that sham-ovariectomized rats cycled normally; vaginal smears of ovariectomized rats treated with sesame oil or saline were typical of spayed rats: continuous diestrus. Ovariectomized rats treated with estrogen alone (group 6) and estrogen plus THC (group 10) showed vaginal estrus. Vaginal smears obtained from rats treated with THC alone (groups 7, 8, and 9) were not uniform; however, in general, the leukocyte counts were depressed and the epithelial cells, some of which were cornified, were increased over those of the controls. The data demonstrate that doses of Δ^9-THC which fall within the heavy, chronic ranges used in human (*3*) and animal (*2*) studies have estrogenic effects in ovariectomized rats as measured by uterine weight gain.

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16. This work was supported by grant 1-R01-DA-01176-01 to J.S. from the National Institute on Drug Abuse. We thank Professor Roy O. Greep and Drs. Cynthia Silbert and Clark Sawin for advice and criticism.

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Binocular Vision: Two Possible Central Interactions Between Signals from Two Eyes

Abstract. *Both foveae of light-adapted subjects were stimulated at the same time with monocularly presented lights of increasing or decreasing luminance. Combinations judged just detectable violated predictions of the energy summation and the probability summation hypotheses of binocular interaction. Rather, the results can be explained by independent central neural mechanisms that signal the sum or the difference of stimuli to two eyes.*

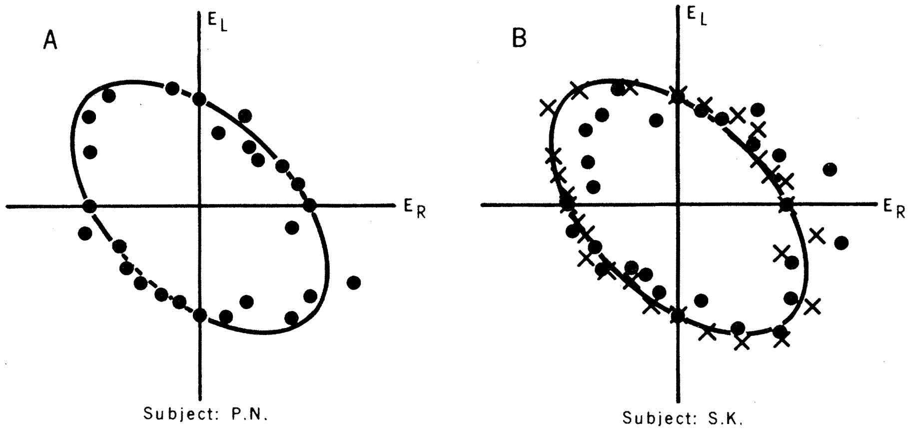
We have studied the interactions of signals from two eyes in human psychophysical experiments. Our binocular stimuli comprised pairs of simultaneous monocular luminance changes of 100-msec duration or less. The changes (of energy denoted E_L and E_R for left and right eyes, respectively) were either increments (E_L or E_R positive) or decrements (E_L or E_R negative). For a wide range of positive and negative values of E_L and E_R binocular thresholds seemed to obey the relation

$$E_\mathrm{L}^2 + E_\mathrm{R}^2 + 2KE_\mathrm{L}E_\mathrm{R} = 1 \qquad (1)$$

where K expresses the relative strengths of the mechanisms. This result is inconsistent with two theories of binocular interaction, the theories of energy summation and of probability summation (*1*). Rather, it supports the theory that two independent mechanisms, one that sums signals from two eyes and one that computes a difference, provide information to a more central decision center. Binocular neurons monitored in neurophysiological investigations appear to sum signals from two eyes and, often, to compute the difference of the signals from two eyes (*2*). Cells like these may be the neural substrate for the behavior we have observed in humans.

One line of research relevant to the study of the interaction of signals from two eyes concerns the comparison of monocular and binocular visual thresholds (*3*). The many studies designed to make this comparison provide an equivocal picture (*4–7*), but differences in reported data can be explained by the range of uncertainty inherent in psychophysical measurement (*8*). Moreover, comparing monocular with binocular thresholds unnecessarily restricts the investigation. We studied binocular stimuli whose monocular components were combinations of positive and negative luminance changes. We could thus test the various theories in circumstances under which their predictions differed (*9, 10*).

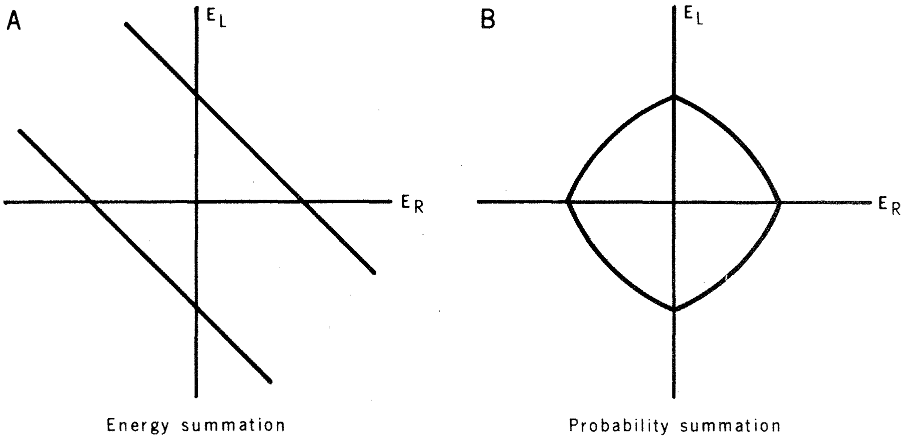
Light-adapted subjects fixated foveal targets of 10 minutes of arc in diameter (Monsanto 5047) in a mirror haploscope that allowed independent control of the stimuli to two eyes (*11*). The targets were continuously illuminated at levels judged by the subject to be equally bright. Stimuli were square pulse luminance changes



Subject: P.N.

Subject: S.K.

Fig. 1. Binocular stimuli judged just visible. The ordinates indicate the luminance change energy to left eye (E_L), and the abscissas indicate the luminance change energy to right eye (E_R). For both axes, the positive coordinates refer to luminance increments, and the negative coordinates refer to luminance decrements. Closed circles represent the data from two series of 28 stimuli, adjusted to be just visible by two subjects; crosses represent the median data from seven runs of subject S.K. Ellipse is fit by eye to the data on the constraint that it intersect axes the same distance from origin. For both subjects, decrements yielded 20 to 30 percent lesser threshold. This difference between the detectability of increment and decrement is well known (*21*). We chose to ignore it rather than to incorporate an additional parameter in our model to account for it. Accordingly, data points in a given quadrant have been normalized so that axis points always fall the same distance from the origin.



Energy summation

Probability summation

Fig. 2. Predictions of two classical theories of binocular interaction. The ordinates and abscissas are the same as in Fig. 1. (A) Prediction of the energy integration hypothesis, that a stimulus is just visible if the sum of its components equals some constant. That is, $|E_L + E_R| = k$. (B) A version of the probability summation hypothesis, constructed from the usual formulation, $P_B = 1 - (1 - P_L)(1 - P_R)$, where P_B is the probability of seeing with binocular stimulation and P_L and P_R are the respective monocular probabilities. One also needs a relation between stimulus energy, E_L, and probability of seeing, P_L. We have assumed that the relation is the same for increments and decrements and that it is the integral of a gaussian probability distribution. Parameters of the distribution are chosen arbitrarily. At their extremes they could produce a contour nearly a circle or nearly a diamond in shape. Neither of these graphs fits the observed relation between E_L and E_R when a binocular stimulus is just visible.

to each eye with a maximum modulation of 100 percent of the steady level (*12*).

Twenty-eight different stimuli were tested. Of these, four were monocular increments and decrements, 12 were binocular increments and binocular decrements with various ratios of E_L/E_R, and the remaining 12 were increments to one eye and decrements to the other, again with various ratios of E_L/E_R (*13*). Subjects adjusted a control knob, which varied the amplitude of stimuli to both left and right eyes while maintaining their ratio and polarity, until the compound stimulus was judged just visible (*14*). One run comprised single adjustments for all 28 stimuli (*15*).

The technique of adjusting stimuli until they are just visible does not necessarily produce a reliable measure of sensitivity. When an observer's decisions are used to draw inferences about his sensitivity, one needs a detailed knowledge of the influence of the decision process itself (*16*). Accordingly we have confirmed these findings with a more acceptable, albeit tedious, measurement procedure known as two-alternative forced-choice testing (*7*). As no important differences emerged from these tests (*17*), the data reported here (Fig. 1) are from the experiment in which stimuli are adjusted to be just visible (*18*).

Typical runs produced fairly regular elliptical contours (Fig. 1A). On Fig. 1B are shown both a single run that deviates from the elliptical shape and median settings of seven runs that fall very close to an ellipse. As there was no systematic deviation from an elliptical shape, we presume that deviations simply reflect the variance of our level setting procedure. The elliptical curve is intended to portray an isosensitivity contour (*19*). It implies an interaction between signals from the two eyes considerably different from those advanced in previous theories. This can be seen from the isosensitivity contours of the energy summation (Fig. 2A) and probability summation (Fig. 2B) hypotheses. Neither of these contours matches our data.

We have explored an alternative hypothesis consistent with these data that rests on simple physiological mechanisms. An examination of the evidence obtained by monitoring the electrical activity of single binocular neurons in the mammalian visual cortex reveals two different interactions of signals from two eyes (*1*). When stimulus disparity (the amount by which two retinal images fail to fall on corresponding retinal points) matches the preferred disparity of the neuron in question, the interaction appears to be one of summation (*20*). Otherwise an occlusive or inhibitory interaction is seen (*21*). Consider, then, two independent neural mechanisms, one that reports the sum of energy falling on corresponding retinal loci in two eyes and one that signals the arithmetic difference. If it is assumed that the outputs of the two mechanisms are noisy but are combined so as to preserve all of the information present useful in detecting the presence or absence of the stimulus, then an isosensitivity contour should obey the relation of Eq. 1 (*22*). The human visual apparatus apparently manifests precisely the behavior that would be expected of interocular summing and subtracting mechanisms (*23*).

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References and Notes

1. The theory of energy summation predicts that if a monocular stimulus is at threshold, its energy may be divided between two eyes yet still be at threshold. According to the theory of probability summation in its simplest form, if the left eye "sees" a stimulus with probability, P_L, and the right eye with P_R, then both eyes will "see" it with probability, $P_B = 1 - (1 - P_L)(1 - P_R)$.
2. D. H. Hubel and T. N. Wiesel, *J. Physiol. (London)* **148**, 574 (1959); *ibid*. **160**, 106 (1962); J. D. Pettigrew, T. Nikara, P. O. Bishop, *Exp. Brain Res*. **6**, 391 (1968); M. L. J. Crawford and S. J. Cool, *Vision Res*. **10**, 1145 (1970).
3. For references prior to 1974, see F. Thorn and R. M. Boynton, *Vision Res*. **14**, 445 (1974).
4. Certain data are consistent with the idea of energy summation [T. E. Cohn and R. D. Freeman (*5*); M. Zingirian, A. Molfino, S. Levialdi, M. Trillo, *Ophthalmologica* **162**, 41 (1971); O. M. Braddick (*6*); A. B. Kristofferson, *University of Michigan Vision Research Laboratories Report No. 2144-290-T* (1958); G. L. Kandel, *Opt. Acta* **19**, 369 (1972)]. F. Thorn and R. M. Boynton (*3*) report performance between that predicted by energy summation and that predicted by probability summation; they consider this evidence for physiological summation. Other data show less binocular improvement (binocular threshold equals approximately $1/\sqrt{2}$ × monocular threshold), which is consistent with the idea of probability summation [L. Matin, *J. Opt. Soc. Am*. **52**, 1276 (1967); W. Crozier and A. H. Holway, *J. Gen. Physiol*. **23**, 101 (1939); R. J. Lythgoe and L. R. Tansley, *J. Physiol. (London)* **91**, 427 (1938); M. H. Pirenne, *Nature (London)* **152**, 698 (1943); R. J. Lythgoe and L. R. Phillips, *J. Physiol. (London)* **91**, 427 (1938)]. See S. L. Guth [*Vision Res*. **11**, 747 (1971)] for a theoretical discussion. This level of binocular improvement has also been interpreted in terms of the reduction of relative variability associated with two independent looks at a stochastic event [D. M. Green and J. A. Swets (*7*); F. W. Campbell and D. G. Green, *Nature* (*London*) **208**, 191 (1965); O. M. Braddick (*6*)].
5. T. E. Cohn and R. D. Freeman, paper presented at the annual meeting of the Association for Research in Vision and Ophthalmology, Sarasota, Fla., 24 to 28 April 1972.
6. O. M. Braddick, *Vision Res*. **12**, 1435 (1972).
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8. Criterion variability, which was uncontrolled in most studies, can cause a threshold variation of 0.3 log unit, which is sufficient to explain the entire range of binocular improvement [see D. M. Green and J. A. Swets (*7*) for a discussion of criterion variability].
9. We have extended methods developed independently by ourselves [T. E. Cohn and D. J. Lasley (*10*)] and by others [D. H. Westendorf and R. Fox, *Percept. Psychophys*. **15**, 61 (1974)]. Both studies showed that the decisive test of the energy summation hypothesis uses as a stimulus an increment-decrement combination in which the monocular components are equally detectable. Both tests with this stimulus reject the energy summation hypothesis. Westendorf and Fox concluded that the interaction between signals from two eyes differed according to the type of stimulus. Our present study is an attempt to test a simpler notion.
10. T. E. Cohn and D. J. Lasley, *Am. J. Optom. Physiol. Opt*. **50**, 752 (1975).
11. Each eye viewed a central illuminated white screen through a half-silvered mirror. Two red light-emitting diodes in the arms of the haploscope were stimulus targets. Stimulus disparity on the retinas was adjusted to zero by varying the orientation of the arms of the haploscope.
12. The intensity of a light-emitting diode can be controlled by controlling current through the

diode because of the known (often linear) relation between current and intensity [T. E. Cohn, *Am. J. Optom. Arch. Am. Acad. Optom.* **49**, 1028 (1972)]. Our light control circuitry provided adjustable steady levels and superimposed square pulse modulations of adjustable amplitude and selectable polarity. Rise and fall times were less than 0.1 msec. Steady levels were always in the low photopic range (calibrated United Detector Technology radiometer).

13. In more compact notation the 28 stimuli were characterized by different ratios: $E_L/E_R = \pm 0$, ± 0.22, ± 0.48, ± 0.80, ± 1.25, ± 2.09, ± 4.28, and $\pm \infty$.
14. The control knob was returned to zero (no stimulus to either eye) between settings.
15. The order of presentation of stimuli was quasi-random.
16. See, for exam → W. P. Tanner, Jr., and J. A. Swets, *Psychol. Rev.* **61**, 401 (1954).
17. We have conducted control experiments using two-alternative forced-choice techniques to verify the essential features of the data shown in Fig. 1. As many as four stimulus alternatives were randomized in a given run. Such testing precludes the effects of both criterion variation and motivational change, since the subject cannot know the type of stimulus to be presented in advance and because the criterion may be presumed to be fixed on a given trial. Control runs with four types of stimulus combination were made. In the first, we used equal modulation luminance changes (the monocular stimuli had been previously found to be of equal detectability) in order to verify that increment-decrement detectability is slightly less than increment-increment or decrement-decrement detectability. Data consistent with this hypothesis were found for all subjects tested. The second control compared the detectability of monocular increments with that of binocular increments [T. E. Cohn and R. D. Freeman (*5*)]. Binocular detectability lay between that predicted by probability summation and that predicted by energy summation. The third control used stimuli all chosen to lie in the second and fourth quadrants, for example, four combinations of increment to one eye and decrement to the other eye differing only in the modulation ratio. The results of this test were consistent with the curvilinear nature of the threshold contour in the second and fourth quadrants (Fig. 1). The fourth control experiment used an increment to one eye presented with one of four low-amplitude increments or decrements to the other eye. This control was designed to test the asymmetrical nature of the threshold contour about horizontal and vertical axes. The results of this test were consistent with the hypothesis that a monocular increment is slightly more detectable when presented with a small monocular increment than with a small monocular decrement.
18. We have tested a total of six subjects, none of whom manifested binocular abnormalities in clinical tests. All exhibited elliptical threshold contours. Two of the subjects made a total of 35 determinations of the threshold contour. No systematic departures from the elliptical shape fit to data points have been observed.
19. This type of data display was first shown by C. Rashbass [*J. Physiol. (London)* **210**, 165 (1970)]. He found elliptical threshold contours for incremental and decremental monocular stimuli separated in time.
20. H. B. Barlow, C. Blakemore, J. D. Pettigrew, *ibid.* **193**, 327 (1967).
21. Suggestions of a subtractive mechanism between two eyes can also be found in the writings of B. Julesz [*Sci. Am.* **212**, 38 (Feb. 1965)], S. M. Anstis [*Vision Res.* **10**, 1411 (1970)], and E. Welpe [*ibid.* **15**, 1283 (1975)]. The visual evoked response data of L. Cigánek [*ibid.* **11**, 1289 (1971)] might also be interpreted as favoring the existence of a binocular subtraction mechanism.
22. The relation

$$E_L^2 + E_R^2 + 2KE_LE_R = 1$$

is derived in the appendix of T. E. Cohn and D. J. Lasley [*Vision Res.* **15**, 387 (1975)]. Assumptions critical to the derivation are (i) monocular thresholds equal unity, (ii) independent gaussian noise of unity variance in both summing and subtracting mechanisms, and (iii) likelihood ratio processing of outputs of the two mechanisms. The symbol K expresses the relative strengths of the mechanisms.

23. We think that the suprathreshold binocular visual phenomenon called stereoscopic luster [J. P. C. Southall, Ed., *Helmholtz's Treatise on Physiological Optics* (Optical Society of America, 1925), vol. 3, p. 525 (reprint by Dover, New York, 1962), p. 515] would also be expected of a visual system that contained interocular summing and subtracting mechanisms. When a dark target in one eye is fused with a light target in the other eye, the fused object appears transparent or lustrous, as if it were polished metal, even though the components may have been various shades of gray matte paper. We hypothesize that a subtraction mechanism would signal strongly in these circumstances and thus provide a percept noticeably different from the usual one comprising brightness and texture, which would be provided by a summing mechanism.
24. We thank D. G. Green for reading an earlier version of the manuscript, D. Greenhouse for statistical assistance, and J. Funnell for technical assistance. Supported in part by Biomedical Sciences support grant FR-5006 from the National Institutes of Health and by grant EY-01481 from the National Eye Institute.

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Complement-Dependent Immunoglobulin G Receptor Function in Lymphoid Cells

Abstract. *Lymphoid cells are unable to lyse antibody-coated target cells in the presence of normal immunoglobulin G (IgG), presumably because their surface receptors for IgG are blocked. However, when target cells are sensitized with antibodies and complement, IgG receptors are unblocked and cytotoxicity occurs even in the presence of normal IgG. Thus, IgG receptors may function in vivo despite the relatively high concentrations of IgG in serum and interstitial fluid.*

Cell-mediated cytotoxicity induced by immunoglobulin G (IgG) antibodies to target cell (antibody-dependent cell-mediated cytotoxicity, ADCC) has been advocated as a possible mechanism involved in allograft rejection (*1*), viral infections (*2*), tumor immunity (*3*), and autoimmune diseases (*4*). However, no direct evidence of its participation in vivo has been obtained. Furthermore, ADCC is inhibited by normal IgG (*5*) at concentrations below those in normal serum or interstitial fluid (*6*). I now report an in vitro model in which ADCC is induced even in the presence of inhibitory concentrations of IgG, providing an experimental basis for a possible in vivo function of the IgG receptors.

Effector cells were obtained from spleens surgically removed from patients undergoing staging laparotomies (*7*). A cell suspension was prepared and mononuclear cells were concentrated by Ficoll-Hypaque centrifugation (*8*). Sheep red blood cells (SRBC), used as target cells, were labeled with 100 μc of ^{51}Cr (Na$_2{}^{51}$CrO$_4$, New England Nuclear) (*9*) and treated with different antibody preparations. The following groups of sensitized target cells were prepared: EA-G, SRBC coated with IgG antibodies (*10*); EA-M, SRBC sensitized with IgM antibodies; EAC-M and EAC-G, SRBC sensitized with IgM or IgG antibodies and complement (C); EA-M-G, SRBC sensitized with IgM first and subsequently with IgG; EAC-M-G, SRBC sensitized with IgM and C and subsequently with IgG.

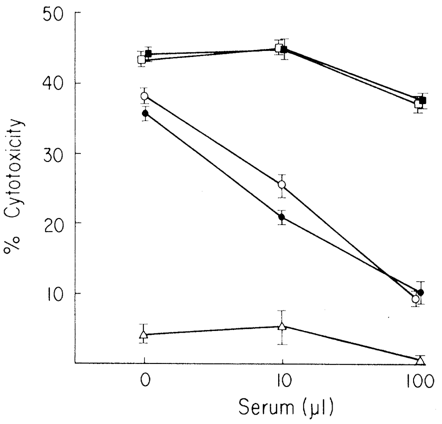

Fig. 1. Inhibition of cytotoxicity by human serum. Human serum, obtained from normal donors, was pooled, inactivated by heat, and absorbed with SRBC. Cytotoxicity was induced by human spleen lymphoid cells against SRBC sensitized in different ways. △, EAC-M; ●, EA-G; ○, EA-M-G; ■, EAC-G; □, EAC-M-G. The total volume of the cell mixture was 1 ml. The bars correspond to the range of duplicate determinations.

Effector cells (30×10^6) and target cells (2×10^6) were placed in plastic petri dishes (35 by 10 mm; Falcon Plastics) in 1 ml of Ham's F-10 medium (Grand Island) supplemented with 20 percent fetal calf serum and 50 μg of gentamicin (Schering) per milliliter. Inhibitors were added prior to the addition of the target cells. The cell mixtures were incubated (on a rocking platform) in an atmosphere of 5 percent CO$_2$ at 37°C for 18 hours and the percentage of cytotoxicity was determined (*11*). Values were expressed as specific cytotoxicity after subtraction of nonspecific lysis obtained in the absence of spleen cells. Nonspecific lysis was determined for each type of target cell (EA-G, EAC-G, EAC-M, and others).

Lymphoid cells carry on their surface receptors for the third component of complement (C3), which enable them to bind SRBC coated with C (*12*). However, such a binding does not induce lysis of the target cell, an observation