The role of GABA in detecting visual motion

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The basic computations underlying the extraction of motion from the visual environment have been characterized in great detail. A non-linear interaction, such as a multiplication, between neighbouring visual elements was shown to be the core of biological motion detectors in different species ranging from insects to man. GABA (γ-aminobutyric acid)-ergic inhibitory synapses suppressing the responses to motion in one direction but not in the other are widely accepted to be the cellular basis for this non-linear interaction. Based on model predictions we can show in combined pharmacological and electrophysiological experiments that in the fly motion detection system GABAergic synapses do not play this role but rather are involved in another important step of motion computation. This makes a reconsideration of the role of inhibition in other motion detection systems necessary.

The analysis of motion plays a central role in biological vision systems. The direction and velocity of a moving object, however, are not explicitly encoded at the level of the retinal input. Instead, they have to be computed from the time-dependent brightness fluctuations of the retinal image in a series of processing steps. There is good evidence in several biological vision systems ranging from insects to different vertebrate species including man in favour of a particular class of motion detection mechanisms, the so-called correlation-type of movement detectors[7,21,22], or mathematically equivalent versions of them[1,23]. Roughly speaking, this type of movement detector has two spatially separated input channels which interact in a non-linear way after one of the signals has been delayed. Various formal operations were proposed for this non-linear interaction. Examples are a logical gate as in the well-known Barlow–Levick scheme[4], a summation followed by a threshold operation[14], or simply a multiplication as in the eldest and most widely discussed scheme of this class of movement detection models[21,22]. It is obvious that a motion detection unit built in this way is directionally selective to some extent. However, under realistic conditions it would also respond to correlated input signals which are independent of the direction of motion, such as fluctuations of the mean light intensity[9,23]. This problem can be alleviated in a simple way by composing the detector of two such units, mirror-symmetrically arranged and subtracted from each other (Fig. 1 left). Since the motion-independent response components are identical in both subunits, they

are eliminated by the subtraction stage[9]. Thus direction selectivity of a movement detector is considerably enhanced, if it is computed by a two-stage process consisting of a non-linear interaction and a subsequent subtraction stage.

Which are the cellular mechanisms responsible for the different operations in the formal movement detector model? To account for the non-linear interaction between the two detector input channels, various cellular models have been proposed[14,26,27]. The so-called shunting-inhibition model is the most popular one among neurophysiologists. This cellular model relies on the non-linear interaction of an excitatory and an inhibitory, GABA (γ-aminobutyric acid)-ergic synapse which receive their input from neighbouring locations in visual space. To some extent, it approximates a multiplication-like interaction[14,27]. During motion in the detector's preferred direction, signals are transmitted by the excitatory synapse, while they are suppressed during motion in the opposite direction. This mechanism owes its popularity to the finding that direction selectivity of motion-sensitive cells in the retina[2,3,8,29] and the visual cortex[25] of various vertebrate species as well as in the fly[24] is greatly reduced by application of GABA antagonists. This has been interpreted as an interference with the essential non-linear interaction of the detector input channels and, thus, in favor of the shunting inhibition model[2,16,24]. This interpretation, however, is only conclusive, if direction selectivity is acquired in a single processing step, i.e. just by the non-linear interaction of the movement detector

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input channels. It may be not cogent in case of a two-stage process such as shown in Fig. 1, since then direction selectivity is not only reduced by disturbance of the non-linear interaction but also when the subtraction process is impaired by GABA antagonists. This suggests that direction selectivity on its own does not represent a good indicator for the performance of the movement detector's non-linear processing stage.

To decide between these alternatives, i.e. effects of GABA antagonists on the non-linear interaction vs subtraction, additional information is required which is more specific than direction selectivity. If the non-linear interaction can be approximated sufficiently well by a multiplication and no other non-linearities distort the detector input signals significantly, this information can be derived from Fourier analysis of local movement detector responses (Fig. 1 right). When a grating with

sinusoidally modulated brightness passes a movement detector with a constant velocity, the signals converging at the multiplication stage should also be sinusoidally modulated in time. The resulting responses of the detector subunits are then modulated with the fundamental frequency and the second harmonic of the input signal[9,14]. After subtracting the subunits' signals from each other, the second harmonic is less pronounced in the final detector output and may even disappear[9]. Since the second harmonic frequency component is produced by the multiplication process and reduced by the subtraction stage (Fig. 1 right), it can be used to decide at which processing stage of a movement detector GABA plays its
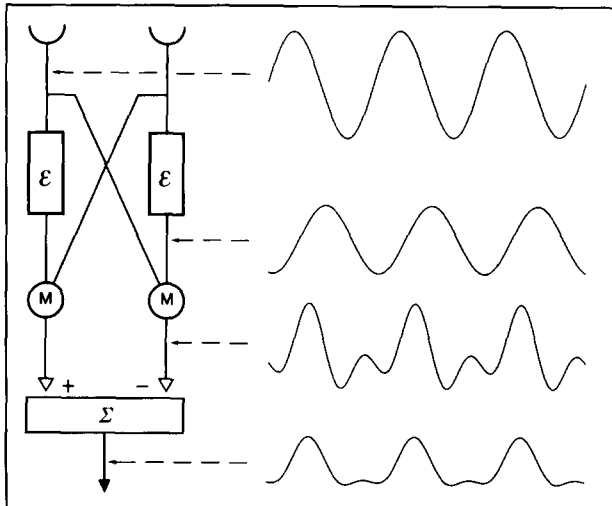

Fig. 1. Correlation-type of movement detector and its response to a grating with sinusoidally modulated brightness moving from the left to the right. A detector in its simplest form consists of two mirror-symmetrical subunits. In each subunit the signal carried by one input channel is delayed in some way (indicated by ε), such as by a low-pass filter, and then interacts non-linearly with the instantaneous signal of the neighbouring input channel. The final detector output is given by the difference of the subunit outputs. The model simulations of the detector signals as displayed on the right hand side are based on two assumptions: (i) the non-linear interaction stage is given by a multiplication; (ii) there are no non-linearities prior to the movement detector which significantly distort the time course of the input signals. The two signals simultaneously arriving at the multiplication stage (shown here for the right detector subunit) are then sinusoids and the result of their multiplication consists of only the fundamental and second harmonic frequency component of the temporal frequency of the stimulus. After subtracting the two detector subunits the amplitude of the second harmonic decreases and may completely vanish in case of mathematically perfect subtraction. For the model simulations shown here, it has been assumed that the two detector subunits are not exactly balanced and that the subunit which contributes to the overall response of the detector with a negative sign has the smaller gain (0.9).
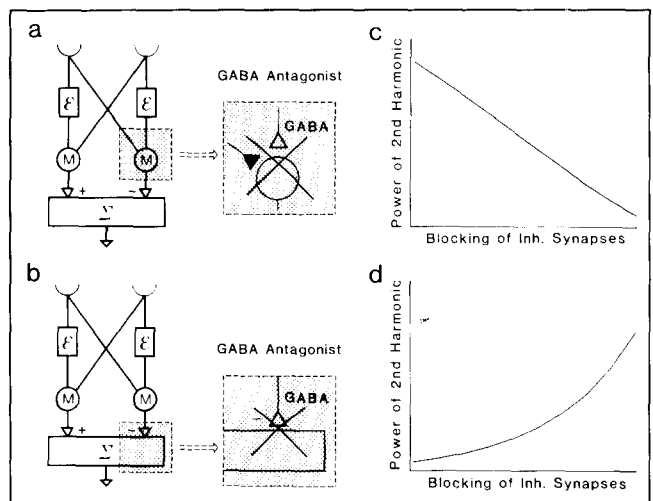

Fig. 2. Predicted consequences of a pharmacological impairment of either the multiplication (a,c) or the subtraction (b,d) stage of the movement detector. a: the neuronal realization of the multiplication-like interaction is assumed to be represented by the interaction of an excitatory and a GABAergic inhibitory synapse as proposed by Torre and Poggio[27]. Blocking of this synapse by a GABA antagonist should gradually reduce the power of the second harmonic frequency component of the movement detector response (c). b: the negative input to the subtraction stage of the formal movement detector model is assumed to correspond to a GABAergic inhibitory synapse in a neuronal implementation of the detector. If this synapse is blocked by a GABA antagonist, the power of the second harmonic frequency component in the output signal of the movement detector is predicted to increase (d). Hence interference with either the multiplication or the subtraction stage leads to qualitatively different predictions with respect to the contribution of the second harmonic frequency component to the overall movement detector response. The model simulations were based on the equation of an electrical equivalent circuit of biological membranes $V(t) = (g_eE_e + g_iE_i + g_lE_l)/(g_e + g_i + g_l)$. g_e, g_i and g_l denote the conductance of the excitatory and GABAergic inhibitory synapses as well as the leak conductance, respectively. E_e, E_i and E_l denote the corresponding batteries. If the non-linear interaction is to be represented by this equation, the following numerical values were chosen: $E_e = -10$ mV, $E_i = E_l = -70$ mV; see ref. 27. In case of the subtraction stage, the numerical values of the different batteries in this equation amounted to: $E_e = -10$ mV, $E_i = -70$ mV, $E_l = -50$ mV. The conductances g_e and g_i were assumed to be proportional to the corresponding input signals of the synapses; g_l was constant. c and d: the inhibitory synapses were weighted by a gain factor which was varied in the simulation between 1 and 0.

critical role (Fig. 2). If inhibitory GABAergic synapses are the basis of the non-linear interaction of the detector input channels, the power of the second harmonic frequency response component is expected to decrease after blocking the GABAergic synapses by an antagonist (Fig. 2a). This prediction is not affected if, in addition to the non-linear interaction, also the subtraction stage is based on GABAergic synapses and blocked pharmacologically. However, if GABAergic synapses are responsible for the subtraction process alone the second harmonic frequency component should increase (Fig. 2b).

These predictions were tested in the motion detection system of the fly which proved to be an excellent model system for studying various visual information processing tasks[6,10]. In particular, its motion detection system can be described satisfactorily by the formal scheme outlined above: it computes motion in a two-stage process with a multiplication-like interaction of the detector input channels and a separate subtraction stage[9]. In the third visual ganglion of the blowfly Calliphora erythrocephala we recorded the responses of a directionally selective motion-sensitive interneurone, the H1-cell, which can be identified individually in different preparations[15]. This cell has an extended receptive field and spatially integrates the output signals of large retinotopic arrays of local movement detectors. Since the local movement detectors all look at a different spatial phase of the stimulus pattern, their response modulations are expected to be phase-shifted in time. Spatial integration then eliminates the temporal modulations of the local detector responses. We prevent spatial integration by presenting the motion stimulus to the fly's eye through a sufficiently small vertical slit. In this way local detector responses can be derived from spatially integrating visual interneurones[9]. When a sinewave grating is moved behind the slit one obtains, as predicted for a multiplication-like movement detector non-linearity, periodic responses to motion in both the cell's preferred and null direction which are modulated in time. The temporal modulations consist of almost only the fundamental and second harmonic frequency component[9]* (Fig. 3). In the present study we combine the slit stimulation technique with injection of picrotoxinin into the fly's haemolymph next to the third visual ganglion. Picrotoxinin is known to be a non-competitive blocker of inhibitory chloride channels, especially, though not exclusively, of those activated by GABA[5]. After a short delay of about 5–20

s the responses, on average, change dramatically for some 20–60 min before returning again to their preinjection shape. Most notably, the power of the second harmonic frequency increases by about a factor of 10. Moreover, there is also a pronounced increase in the mean spike rate during motion in both the preferred and null direction resulting in a reduction of direction selectivity. The latter feature was already reported before and interpreted as evidence for the shunting inhibition model[24]. According to our model predictions, however, the concomitant increase of the second harmonic frequency component following picrotoxinin injection suggests that in the fly visual system GABA is involved in the subtraction and not in the multiplication process of motion detection.

Whether this holds also true for other systems where GABA was found to impair direction selectivity cannot yet be decided. Other criteria than were used here may be required for distinguishing between an elimination of the non-linear interaction stage and the subtraction stage in two cases: (i) if the non-linear interaction cannot be approximated sufficiently well by a multiplication, or (ii) if sinusoidal movement detector input signals are distorted by additional non-linearities. Some experimental evidence, in addition to the pharmacological one, has been adduced in favour of a direct involvement of inhibitory processes in the non-linear interaction stage in the retina of various vertebrate species[4,16,18,28,29]. None of these studies, however, considers the significance and possible involvement of a subtraction stage, separate from the non-linear interaction, in generating direction selectivity. Interestingly, there are specific features commonly found in the responses of directionally selective cells to apparent motion stimuli which suggest that both these processes may be involved in computing direction selectivity: during apparent motion in the null direction, suppression of the responses is frequently observed in directionally selective cells of the retina[4] and lateral geniculate nucleus[17] of the rabbit, the cat striate cortex[11,13], as well as in area MT of monkeys[19]. In many of these cells, however, also an enhancement of the responses during apparent motion in the cell's preferred direction can be detected[11,13,19,20]; this is even true for the rabbit retina as is revealed by the seminal paper of Barlow and Levick[4]. It is obvious that an enhancement and a suppression in a single cell can hardly be explained by a single-stage process of motion detection based on a

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* A second harmonic frequency component could alternatively arise, if the input signals are half-wave rectified and processed in separate on- and off-detectors, the outputs of which are then summated to form the final detector response. This kind of preprocessing of the movement detector input has recently been proposed[12]. Since the on- and off-detectors act in counterphase when stimulated by motion of sinewave gratings, the final response is expected to contain a strong second harmonic as long as the detector responds to motion at all. Moreover, the relative contribution of the second harmonic and the fundamental frequency should be more or less invariant with respect to the direction of motion as well as the strength of the subtraction stage. This, however, is in contrast to our experimental data (see Fig. 3 and ref. 9).
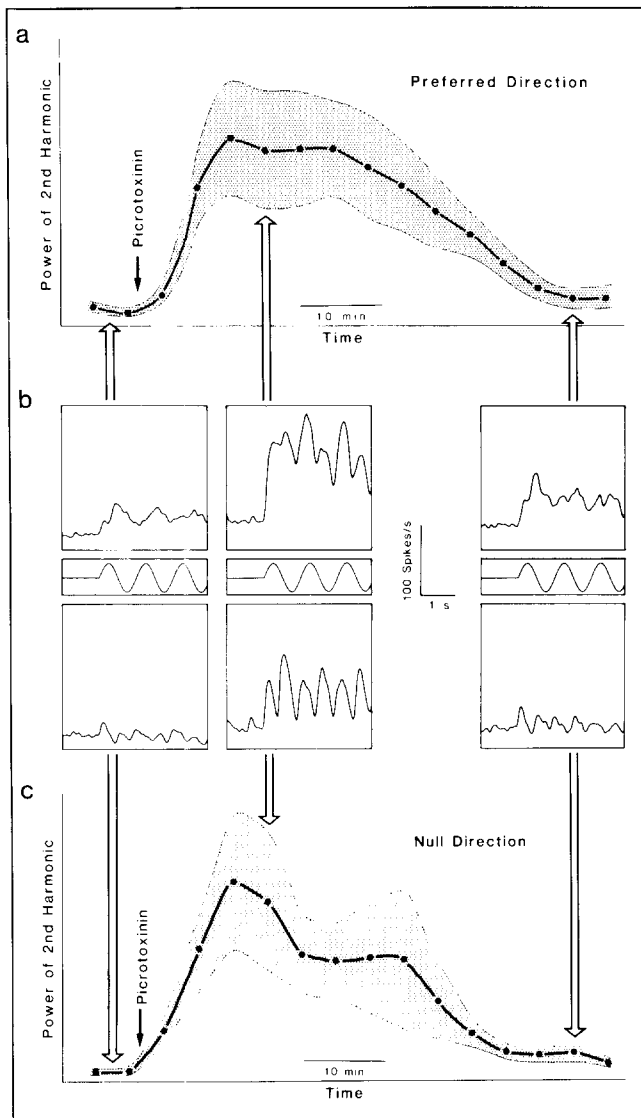
non-linearity of the shunting inhibition type. In contrast, *both* a suppression and an enhancement, with only their relative strength depending on the exact stimulus conditions, are an almost inevitable consequence of a two-stage process of computing direction selectivity with a separate non-linear interaction and a subtraction stage. ·

Thus, the role of inhibition in motion detection systems other than the fly has to be reconsidered.

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