Figure 3A shows the distribution of preferred luminance fraction of 159 V1 (blue) and 98 V2 (red) neurons. Across both populations, the preferred luminance fractions span a wide range but are strongly biased toward near-minimal and low-intermediate values compared to high-intermediate and near-maximal values. This bias for lower values appeared even more prominent when plotted on a linear scale (data not shown). The preferred luminance fraction of 50 V1 (31%) and 38 V2 (39%) neurons was within an intermediate range, between 0.03 and 0.63. The upper bound (38 and 50 cd/m² for the 2 monitors) and lower bound (1.8 and 2.3 cd/m² for the 2 monitors) were chosen on the basis that all intervening levels appear distinctly gray to human observers under the same viewing conditions (note the 7.5-fold ratio between the lower bound and the minimal luminance). For 22 V1 (14%) and 12 V2 (12%) neurons the preferred luminance was significantly above the lower cut-off and significantly below the higher cut-off ($P < 0.05$; shown in dark colors, see METHODS). We used this stringent criterion and consider these cells to be gray-preferring neurons (shown in dark colors). The percentage of gray-preferring neurons was not significantly different between V1 and V2 for both monkeys ($\chi^2$ test, $P > 0.05$ and $P > 0.1$, respectively, for the 2 animals).

To test whether the incidence of gray-preferring cells might critically depend on the particular choice for response delay, which in fact varies with absolute luminance and spectral composition (Cottaris and De Valois 1998; Schneeweis and Schnapf 1999), we varied the compensatory delay from 20 to 200 ms (in 10-ms intervals) and computed the incidence of gray-preferring cells separately for each delay. For all response delays tested, a substantial subset of V1 and V2 neurons showed a significant preference for intermediate luminance values (minimal percentage 11% in V1 and V2). We also examined the relation between individual response delays and preferred luminance in two additional tests described more fully in subsequent sections. One test (17 V1 neurons and 5 V2 neurons) involved static large patches presented at different luminance levels. The estimated response delays varied between 40 and 90 ms and were not significantly correlated with preferred luminance (correlation coefficient $= 0.09$, $P > 0.7$). In another test (47 V1 neurons and 38 V2 neurons), we measured neural responses to luminance oscillation of three temporal frequencies (0.2, 0.4, and 1 Hz). We estimated response delays based on phase shifts by determining the mean cross-correlation between response profiles at different frequency pairs. All the estimated response delays were <120 ms. More importantly, the response delays and estimated preferred luminance were not significantly correlated (correlation coefficient $= 0.01$, $P > 0.9$). These results indicate that variability of response delays does not account for the variability of preferred luminance.

The gray-preferring neurons were as strongly modulated by luminance oscillation as the other categories of luminance-sensitive cells across all populations. Figure 3B shows a scatter plot of the percentage of the combined fundamental and second harmonic components in the response power spectrum ($f_1 + f_2$) versus the preferred luminance. The value of ($f_1 + f_2$)% was not significantly different between the gray-preferring (shown in filled symbols) and the other cells for both V1 ($P > 0.9$) and V2 populations ($P > 0.7$). For gray-preferring neurons, the difference between maximal and minimal firing rates in the collapsed response profiles averaged $28 \pm 15$ (SD) spikes/s for V1 and $29 \pm 20$ spikes/s for V2, which was comparable to that for the entire populations ($33 \pm 18$ spikes/s for V1 and $31 \pm 21$ spikes/s for V2). In addition, the gray-preferring neurons were on average as narrowly tuned as the rest of the population (Fig. 3C).

Figure 3D illustrates the scatter plot of the direction index versus the preferred luminance of V1 and V2 neurons for all populations. The direction index (see METHODS) quantifies a preference for direction of luminance that was dependent on luminance level. We considered a neuron as having a strong direction preference if the absolute values of direction index exceeded 0.33 significantly (a 2-fold difference between response to preferred and nonpreferred direction, at 0.05 level, randomization test, see METHODS). This criterion was met by 31 (20%) V1 cells and 15 (15%) V2 cells, including 8 (36%) of the V1 gray-preferring and 4 (36%) of the V2 gray-preferring cells.
In this slow oscillating paradigm, it is important to consider whether adaptation to the large spatially uniform stimulus itself might substantially contribute to the observed response pattern. Previous psychophysical and physiological studies have revealed fast (\(\sim 100\) ms) and slow (several seconds to minutes) adaptation mechanisms that change detection thresholds for luminance after exposure to an adapting luminance level, in a fashion predicted by Weber's law (Boynton and Whitten 1970; Geisler 1983; Knau 2000). In the oscillating paradigm, adaptation would be expected to shift the preferred luminance in opposite directions for decreasing versus increasing luminance (to a higher preferred luminance during the decreasing phase, \(L_{\text{dp}}\), and a lower preferred luminance during the increasing phase, \(L_{\text{ip}}\)). However, for the 33 neurons showing clear double peaks (response magnitudes of the 2 peaks differed \(<2\)-fold), the difference between peaks (\(L_{\text{dp}} - L_{\text{ip}}\)) averaged \(-0.01 \pm 0.36\) (SD) and was not significantly from zero (\(P > 0.8\)). This suggests that rapid adaptation played little if any role in determining the response peaks in the oscillating patch paradigm. Slow adaptation, on the other hand, including that contributed by the texture surround, is likely to be important (see following text).

The temporal frequency of the luminance oscillation used in the oscillating paradigm, 0.4 Hz, is low compared with the range of optimal temporal frequency for V1 and V2 neurons (2–8 Hz) (Foster et al. 1985), suggesting that there should be relatively little interaction between the temporal characteristics of the stimuli and those of the neurons under study. This issue was further addressed using stimuli oscillating at different temporal frequencies, as discussed in a later section. However, it is obviously desirable as well to examine directly the responses to static stimuli at different luminance levels.

![Figure 3](http://jn.physiology.org/)

**FIG. 3.** Population data for V1 and V2 neurons. **A:** histogram of preferred luminance of V1 and V2 neurons. Dark colors (and filled symbols in B–D): neurons that showed response peaks significantly within the intermediate range. Preferred luminance is normalized to maximal and shown on a conventional logarithmic scale. **B:** scatter plot of percentage of stimulus fundamental and 2nd harmonic components in the response power spectrum versus preferred luminance. **C:** scatter plot of full width at half-maximum of the response peak in relation to a full cycle of luminance oscillation in the collapsed profiles vs. preferred luminance. **D:** scatter plot of direction index versus preferred luminance. In all 4 panels, V1: blue, V2 in red; circles and triangles: data from 2 monkeys; dashed vertical lines: left, luminance fraction = 0.03, right, luminance fraction = 0.63.
Luminance tuning in response to large static patches

We tested 22 luminance-sensitive neurons with a static paradigm as well as the slow oscillating paradigm. In the static test, a uniform patch (1 of the 6 luminance values) was presented for 1.4 s over a texture background (Fig. 1E) and was preceded by different luminance levels. The spatial configuration was the same as in the oscillating paradigm (Fig. 1B).

Figure 4 shows an example V1 cell that preferred a luminance fraction of 0.12 in the oscillating paradigm (Fig. 4A). In response to static patches, it exhibited a response transient followed by sustained firing that depended on luminance level (Fig. 4B, solid curves, luminance fraction: 0.072; dashed curves, luminance fraction: 0.006). The transient responses varied with preceding luminance values (different color lines), whereas the sustained response was largely independent of preceding luminance. Figure 4C shows the luminance tuning profiles calculated separately for transient (average response during 0.02–0.2 s) and sustained (average response during 0.5–1.4 s) components. The luminance tuning of the sustained response did not vary with the preceding level and exhibited a clear preference for an intermediate luminance fraction of 0.072 (bold black line, very small error bars). The luminance tuning of the transient response depended on the preceding luminance but also showed a consistent peak at 0.072 (thin color lines).

Figure 5A and B, illustrates two more example gray-preferring cells that showed a preference for intermediate luminance values in the static patch experiment. The V1 cell in Fig. 5A shows a striking peaked pattern of luminance tuning profiles in response to static patches (preferred luminance 0.11 in oscillating experiment; oscillating luminance responses shown in Fig. 6A). In Fig. 5B, a gray-preferring V2 cell shown in Fig. 2C (preferred luminance fraction: 0.04) responded maximally to luminance 0.013. In all three of these examples, the peak of the transient response was consistent for all but one of the preceding luminance values.

In the 22 cells tested (17 V1 and 5 V2 neurons), the ratio of maximal sustained response to maximal transient response was 0.72 ± 0.24 (SD), indicating consistently prominent firing evoked during the sustained period. Luminance tunings for all these neurons were significant (t-test with Bonferroni correction). Figure 5E compares the peak tuning values for the oscillating paradigm and the sustained responses in the static paradigm (* indicates 2 data points that are close together). The preferred luminance values obtained from the two experiments correlated significantly (correlation coefficient: 0.54, P < 0.02). Importantly, of nine gray-preferring cells (Fig. 5E, ▲), six showed convincing peaked luminance tuning profiles, peaking at an intermediate luminance value within 1 log unit of the preferred luminance in the oscillating paradigm. The remaining three cells showed a local peak at a matching luminance but also responded maximally to the lowest luminance fraction (0.004). Figure 5, C and D, illustrates a broadly tuned V2 cell that preferred luminance 0.072 in the oscillating test (Fig. 5C). In the static experiment, the luminance tuning profile of the sustained response showed a small but significant local peak at 0.072 and a maximal response at the minimum luminance (Fig. 5D). Note that for transient responses, this cell responded best to 0.072 when the preceding luminance level was 1.0, consistent with its preference for decreasing luminance in the oscillating test.

These results, although from a modest sample of neurons, unequivocally indicate the existence of neurons preferring intermediate luminance values. Although there are some exceptions, the general consistency of the preferred luminance values also supports the validity of the slow oscillating paradigm as an effective approach for probing luminance tuning using much more finely spaced luminance values.
Response to luminance oscillation of reduced amplitude

To further validate our interpretation of the data from the slow oscillating experiment, it is important to assess the degree to which the responses may have been influenced by temporal aspects of the stimulus other than sign of luminance change. To examine whether the data reflect a preference for luminance values versus the rates of luminance change or particular phases in the oscillation cycle, we performed several control experiments. The first involved luminance oscillation at half the maximal amplitude, without altering other stimulus parameters. For the example V1 cell shown in Fig. 6, A and B, the full amplitude test resulted in maximal firing at both increasing and decreasing intermediate luminance values (Fig. 6A, preferred luminance fraction 0.11, peak \( \frac{dluminance}{dt} \) 0.33, after response delay compensation). In the half-amplitude test, this neuron exhibited a single response peak at the stimulus trough (Fig. 6B, preferred luminance fraction 0.24, the minimal luminance presented, peak \( \frac{dluminance}{dt} \) −0.33). For the example V2 cell shown in Fig. 6, C and D, the full amplitude test yielded a narrowly tuned peak to low luminance (Fig. 6C). The half-amplitude oscillation never reached the preferred luminance, and the cell gave only a weak response (Fig. 6D). In every cell tested with this control experiment (15 V1 and 11 V2 neurons), we observed either merging of double peaks (10 cells) or a marked decrease in response magnitude (16 cells), similar to the two example cells. These results strongly suggest that under our experimental condition in the oscillating experiment the response modulation is mainly driven by the luminance level and the sign of luminance change; the rate of luminance change is much less important.
Response to stimuli of multiple temporal frequencies

We also evaluated the influence of temporal components of the oscillating stimulus by testing 47 V1 and 38 V2 neurons with full amplitude oscillation at three frequencies: 0.2, 0.4 (used in the main oscillating experiments), and 1 Hz (corresponding to 1, 2, and 5 cycles/5 s, respectively). Figure 7 illustrates the collapsed profiles of two example cells in response to stimuli of the three temporal frequencies (top: 0.2 Hz; middle: 0.4 Hz; bottom: 1 Hz). The V2 cell shown in Fig. 7A exhibited a sharp response peak immediately after the trough of luminance oscillation. The basic pattern persisted, but the phase lag increased slightly with increased temporal frequency, in a manner consistent with an approximately constant response delay for different oscillation frequencies. After delay compensation (50 ms), the estimated preferred luminance fraction at three temporal frequencies was similar: 0.013 (0.2 Hz), 0.015 (0.4 Hz), and 0.014 (1 Hz). In contrast, the luminance derivatives at the peak response for the three frequencies differed markedly: 0.17 s$^{-1}$ (0.2 Hz), 0.38 s$^{-1}$ (0.4 Hz), and 0.97 s$^{-1}$ (1 Hz). Figure 7B shows a V1 cell that fired maximally at intermediate luminance fractions: 0.34 (0.2 Hz), 0.24 (0.4 Hz), and 0.36 (1 Hz). Results from the same calculations for luminance derivatives at peak response (after response delay compensation of 40 ms) were quite different: $-0.58$ s$^{-1}$ (0.2 Hz), $-1.06$ s$^{-1}$ (0.4 Hz), and $+1.89$ s$^{-1}$ (1 Hz). The response pattern to the 1-Hz stimuli of this cell was markedly more directional than for 0.2 and 0.4 Hz, suggesting that the rate of luminance change did affect this cell, especially at the highest frequency tested (1 Hz).

The estimated luminance corresponding to peak firing (but not the luminance derivative) remained relatively constant across frequencies (especially between 0.2 and 0.4 Hz) for most of the 47 V1 and 38 V2 cells tested. The correlation coefficient between the estimated preferred luminance at 0.2 and 0.4 Hz was 0.73 ($P < 0.0001$) for V1 and 0.74 ($P < 0.0001$) for V2 neurons. The preferred luminance velocities (luminance derivative corresponding to the peak firing after delay compensation) at different temporal frequencies were less well correlated. Between 0.2 and 0.4 Hz, the correlation coefficients were 0.51 ($P < 0.001$) in V1 and 0.56 ($P < 0.001$) in V2. These results further support the suitability of our slow (0.4 Hz) luminance oscillation paradigm as an effective way to measure luminance coding.

Influence of average background luminance in the oscillating experiment

In the oscillating experiment, we tested 10 luminance-sensitive neurons with an additional experiment in which the background luminance level was varied. Six were tested with a texture background of mean luminance fraction 0.25, four with a uniform black background (luminance = 0), and three with a uniform white background (luminance = 1). We encountered two sharply tuned example V1 cells that showed a convincing shift in preferred luminance for different background luminance levels. Figure 8A illustrates a V1 cell that preferred a decreasing luminance at 0.013 (top) in the main oscillating test (texture background, mean luminance fraction = 0.5). When tested with the same stimulus surrounding by a white background (luminance = 1.0), the preferred luminance of this neuron shifted upward to 0.09 (bottom). This shift is in the same direction as predicted for a representation that correlates with perceived luminance. The V1 cell in Fig. 8B exhibited a response peak at 0.013 when the patch luminance was increasing in the main test. In response to luminance oscillation over
a completely black background (luminance = 0), the response peak shifted downward to 0.007, again in the same direction as that of luminance perception. There was also sharpening of the response peak when the background was black. Thus in at least some cells, the influence of background luminance levels is consistent with a role in encoding relative luminance that contributes to brightness and lightness perception. The remaining cells tested with this paradigm had relatively broad peaks and did not show an obvious shift.

Response to large chromatic patches oscillating in intensity

We examined chromatic properties using a paradigm designed to address two questions: are gray-preferring neurons purely luminance selective or do they also convey chromatic information and might a preference for gray arise from simple linear summation of excitatory inputs from one excitatory cone mechanism and inhibitory inputs from another cone mechanism that saturates at different intensities, as reported for LGN neurons (Valberg et al. 1987)?

The paradigm used a stimulus patch of a particular hue (3 or 6 hues tested) that oscillated in luminance at 0.66 Hz. We observed a variety of response patterns, suggesting diverse underlying mechanisms involved. The example V2 cell in Fig. 9, A and B, significantly preferred an intermediate luminance fraction of 0.04 in the achromatic test. In the chromatic test, it showed strong color selectivity, with a preference for red and a peak at intermediate increasing red intensity (preferred luminance fraction: 0.03 normalized to maximal achromatic luminance). The sharper tuning for achromatic than for red presumably reflects opponency between long-wavelength and medium- and/or short-wavelength cone mechanisms. However, simple opponency cannot account for the larger peak response to the achromatic stimulus or the shape of the response profile to the red stimulus. The example cell shown in Fig. 9, C and D, did not show color selectivity or color opponency and responded similarly to achromatic and chromatic stimuli. The peak responses occurred at closely similar phases for the different chromatic conditions, and the normalized preferred luminance fractions for achromatic, red, green, blue, magenta, and cyan patches varied substantially (0.03, 0.03, 0.01, 0.05, 0.03, and 0.02, respectively), indicating that the luminance value irrespective of spectral composition was not the sole determinant of this cell’s response. The example V2 cell shown in Fig. 9, E and F, responded well to dark stimuli in the achromatic test but fired well to high intensity for all three color patches, suggesting a complex interaction between cone mechanisms.

**FIG. 9.** Comparing results in the achromatic and chromatic paradigms. A: collapsed response profile of an example V2 cell, which fired best to increasing dark gray in the achromatic oscillation test (shifted in phase for comparison). B: collapsed response profile of the neuron in A to oscillation of intensity of red, green, and blue phosphors (shown in corresponding colors). The neuron was excited by increasing intermediate and high red gun intensity but gave no response to green or blue stimuli. The dashed curve shows oscillation in red, green, blue (RGB) fractions. All the profiles are after latency compensation. C and D: an example V1 cell that showed similar response profiles (preferring a decreasing low luminance level) when tested with achromatic and chromatic patches. Note that the preferred luminance values for the various hues were different. E and F: an example V2 cell that preferred dark in the achromatic experiment but was excited by red, blue, and green stimuli at high luminance.
The average color selectivity indices for 53 V1 and 12 V2 neurons were $0.40 \pm 0.24$ and $0.40 \pm 0.22$ (SD), respectively, indicating relatively strong color selectivity for the population as a whole. Nineteen cells (including 7 of the 13 gray-prefering cells) showed color selectivity indices exceeding 0.5, indicating a more than twofold difference between peaks for the preferred and nonpreferred colors. The maximal response to the preferred color of most cells exceeded their maximal response to the achromatic stimuli even though the highest luminance value during achromatic oscillation was always lower than that during achromatic oscillation. The color to gray index was significantly greater than zero for both V1 ($P < 0.0001$) and V2 ($P < 0.03$) populations, averaging $0.17 \pm 0.35$ in V1 and $0.24 \pm 0.31$ (SD) in V2. These data suggest a role of luminance-sensitive cells in encoding color information in three-dimensional color space.

We calculated the preferred luminance and direction index of all 65 cells in response to chromatic as well as achromatic stimuli. Figure 10, A (V1) and B (V2), presents the preferred luminance fraction in the achromatic test (black symbols; filled vs. open reflect significant versus nonsignificant preferences for intermediate luminance) and in the chromatic test (normalized to the maximal achromatic luminance; filled or open symbols of the corresponding hue respectively indicate significant or nonsignificant preference for intermediate luminance in the achromatic test); results for each cell are displayed along a horizontal row. The cells are sorted by the preferred luminance in the achromatic test. The preferred

FIG. 10. Comparing preferred luminance and direction index in the chromatic and achromatic test. A: preferred luminance (all normalized to maximal achromatic luminance, on a logarithmic scale) in the achromatic test (black symbol) and chromatic test (color symbols) for 53 V1 luminance-sensitive cells (sorted by preferred luminance in achromatic test). The 4 symbols lined parallel to the abscissa are the preferred luminance (normalized to maximal achromatic luminance) of 1 in different tests. Vertical dashed lines denote conservative arbitrary boundaries for dark and light gray in the achromatic test, as in Fig. 3. The filled symbols are gray-prefering neurons identified in the achromatic experiment. B: preferred luminance in the achromatic test and chromatic test for 12 V1 luminance-sensitive cells (sorted by direction index in achromatic test). C and D: direction index in the achromatic test and chromatic test for V1 and V2 luminance-sensitive cells, respectively.
luminance in response to chromatic patches was widely distributed and differed substantially for different colors, consistent with a role in chromatic information encoding by these cells. For V1 but not V2 neurons, the preferred luminance in response to green and blue was significantly correlated with their preferred luminance in the achromatic test (correlation coefficients: 0.75, \( P < 0.0001 \) for green; 0.69, \( P < 0.0001 \) for blue). In particular, most of the 13 gray-prefering cells (9 in V1 and 4 in V2, shown in filled symbols) fired best to a chromatic patch at intermediate luminance within the “intermediate zone” (luminance fraction: 0.03–0.63) for at least one hue. Also, a number of cells that preferred the extreme (black or white) in the achromatic test showed peaks clearly in the intermediate luminance zone for one or more hues. This result suggests that a peaked luminance encoding strategy is not unique to achromatic stimuli in early visual areas.

Many of the luminance-sensitive neurons also showed relatively strong selectivity for the direction of luminance change in the achromatic test, as illustrated in Fig. 10C (V1) and Fig. 10D (V2). In V1, the absolute values of direction bias indices significantly exceeded 0.33 for 14 (26%), 13 (24%), and 15 (28%) neurons in response to red, green, and blue patches, respectively, indicating a more than twofold difference between responses to preferred versus nonpreferred direction. In V2, these numbers were 4 (33%), 2 (17%), and 4 (33%). V1 but not V2 neurons showed a significant correlation between the direction indices in response to red, green and blue patches versus achromatic stimuli (correlation coefficients: 0.38, \( P < 0.005 \); 0.80, \( P < 0.001 \); 0.55, \( P < 0.001 \)).

**DISCUSSION**

**Peaked luminance encoding and comparison with previous results**

The main finding of this study is that a substantial minority of luminance-sensitive neurons in both V1 and V2 respond best to intermediate luminance, thus exhibiting a peaked luminance encoding function. The validity of our main paradigm, which used oscillating luminance patches to probe luminance coding, is supported by three independent sets of data, most importantly the static patch test. Given the lack of support for peaked luminance encoding described in previous studies, it is important to consider methodological and/or interpretive factors that may reconcile this apparent discrepancy.

Maguire and Baizer (1982), using static large uniform patches of different luminance levels, illustrated monotonic response profiles in V1. But they also reported that 10 of 43 luminance-responsive, nonoriented cells “showed unique or complex responses, such as inhibition at high intensities and excitation at low intensities.” This description presumably reflected a nonmonotonic or peaked luminance encoding analogous to that reported here and similar to our results using circular blob stimuli on a uniform gray background (unpublished observations). Despite these unillustrated observations, Maguire and Baizer explicitly stated an assumption of monotonic luminance encoding in area V1 based on how they interpreted their own data and earlier studies on LGN neurons.

Kinoshita and Komatsu (2001) studied V1 cells using static large homogenous stimuli at seven luminance levels (spanning 3 log units) relative to a uniform background. They categorized luminance tuning as “monotonic” or “V-shape” according to the slopes for the best linear fit to the data for luminance lower than background and those for luminance higher than background (3 data points in each case). They reported that 92% of luminance-responsive neurons were monotonic (including those with slopes of different signs and a difference in absolute value larger than 3-fold) and 8% were V-shaped. However, their population data included several cells with a positive slope for dark stimuli and a negative slope for bright stimuli (lower right quadrant in Fig. 5, Kinoshita and Komatsu 2001), consistent with peaked luminance tuning. Two factors may account for the apparent discrepancy between their conclusion and ours. First, the coarse sampling of luminance in their study (0.5 log unit as intervals) may have missed the response peak of neurons with narrowly tuned luminance profiles, thereby reducing the peak magnitude or eliminating the peak altogether. Second, tests that begin with a uniform gray field followed by a luminance increment or decrement relative to the background may be influenced by factors other than luminance level per se and may be biased against gray-prefering cells. For instance, having little or no temporal change relative to the baseline stimulus reduces transient responses, and having little or no spatial contrast relative to the uniform background (no “figure”) can reduce sustained responses (Zipser et al. 1996).

Hence, the gray-prefering cells described in the present study might well show the “dip” at intermediate luminance values associated with the V-shaped luminance tunings encountered in the paradigm used by Kinoshita and Komatsu. Combined with the assumption of piecewise linearity of the data, this may contribute to the apparent discrepancy in results. We did not encounter neurons that showed a prominent dip at intermediate luminance values in either the slow oscillating paradigm or the static paradigm, where the stimulus was embedded in a texture background.

Rossi et al. (1996) and Rossi and Paradiso (1999) reported that some luminance-sensitive neurons modulated their responses to oscillation of the surround luminance in the opposite phase as they would in response to oscillation of central stimulus luminance. They proposed this as a physiological correlate of brightness perception. Given the similarity of their paradigm with ours, we predict that the response patterns revealing a peaked luminance encoding should also exist in their data set (central stimulus oscillation). Indeed, among the three example V1 cells illustrated in their study (Rossi and Paradiso 1999), two exhibited maximal firing clearly at intermediate luminance values in response to luminance modulation of a large central stimulus (0.5 Hz, top, their Figs. 4 and 9; the luminance profile is shown in their Fig. 1).

**Emergence of peaked luminance tuning in visual cortex and its functional significance**

We found that about one-third of the cortical neurons encountered were responsive to luminance modulation of a large stimulus patch. Among these neurons, \( \geq 10\% \) reliably prefer an intermediate luminance value; the actual percentage may be higher given the conservative nature of our statistical test. Neurons in the retina or LGN that respond best to intermediate luminance values have not been reported (except a hint from the example cell in Fig. 13 of Rossi and Paradiso 1999),
perhaps because these subcortical centers must convey a vast amount of visual information to cortex using a limited number of neurons. It is possible that this property exists in a subset of koniocellular neurons that have not been extensively studied physiologically. On the other hand, it is not surprising that a sparser representation (Ohlhausen and Field 1997) involving peaked coding for luminance would be postponed to the cortical level. An interesting analogy occurs in the auditory pathway of barn owl: interaural level difference (ILD), a cue for sound localization, is initially represented by monotonic tuning functions in the ventral lateral lemniscus pars posterior (VLP) and is subsequently encoded with peaked tuning functions in the inferior colliculus (Adolphs 1993).

Gray-preferring neurons may be specialized for encoding low spatial frequency luminance information that contributes to brightness and lightness perception. Whereas the simplest scenario might involve a uniform distribution of preferred luminance values, this is not what we observed in V1 or V2. However, the existence of modest numbers of cells with peaked luminance tuning may be sufficient to provide computational advantages in processing intermediate luminance, especially if they are conveying information at low spatial frequency and therefore can be pooled across large regions of cortex without compromising spatial resolution. Peaked tuning curves of relatively narrow width provide individual neurons with higher fidelity for encoding one-dimensional features (Zhang and Sejnowski 1999) and facilitate the representation of multiple values at a single location (Rakshit and Anderson 1997), such as objects seen through translucent materials or on reflective surfaces in the case of luminance. An explicit strategy of “voting for gray” by a subpopulation of neurons (analogous to a place coding scheme) may also facilitate information extraction and readout at higher processing stages that combine low- and high-level cues to mediate brightness and lightness perception.

Consistent with Rossi et al.’s (1996) finding, some of the luminance-sensitive neurons in our study showed shifted in preferred luminance when the background luminance level was altered. This suggests integration of luminance information over an even larger area than the stimuli used in our paradigm (in most cases 10 times that of the classical receptive field in diameter).

Compartmentalization of luminance-sensitive neurons?

An important issue is whether luminance-sensitive neurons, including the “gray-preferring” cells in V1 and V2 are concentrated in specific anatomical compartments. Neurons in the blobs of V1 and the thin stripes of V2 are often selective for color or luminance but less so for orientation according to some reports (Livingstone and Hubel 1988; Tootell and Hamilton 1989; Tootell et al. 1988; Xiao et al. 2003) but not others (Friedman et al. 2003). In our experiments, there were hints of clustering of luminance-sensitive neurons in some electrode tracks and nonluminance-sensitive neurons in others. Our oscillating chromatic paradigm results suggest luminance-sensitive cells may encode color as well as achromatic luminance information. The physiological and anatomical characterization of these neurons awaits further exploration, bearing in mind that the functional specializations of the different compartments in V1 and V2 may reflect statistical biases rather than absolute dichotomies (Friedman et al. 2003; Johnson et al. 2001).

Mechanistic considerations

The gray preference of some cortical neurons may involve complex cortical circuitry. Our results indicate that a simple color opponency mechanism cannot explain all the observed preference for intermediate achromatic luminance. An alternative model to consider involves opposing inputs from neurons having monotonic tuning that differ in threshold and/or saturation levels. For example, suppose that layer 4C of V1 contains excitatory and inhibitory neurons that all have monotonic luminance tuning curves but with different thresholds and saturation values. A neuron in layer 2 or 3 receiving inputs from excitatory and inhibitory intermediate-level neurons with different characteristics could exhibit peaked luminance tuning. These putative excitatory and inhibitory mechanisms might overlap spatially rather than being spatially separated. In another set of experiments, we measured V1 and V2 responses to static blobs comparable to or smaller than the size of the receptive field and surrounded by a uniform dark gray background and found a substantial minority of neurons with a pronounced peaked luminance contrast tuning profile but a monotonic contrast tuning profile in response to conventional gratings (unpublished data). A related explanation may apply to the preference for direction of luminance change observed in the chromatic oscillation experiments. To test whether or not this is indeed the case requires exploration of local circuitry in the cortex, which is challenging but technically feasible.

The high incidence of selectivity for direction of luminance in association with luminance level suggests an important temporal component to luminance processing and is consistent with psychophysical evidence for independent mechanisms mediating detection of luminance increments and luminance decrements (Krauskopf 1980; Roufs 1974), but the underlying mechanism remains to be resolved. The strong bias favoring dark over bright in the preferred luminance distribution for both V1 and V2 luminance-sensitive neurons is puzzling (e.g., many neurons preferred luminance <6% that of the average background luminance) because physiological precedents and well-studied perceptual correlates are lacking. One intriguing possibility is suggested by considering shadows, which cause a sharp reduction in mean luminance relative to fully lit portions of a scene. If the visual system processes different shades of gray within a shadow with similar efficiency and strategy as it processes fully lit regions (the luminance of which is ~20 times more than that in the shadow) (Xiao et al. 2002), this might contribute to the overemphasis on darker shades of gray in the luminance-sensitive neuronal population as a whole.

Acknowledgments

We thank Drs. Aki Anzai, Greg DeAngelis, Larry Snyder, and John Maunsell for critical reading of earlier versions of the manuscript.

Present address of X. Peng: Dept. of Neuroscience, Baylor College of Medicine, One Baylor Plaza, Houston, TX, 77030.

Grants

This work was supported by a grant from the Mathers Foundation.

References


