First-order and second-order signals combine to improve perceptual accuracy

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The question of whether first-order (luminance-defined) and second-order (contrast-defined) stimuli can be combined in order to improve perceptual accuracy was examined in the context of two suprathreshold discrimination experiments, one spatial and the other temporal. The stimuli were either gratings of one type of image alone or else the sum of two gratings of the same orientation, spatial frequency, temporal frequency, and phase, but of different types. For both spatial frequency discrimination (static gratings) and speed discrimination (1-c/deg drifting gratings), performance was markedly better for a combined grating stimulus than predicted on the basis of independent processing of the two types of stimulus. But this was true only for stimuli of low contrast. Facilitation of discrimination performance occurred only in the contrast range where discrimination performance is contrast dependent. At higher contrasts, where performance has reached an asymptote for each type of pattern alone, there was no facilitation. The results suggest that first- and second-order stimuli, although believed by most researchers to be detected separately, can subsequently be combined in order to improve perceptual accuracy in conditions of low visibility. © 2001 Optical Society of America

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1. INTRODUCTION

Despite an extensive literature documenting phenomena that seem to suggest the existence of mechanisms specialized for the detection of second-order motion[1–8] and form,[9–11] considerable doubt persists as to whether it is truly necessary to invoke such mechanisms. Doubt is perhaps particularly prevalent in the case of second-order motion. Conversation with researchers commonly reveals a reason for doubt that has only the loosest of connections with the published data on the topic, namely, the question, "Why do we need second-order mechanisms?" Second-order signals seldom, if ever, exist in natural images without accompanying, highly correlated first-order signals, so it is not clear that it is beneficial to be able to detect them. If their detection were a cost-free by-product of first-order processing, then nothing would be lost by being sensitive to them and even the sternest critic could probably see occasional gains. But the prevalent view is that we have evolved specialized, sophisticated second-order processing mechanisms that presumably have costs in terms of gray-matter volume and metabolic demands. A further source of skepticism is that our sensitivity to second-order stimuli is low, particularly in the case of motion. For example, the threshold for detecting the direction of motion of a contrast envelope is typically around 20% modulation depth when all first-order cues are eliminated,[5] so the strongest possible stimulus (100% modulation depth) is only about five times detection threshold. This compares with motion of a 100% luminance contrast signal whose direction detection threshold may be less than 1% contrast,[12] giving a factor of at least 100 times threshold.

There are several possible answers to the question of why we might need second-order mechanisms. One that is sometimes invoked is that they evolved to help us to segment images. When a zebra is seen against a background of similar mean intensity, the high contrast of its stripes in comparison with the lower contrast of the background scene provides an efficient way to distinguish it. Identifying the shape of the region of high contrast reveals the shape of the animal. Even in the case of animals and objects more subtly patterned than the zebra, there may be important texture differences that allow segmentation when luminance cues are weak. A large literature documents our ability to segment textures (see Ref. 13 for a recent review), although little of it bears directly on whether we use mechanisms that are the same as or different from those used for luminance-based segmentation. In the case of motion, it is less clear that second-order cues aid segmentation. But, in principle, second-order motion mechanisms could improve detection and segmentation in the same way that motion of a luminance-defined target improves segmentation, particularly in a noisy scene.

An alternative explanation, which we explore here, is that we have independent first- and second-order systems in order to provide two separate estimates of the same spatial structure or movement. The computation of form and motion is not trivial, and in some instances accuracy is critically important. Although the two cues are normally highly correlated and convey much the same information, estimating both and then combining the results could improve perceptual precision, particularly when the estimates are noisy or unreliable.

Our experimental strategy is to compare perceptual accuracy for stimuli of each type alone with accuracy for mixed stimuli in which the two types are combined and both carry the same spatial and temporal information. One previous study has taken this approach. Schofield and Georgeson[14] examined whether facilitation occurs be-

tween stationary first- and second-order stimuli, using the "dipper function" paradigm of Legge and Foley.[15] They concluded that no such facilitation occurs at the detection stage. They also studied the detectability of stationary sine gratings defined by mixtures of luminance modulation and contrast modulation. They considered various models of performance and found that the best was one in which the two types of motion are detected independently by mechanisms whose outputs are then combined by energy summation.

Schofield and Georgeson's study addresses second-order form but not motion and does so only in terms of threshold-detection sensitivity. In this paper we report experiments investigating whether summation of the two types of stimulus occurs in the context of two types of suprathreshold discrimination: speed discrimination for drifting gratings and spatial frequency discrimination for stationary gratings.

2. GENERAL METHODS

A. Subjects
The subjects were one of the authors (NSS) and two paid volunteers who were given extensive practice before commencing the experiments.

B. Stimuli
The stimuli were vertically oriented sine gratings of spatial frequency 1 cycle per degree (c/deg). The gratings were defined in terms of either luminance modulation (first-order) or contrast modulation (second-order) and are illustrated in Fig. 1. In the case of second-order stimuli, the carrier was static two-dimensional noise that had been high-pass filtered in spatial frequency (cutoff 2 c/deg) to avoid the presence of local first-order artifacts.[5] The contrast of the noise was 50% Michelson (43% rms). In the case of first-order stimuli, a luminance grating was added to the same filtered static noise. The two stimulus

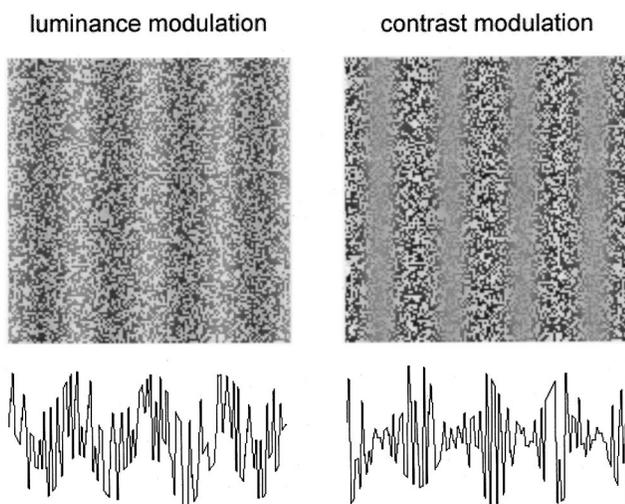luminance modulation   contrast modulation

Fig. 1. Luminance and contrast modulations of the type used in the experiments. Both have a carrier consisting of static two-dimensional noise that has been high-pass filtered with a cutoff one octave above the grating spatial frequency. The waveforms beneath the gratings show luminance as a function of position for a one-dimensional horizontal slice through each image.

types could be mixed by adding a luminance grating to contrast-modulated noise instead of to unmodulated noise. When this was done, the two modulations were always added in the same phase. The mean luminance of all stimuli was 16 cd/m^2.

C. Methods
Suprathreshold discrimination performance was measured by a two-alternative forced-choice paradigm with successive presentation. In each trial two grating stimuli were presented, referred to as standard and comparison. Each had a duration of 0.5 s, and they were separated by an interval of 0.5 s during which time the screen was blank. Trials were separated by a blank interval of variable duration during which the subject made a response. The subject was required to specify which grating, first or second, had the higher spatial frequency (Experiment 1) or speed (Experiment 2).

Four conditions were employed in each experiment:

1. Luminance modulation (LM) alone. In this condition, discrimination thresholds were determined for luminance modulated (first-order) gratings alone. Performance was measured at each of a range of grating contrasts, ranging from 0.8% to 50%.
2. Contrast modulation (CM) alone. In this condition, discrimination thresholds were determined for contrast-modulated (second-order) gratings alone. Performance was measured at each of a range of contrast modulation depths, ranging from 6% to 100%. The purpose of the LM alone and CM alone conditions was to provide baseline data for comparison with the two mixed conditions.
3. LM plus 100% CM. In this condition, a second-order grating of 100% modulation depth was added to luminance gratings of various contrasts. The purpose was to establish whether performance obtained with first-order stimuli could be enhanced by the addition of correlated, second-order cues.
4. CM plus matched LM. In this case, for each second-order contrast-modulation depth, a luminance grating was added of a contrast that gave the same discrimination performance when viewed alone as the CM grating to which it was added. The purpose was to see whether facilitation between the two stimulus types occur to yield better performance than that obtained with either of the component stimuli alone.

In the critical fourth condition, considerable care was taken to create images whose two components gave equal discriminability, in terms of spatial frequency, when viewed alone. The LM alone and CM alone conditions were conducted first. Curves were then fitted to the respective functions, relating Weber fractions to stimulus contrast (see curve fits in Fig. 3 below). These were of the form

$$y = a/x^b + c,$$

where a, b, and c are constants. For each of the contrast-modulation depths used in the CM alone condition, the curve fits were used to establish the LM contrast that gave the Weber fraction of the same spatial frequency. This LM component was then combined with the CM com-

ponent to produce the matched images. For one subject (AP) in Experiment 1, the experiment was then restarted and trials from all four conditions were interleaved. This was to ensure that any performance advantage in the mixed condition over the CM alone condition could not be due to practice effects. The new set of results for LM alone and CM alone were used and the originals discarded, after it was checked that there was no significant change. For the more experienced observer NSS this time-consuming procedure was not used. The subject simply practiced the task until performance reached a plateau, then performed the LM alone and CM alone conditions interleaved, and finally ran the two mixed conditions interleaved, the contrasts used for CM plus matched LM being based on the results from the first two conditions. This method was also used for both subjects in Experiment 2.

3. EXPERIMENT 1: SPATIAL FREQUENCY DISCRIMINATION

A. Stimuli and Methods

In this experiment, each stimulus was a single, stationary grating with a static-noise background. The standard grating always had a spatial frequency of 1 c/deg. The comparison grating was one of a set of 11 gratings whose spatial frequency varied in small steps spanning the test spatial frequency. The two gratings always had the same contrast (first-order) or contrast-modulation depth (second-order). Each comparison was tested 10 times during the course of one run of trials. The order of testing was randomized, and in each trial the order of the two gratings (test and comparison) was random. The relative spatial phase of the two gratings on each trial was random and varied from trial to trial. At least four identical runs were conducted for each stimulus condition to give a total of at least 40 trials per comparison spatial frequency. A sigmoid function, constrained to asymptote at 0% and 100% correct, was fitted to the psychometric function. This had the form

$$y = 100/[1 + e^{(a - x)/b}],$$

where a and b are constants. Each discrimination threshold was expressed as a Weber fraction, $\Delta f/f$, where f is the standard spatial frequency and Δf is the smallest discriminable difference in spatial frequency.

B. Results

Figure 2 shows a representative set of psychometric functions. For the naïve subject AP in the CM alone condition, the proportion of trials in which the subject chose the comparison as having the higher spatial frequency is shown as a function of true comparison spatial frequency. Each plot shows data for a different level of contrast-modulation depth. The slopes of the psychometric functions are steepest, reflecting the best performance, for the highest stimulus contrasts and become progressively shallower as contrast falls. For each function the points at which the fitted curve intersects with the 75% and 25% response levels were found and the difference between the two taken as $2\Delta f$ for the purpose of computing Weber

fractions. The results are shown in terms of Weber fractions for this and all other conditions in Fig. 3.

1. LM Alone Condition

Figure 3(a) shows spatial frequency Weber fractions as a function of grating contrast for the LM alone condition (solid circles). At very low contrasts, performance is poor. As contrast increases, performance rapidly improves, reaching a maximum at a contrast of ~4% for
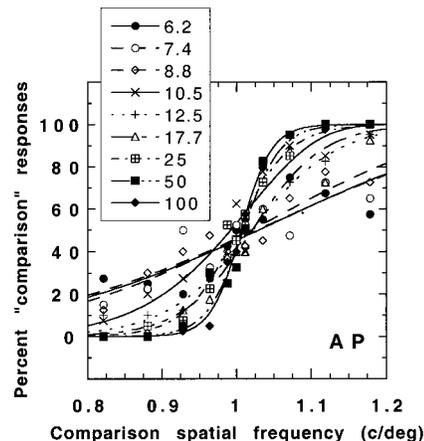
Fig. 2. Psychometric functions obtained for one subject in the CM only condition of Experiment 1. The plots show, for nine different contrast modulation depths, the proportion of trials in which the subject reported that a comparison grating of the spatial frequency shown on the abscissa appeared to have a higher spatial frequency than a standard of 1 c/deg.
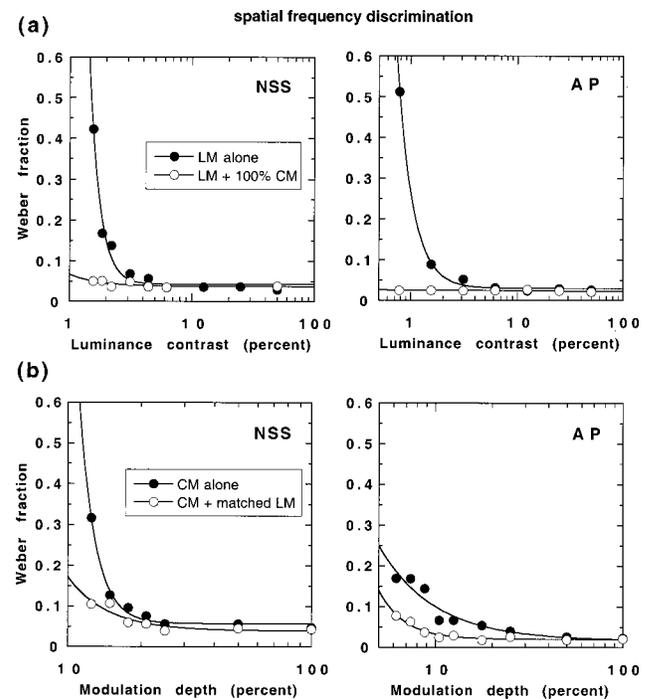
Fig. 3. Results of Experiment 1 (spatial frequency discrimination) expressed as Weber fractions. (a) Spatial frequency Weber fractions in the LM alone (solid circles) and LM + 100% CM (open circles) conditions (see text for details). Results are shown separately for two subjects. (b) Weber fractions in the CM alone and CM + matched LM conditions for the same two subjects. Note that the range of the abscissa is different for the two subjects in both (a) and (b).

both subjects, beyond which there is little further improvement. The peak discrimination performance is a Weber fraction of ~0.03 to 0.04. These results are in agreement with previous findings.[16–18]

2. CM Alone Condition

Figure 3(b) shows spatial frequency Weber fractions as a function of grating contrast for the CM alone condition (solid circles). At low contrast-modulation depths, performance is poor. As modulation depth increases, performance improves, reaching a maximum at a modulation depth of ~25% (NSS) or ~50% (AP), beyond which there is little further improvement. For subject AP, peak discrimination performance is similar (Weber fractions near 0.03) to the LM alone condition, and in subject NSS it is only slightly worse (around 0.05). Thus subjects are able to use second-order spatial information with a high degree of precision. Few data exist with which to compare our results, although Lin and Wilson[19] have shown that spatial frequency discrimination with high-contrast second-order patterns is similar to or slightly worse than for luminance patterns. A systematic investigation of the effect of contrast-modulation depth does not seem to have been conducted previously.

3. LM Plus 100% CM Condition

Spatial frequency Weber fractions as a function of first-order grating contrast are shown for the LM plus 100% CM condition in Fig. 3(a) (open circles). They are presented in the same plot as results for the LM alone condition to allow direct comparison. The question of interest is, Is performance for LM plus 100% CM better than for either LM or CM alone? Since performance is, if anything, better for LM alone than CM alone, a comparison with LM alone is appropriate. For most of the contrast range, discrimination performance for a luminance grating is very similar with or without the addition of a correlated contrast modulation to 100% modulation depth, so there is little sign that the two types of grating facilitate each other in terms of discrimination performance. At very low luminance contrasts, performance is clearly better with than without the addition of the contrast modulation. However, this is expected since in this range, performance for a 100% CM grating is better than for the low-contrast LM grating. In this range, performance is similar to that seen with 100% CM alone [see Fig. 3(b)]. These results suggest that, although first-order and second-order cues may be combined, such combination does not lead to improved (or "supraoptimal") discrimination performance, at least at medium and high luminance contrasts. It does not provide a strong test of what happens at low luminance contrasts.

4. Matched LM Plus CM Condition

Spatial frequency Weber fractions, as a function of contrast modulation depth of the second-order grating, are shown for the matched LM plus CM condition in Fig. 3(b) (open circles) in the same plot as the CM alone condition for comparison. Again, at very high CM modulation depths there is little sign that adding a luminance grating of the same discriminability improves performance. However, this is not the case for low modulation depths.

Below ~25% (NSS) or ~50% (AP) modulation depth, there is a marked improvement when equally discriminable gratings of the two types are added. In this case (unlike the LM plus 100% CM case) the improvement is genuine in the sense that performance is considerably better than that obtained with either component grating alone.

4. EXPERIMENT 2: SPEED DISCRIMINATION

A. Stimuli and Methods

In Experiment 2, each stimulus was an animation sequence lasing 0.5 s that produced a percept of smooth drift. All stimuli were vertical gratings of spatial frequency 1.0 c/deg. The design was the same as in Experiment 1, but the standard and comparison differed in drift speed, not spatial frequency, and the task was to say which grating, first or second, was moving faster. The standard drift speed was 4°/s (4 Hz), and the comparison speeds varied in small steps around this value. Again there were 11 comparison stimuli for each standard, and they were presented 10 times each per run of trials, in random order, with a minimum of four runs for each stimulus condition. Discrimination thresholds were calculated in the same way as in Experiment 1.

B. Results

1. LM Alone Condition

Figure 4(a) shows speed Weber fractions as a function of grating contrast for the LM alone condition (solid circles). Performance is largely independent of contrast, although
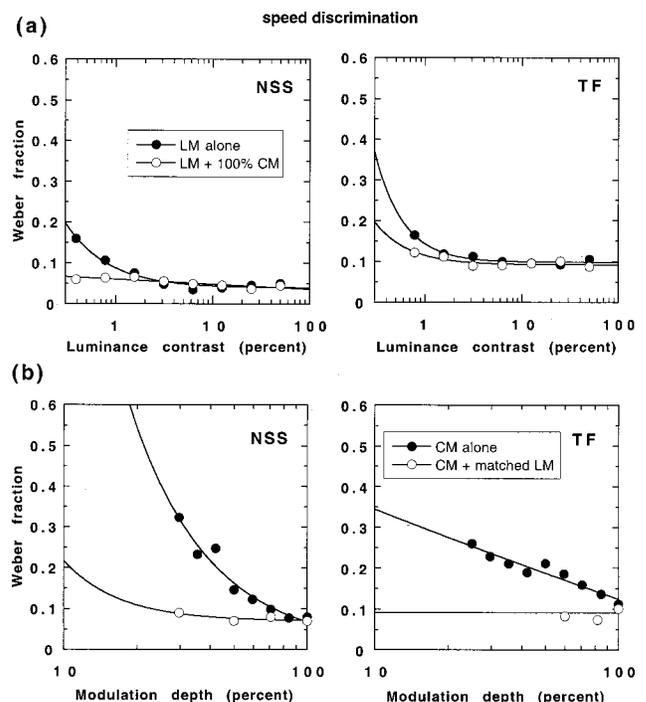

Fig. 4. Results of Experiment 2 (speed frequency discrimination) expressed as Weber fractions. (a) Speed frequency Weber fractions in the LM alone (solid circles) and LM + 100% CM (open circles) conditions. (b) Weber fractions in the CM alone and CM + matched LM conditions.

it shows signs of deteriorating at the very lowest contrasts. Weber fractions are ~0.05 (NSS) or ~0.1 (TF). These results are in line with previous findings,[20–22] although subject TF performs less well than either NSS or the typical observers used in other published studies.

2. CM Alone Condition

Figure 4(b) shows speed Weber fractions as a function of grating contrast for the CM alone condition (solid circles). At low contrast-modulation depths, performance is poor. As modulation depth increases, performance improves, reaching a maximum only at 100% modulation depth for both subjects. For both subjects, peak performance in the CM alone condition approaches that obtained in the LM alone condition, although it is very slightly worse. Thus, at least for highly visible stimuli, subjects are able to use second-order speed information with a high degree of precision. The results are in line with those of previous studies[23–25] that show that speed discrimination for moving contrast modulations is similar to or only slightly worse than for high-contrast luminance modulations. As with spatial frequency discrimination, a systematic investigation of the effect of contrast-modulation depth does not seem to have been conducted previously.

3. LM Plus 100% CM Condition

Speed Weber fractions as a function of first-order grating contrast are shown for the LM plus 100% CM condition in Fig. 4(a) (open circles) in the same plot as results for the LM alone condition. The results are very similar to those for spatial frequency discrimination [Fig. 3(a)]. For most of the contrast range, discrimination performance for a luminance grating is very similar in the LM alone and LM plus 100% CM conditions, so there is little sign that the two types of grating facilitate each other in terms of speed discrimination performance. At very low luminance contrasts, performance is again better with than without the addition of the contrast modulation, but, as before, this would be expected on the basis of a comparison with the more sensitive of the two components alone. The results suggest that, as with spatial frequency discrimination, such combination does not yield any significant degree of improvement in discrimination performance, at least at medium and high luminance contrasts.

4. Matched LM Plus CM Condition

Speed Weber fractions, as a function of contrast modulation depth of the second-order grating, are shown for the matched LM plus CM condition in Fig. 4(b) (open circles) in the same plot as the CM alone condition. The data are sparse, because luminance gratings yielding the same speed Weber fraction could be found only for a narrow range of contrast modulations, particularly for subject TF. Nonetheless, it is clear that at all but the highest modulation depth there is a marked improvement when equally discriminable gratings of the two types are added compared with the CM alone condition. As with the corresponding spatial-frequency-discrimination condition, performance with the matched stimulus is considerably better than that obtained with either component grating alone.

5. DISCUSSION

Two major conclusions may be drawn from the experiments reported here. First, we have mapped out the effect of changing contrast-modulation depth and luminance contrast (in second-order and first-order stimuli, respectively) on Weber fractions for spatial frequency and speed discrimination. At higher modulation depths and contrasts, Weber fractions saturate at similar levels for both first-order and second-order stimuli, while as modulation depth and contrast is reduced, Weber fractions increase for both types of stimulus.

Second, our experiments show that in conditions of low image contrast, first-order cues and second-order cues can be combined in such a way as to improve perceptual accuracy. This is true both for spatial structure (spatial frequency discrimination) and motion (speed discrimination). Thus the human visual system is able to exploit the fact that luminance modulations are frequently accompanied by correlated contrast modulations in natural images. The effect of combining the two cues seems to be to preserve the levels of perceptual accuracy that would prevail in any case at high contrasts, even when contrast is low. At high image contrasts, there appears to be little or no benefit in combining the two cues, but at low contrasts the benefit is striking. If we do indeed have separate detection systems for second-order image characteristics, this may be why they have evolved.

Schofield and Georgeson[14] have addressed the question of facilitation between LM and CM stimuli in the context of threshold-detection experiments. They found a complete absence of facilitation between static luminance modulations and contrast modulations at threshold. They interpret this absence of facilitation as strong evidence that there are separate LM and CM detection mechanisms for spatial structure, which is also our belief in the case of motion[4,26] and which has been argued by several other groups.[1,27] However, the question of whether LM and CM are initially detected separately is distinct from the question of whether suprathreshold LM and CM signals that have already been detected are subsequently combined. Our results are consistent with the notion that the two image types are initially detected independently but that the outputs of the two systems are then combined, a position that we have taken previously on grounds of transfer of adaptation effects between stimuli of the two types.[28,29] Such a scheme has been modeled by Wilson et al.[30] Schofield and Georgeson themselves suggest a model in which the outputs of two detection mechanisms are summed, and they show that it predicts their threshold data for mixed stimuli. We have not attempted to model our discrimination data, but their model could be taken as a plausible starting point for a model of suprathreshold discrimination. Such a model could entail either (a) pooling of LM and CM signals only after discrimination of spatial frequency and speed occurs independently in each system or (b) a single suprathreshold discrimination process based on the summed signal generated by their detection model. In either case, it is not hard to imagine that the benefits of pooling might arise principally when each system alone yields a weak and noisy (but detectable) signal, as suggested by our ex-

periments.   Currently, very few data exist that help to specify exactly at what level(s) of processing the combination of first-order and second-order signals occurs.

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REFERENCES

1. A. M. Derrington and D. R. Badcock, "Separate detectors for simple and complex patterns?" Vision Res. **25**, 1869–1878 (1985).
2. C. Chubb and G. Sperling, "Two motion perception mechanisms revealed through distance-driven reversal of apparent motion," Proc. Natl. Acad. Sci. USA **86**, 2985–2989 (1989).
3. G. Mather and S. West, "Evidence for second-order motion detectors," Vision Res. **33**, 1109–1112 (1993).
4. T. Ledgeway and A. T. Smith, "Evidence for separate motion-detecting mechanisms for first- and second-order motion in human vision," Vision Res. **34**, 2727–2740 (1994).
5. A. T. Smith and T. Ledgeway, "Separate detection of moving luminance and contrast modulations: fact or artifact?" Vision Res. **37**, 45–62 (1997).
6. S. Nishida, T. Ledgeway, and M. Edwards, "Dual multiple-scale processing for motion in the human visual system," Vision Res. **37**, 2685–2698 (1997).
7. N. E. Scott-Samuel and M. A. Georgeson, "Does early non-linearity account for second-order motion?" Vision Res. **39**, 2853–2865 (1999).
8. A. T. Smith, "The detection of second-order motion," in *Visual Detection of Motion*, A. T. Smith and R. J. Snowden, eds. (Academic, London, 1994), pp. 145–176.
9. H. Northdurft, "Orientation sensitivity and texture segmentation in patterns with different line orientation," Vision Res. **25**, 551–560 (1985).
10. B. Julesz, "Textons, the elements of texture perception, and their interactions," Nature **290**, 91–97 (1981).
11. R. Gray and D. Regan, "Spatial frequency discrimination and detection characteristics for gratings defined by orientation texture," Vision Res. **38**, 2601–2617 (1998).
12. F. W. Campbell and J. G. Robson, "Application of Fourier analysis to the visibility of gratings," J. Physiol. **197**, 551–566 (1968).
13. D. Regan, *Human Perception of Objects* (Sinauer, Sunderland, Mass., 2000).
14. A. J. Schofield and M. A. Georgeson, "Sensitivity to modulations of luminance and contrast in visual white noise: separate mechanisms with similar behaviour," Vision Res. **39**, 2697–2716 (1999).
15. G. E. Legge and J. M. Foley, "Contrast masking in human vision," J. Opt. Soc. Am. **70**, 1458–1471 (1980).
16. D. Regan, S. Bartol, T. Murray, and K. Beverley, "Spatial frequency discrimination in normal vision and in patients with multiple sclerosis," Brain **105**, 735–754 (1982).
17. J. Thomas, "Underlying psychometric function for detecting gratings and identifying spatial frequency," J. Opt. Soc. Am. **73**, 751–758 (1983).
18. S. F. Bowne, "Contrast discrimination cannot explain spatial frequency, orientation or temporal frequency resolution," Vision Res. **30**, 449–461 (1990).
19. L.-M. Lin and H. R. Wilson, "Fourier and non-Fourier pattern discrimination compared," Vision Res. **36**, 1907–1918 (1996).
20. S. P. McKee, G. Silverman, and K. Nakayama, "Precise velocity discrimination despite random variations in temporal frequency and contrast," Vision Res. **26**, 609–619 (1986).
21. G. Orban, J. D. Wolf, and H. Maes, "Factors influencing velocity coding in the human visual system," Vision Res. **24**, 33–39 (1984).
22. S. C. Panish, "Velocity discrimination at constant multiples of threshold contrast," Vision Res. **28**, 193–201 (1988).
23. K. Turano and A. Pantle, "On the mechanism that encodes the movement of contrast variations: velocity discrimination," Vision Res. **29**, 207–221 (1989).
24. S. J. Cropper, "Velocity discrimination in chromatic gratings and beats," Vision Res. **34**, 41–48 (1994).
25. A. Johnston and C. P. Benton, "Speed discrimination thresholds for first- and second-order bars and edges," Vision Res. **37**, 2217–2226 (1997).
26. N. Scott-Samuel and A. Smith, "No local cancellation between directionally opposed first-order and second-order motion signals," Vision Res. **40**, 3495–3500 (2000).
27. C. Chubb and G. Sperling, "Drift-balanced random stimuli: a general basis for studying non-Fourier motion perception," J. Opt. Soc. Am. A **5**, 1986–2006 (1988).
28. T. Ledgeway, "Adaptation to second-order motion results in a motion aftereffect for directionally-ambiguous test stimuli," Vision Res. **34**, 2879–2889 (1994).
29. T. Ledgeway and A. T. Smith, "Changes in perceived speed following adaptation to first-order and second-order motion," Vision Res. **37**, 215–224 (1997).
30. H. R. Wilson, V. P. Ferrera, and C. Yo, "A psychophysically motivated model for two-dimensional motion perception," Visual Neurosci. **9**, 79–97 (1992).
31. N. Scott-Samuel and A. Smith, "Greater than the sum of its parts: first- and second-order stimuli combine to improve perceptual accuracy for both motion and form," Invest. Ophthalmol. Visual Sci. Suppl. **40**, S425 (1999).