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"Combining Neuropharmacology and Behavior to Study Motion Detection in Flies"

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Combining Neuropharmacology and Behavior to Study Motion Detection in Flies

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Abstract. The optomotor following response, a behavior based on movement detection was recorded in the fruitfly *Drosophila melanogaster* before and after the injection of picrotoxinin, an antagonist of the inhibitory neurotransmitter GABA. The directional selectivity of this response was transiently abolished or inverted after injection. This result is in agreement with picrotoxinin-induced modifications observed in electrophysiological activity of direction-selective cells in flies (Bülthoff and Schmid 1983; Schmid and Bülthoff, in preparation). Furthermore, walking and flying flies treated with picrotoxinin followed more actively motion from back to front instead of front to back as in normal animals. Since the difference in the responses to front to back and back to front motions is proposed to be the basis of fixation behavior in flies (Reichardt 1973) our results support this notion and are inconsistent with schemes explaining fixation by alternative mechanisms.

1 Introduction

There are numerous strategies to investigate experimentally the mechanism of elementary movement detectors (EMDs) in flies. Beyond general methods like anatomy, neural development or mapping of neurochemicals in the brain, procedures more specific for the study of movement detection are used. The major ones are (1) electrophysiology for recording intra- or extracellularly electrical activity of single movement-sensitive cells (Hausen 1981, 1984; Hengstenberg 1982), (2) behavioral studies for measuring the output of the complete movement detection system (Buchner 1976; Götz et al. 1979; Reichardt and Poggio 1976), (3) functional mapping with the deoxyglucose method for getting a pictorial representation of regional movement-induced neuronal activity in the whole visual neuropil (Buchner et al. 1979, 1984; Buchner and Buchner 1980). They can be combined with tools inducing modifications in the neuronal processing of movement stimuli, i.e. in the mechanism of the elementary movement detectors (EMDs). These tools can be methods inducing mutations in the visual system (Benzer 1967; Bülthoff and Buchner 1985; Heisenberg et al. 1978; Heisenberg and Böhl 1979), direct intervention in the nervous system with laser beam or scalpel (Geiger and Nässel 1981, 1982; Hausen and Wehrhahn 1983) or the application of pharmacological substances interfering in neurotransmission (Takeuchi and Takeuchi 1969; Yarom et al. 1982). We have studied pharmacological-induced alterations in the motion detection mechanism by observing a movement-induced behavior, the optomotor response of the fruitfly *Drosophila melanogaster*. In another paper, we describe our results obtained by combining extracellular recordings of a movement-sensitive direction-selective cell (H1) of the blowfly *Calliphora erythrocephala* with the application of the same pharmacological substance (Schmid and Bülthoff, in preparation). The results of both types of experiments are compared in the second paper.

2 Material and Methods

Flies present a rich repertoire of thoroughly studied visually induced behaviors which have been used as indicators for the visual perception of the fly. The optomotor following response has been chosen because it is a basic behavior based on direction-specific processing of movement. This behavior serves the fly to stabilize its course in the case of an involuntary deviation of its intended course by following the movement of the visual surrounding (reviews:

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Reichardt and Poggio 1976; Poggio and Reichardt 1976; Buchner 1984). The input-output analysis of the optomotor response is, of course, an indirect way to study the elementary movement detection and different models of EMDs could fit the same input-output relation. Nevertheless the class of different movement detector models can be reduced by this method, e.g., the gradient-type models have been eliminated and the correlation-like models confirmed by this method (Buchner 1984).

The tiny fruitfly *Drosophila melanogaster* walks and flies for long periods of time, which allows to measure its behavioral responses with great precision. Female flies (3–6 days old) where exclusively used throughout the study.

2.1 Optomotor Following Response of Walking Flies

The thorax of the fly immobilized by cold anaesthesia was tethered dorsally to a support by a non-toxic dental cement (Scutan, ESPE). Simultaneously, the head was rigidly attached to the holder in its normal position. The fly was placed on a small ball free to rotate on a gentle stream of air (Fig. 1a). The locomotor activity of the fly on the ball induces rotatory revolutions of the ball (rev R) around the vertical axis for intended turning and forward revolutions (rev F) around the horizontal axis for intended straight course. These revolutions were registered by a locomotion recorder described elsewhere (Bülthoff 1982). Table 1 shows how the direction-sensitive component (R_{ds}) and the direction-insensitive component (R_{di}) of the optomotor response are calculated from the data. The stimulus-induced locomotor activity of the fly was registered initially for one hour. Flies showing poor locomotor activity (translation less than 2 m/h) or strong bias in their response during this period, indicating poor physical condition or bad positioning in the locomotion recorder, were discarded. The remaining flies were removed from the recorder after 60 min of this pretest. 20–30 nl water with or without 20–30 pmol picrotoxinin was injected through a broken-off micropipette into the hemocoel of their abdomen under binocular control. Immediately after the flies were replaced into the locomotion recorder the optomotor response was monitored for two hours or as long as they showed locomotor activity. Again flies with too low locomotor activity were not taken into account.

2.1.1 Large-Field Stimulation. Sine wave gratings with parameters similar (wavelength 10°, contrast 30%, mean intensity 50 cd/m^2, stimulus field 40°) to those used in electrophysiological studies (Schmid and Bülthoff, in preparation) were presented to both eyes. Gratings were alternatively stationary or moving (pattern velocity 40°/s) progressively (from front to back) (Table 1) or regressively (from back to front) in a sequence presented repetitively to the fly. The optomotor response induced by these stimuli was recorded in the locomotion recorder. The direction-sensitive (R_{ds}) and direction-insensitive (R_{di}) components of the response were calculated every 3 min before and after injection.

2.1.2 Small-Field Stimulation. A single black stripe (12° wide) extending 20° above and below the equato-

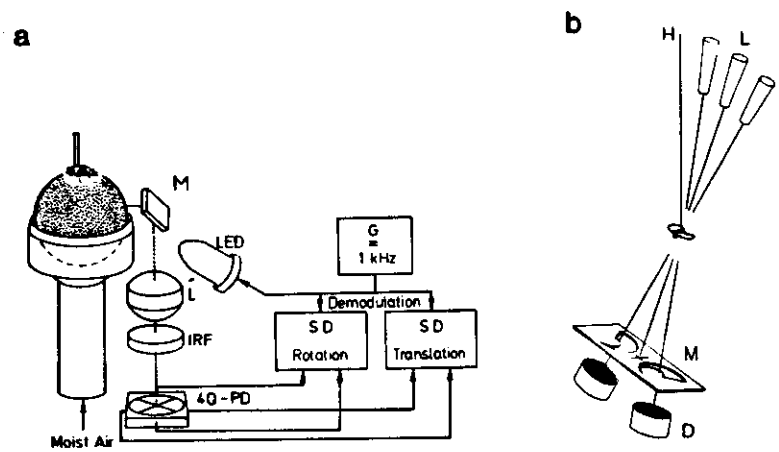

Fig. 1. a Locomotion recorder. The fixed fly is allowed to walk stationarily on an air-suspended dotted ball. The rotations of the ball (i.e., motion of the dots) induced by the translatory or rotatory locomotor activity of the fly are evaluated by a sequence detecting unit (for more details, see Bülthoff 1982). M front-silvered mirror, L lens, IRF infrared filter, 4Q-PD 4-quadrant photodiode, SD sequence detecting logic, LED light emitting diode. **b** Flight recorder developed by Götz (1983) for measuring the wingbeat amplitude of stationarily flying flies. L light sources for adjustment of the measuring set-up and for projection of the wingshadows onto the facing mask-openings (M), D photoelectric detectors of wing position for measurement of beat amplitudes, H holder. (Courtesy of Prof. K.G. Götz)

Table 1. Locomotion recorder

Torque-inducing stimuli		Measured optomotor response	Computed components R_{ds} and R_{di}
Left	Right		
Eye			
reg	prog	R_{cw}	$R_{ds}^{bin} = R_{cw} - R_{ccw}$
prog	reg	R_{ccw}	$R_{di}^{bin} = R_{cw} + R_{ccw}$
–	prog	R^r_{prog}	$R_{ds}^{mon} = 1/2(R^r_{prog} - R^l_{prog} + R^l_{reg} - R^r_{reg})$
–	reg	R^r_{reg}	
prog	–	R^l_{prog}	
reg	–	R^l_{reg}	$R_{di}^{mon} = 1/2(R^r_{prog} - R^l_{prog} - R^l_{reg} + R^r_{reg})$
Other stimuli			
prog	prog		
reg	reg		
–	–		

In the first column the stimuli presented repetively to the flies are listed. In the second column the abbreviations of the corresponding measured optomotor responses are given. In the last column the way how R_{ds} and R_{di} are calculated is shown

reg regressive, prog progressive, – standing grating; cw, (ccw) clockwise (counterclockwise) moving stimuli; r right, l left; mon (bin) monocular (binocular) stimulation

rial line of the eyes was rotating with 10°/s alternatively clockwise (cw) and counterclockwise (ccw) around the fly in front of a homogeneously illuminated white background (about 1000 cd/m^2). The direction of movement was switched behind the fly. The transient optomotor response was registered for one complete cycle of 1 cw and 1 ccw rotation lasting 72 s. The responses were averaged for 30 min (25 cycles) or 60 min (50 cycles). R_{ds} and R_{di} were calculated as in the previous type of stimulation.

2.1.3 Optomotor Following Response of Flying Flies. Flies were carefully glued between head and thorax onto the tip of a needle. The flying flies were hung in front of two screens for large-field stimulation with parameters similar to those used previously. One sequence included 48 different sets of stimuli (Table 2). A new stimulus was given every 15 s, one stimulus lasting 10 s and the interstimulus time 5 s. One non-interrupted sequence of 48 stimuli lasted 12 min. In these experiments the left and right wing beat amplitude (A_l, A_r) was used as a measure of optomotor turning tendency and was recorded in the flight recorder (Fig. 1b) developed by Götz (1983). The mean wingbeat amplitude was evaluated only when the fly was flying during the whole stimulus period of 10 s, otherwise the stimulus was repeated. R_{ds} and R_{di} were calculated as for walking flies.

Table 2. Flight recorder

Torque-inducing stimuli		Optomotor response measured by $A_r - A_l$
Left	Right	
Eye		
reg	prog	R_{cw}
prog	reg	R_{ccw}
–	prog	R^r_{prog}
–	reg	R^r_{reg}
prog	–	R^l_{prog}
reg	–	R^l_{reg}
Other stimuli		
prog	prog	
reg	reg	

A_r(A_l) beat amplitude of the right (left) wing; other symbols and abbreviations as in Table 1

Note: In this experiment, each set of stimuli was presented to the fly with various inclinations (horizontal, 30°, 60°, −30°, −60°, vertical) so that 48 sets of stimuli were presented in one sequence

3 Results

Throughout the pretest period, the direction-sensitive component (R_{ds}) of the optomotor response of all flies is positive in both binocular (bin) and monocular (mon) stimulation. Furthermore in case of monocular

stimulation, all flies show the progressive-regressive asymmetry described by Reichardt (1973) and Götz (1975a, b), i.e., their optomotor following response is greater for progressive movement than for regressive movement. This asymmetry implies that the direction-insensitive component (R_{di}^{mon}) is positive (see Table 1).

3.1 Flies Tested in the Locomotion Recorder

3.1.1 Binocular Stimulation. After injection of picrotoxinin, 13 of the 14 *Drosophila* tested presented a noticeable change in their direction-sensitive response R_{ds}^{bin}. Seven flies showed an inverted optomotor response (negative R_{ds}^{bin}); six showed reduced or no directional selectivity within the first 10 min *post* injection (pi) and presented at least one negative value of R_{ds}^{bin} within the first 30 min pi. The last fly showed a delayed modification of its R_{ds}^{bin} towards negative and null values which began 50 min after injection. For seven flies, time of recovery to normal optomotor response varied between 30 and 180 min pi; otherwise three flies did not show complete recovery during this period and three died two hours after injection. The mean R_{ds}^{bin} of the 14 flies (Fig. 2a) is negative for the first 10 min pi, recovering gradually during the next 2 to 3 h.

3.1.2 Monocular Stimulation. The direction-specific component of the optomotor response of the same 14 flies was also registered along the same period using monocular stimulation. The monocular response (R_{ds}^{mon}) varies more from one fly to the other than the binocular response (R_{ds}^{bin}), so that no meaningful grouping of the individual results can be done. Surprisingly with monocular stimulation, no inversion of R_{ds}^{mon} was observed after picrotoxinin injection (Fig. 2c); on the contrary, an enhancement of R_{ds}^{mon} occurs within the first 10 min pi. Afterwards, R_{ds}^{mon} remains at a level somewhat lower than prior to injection for the next 180 min. The direction-insensitive response R_{di}^{mon} (Fig. 2e) is interesting because it depends directly on the asymmetry between the optomotor following response to progressive and regressive movement. After injection, this asymmetry is inverted, therefore R_{di}^{mon} is negative. This component is strongly negative at the beginning, and stabilizes later at a less negative level. This indicates that after injection of picrotoxinin, the flies followed more strongly a regressive than a progressive movement. The R_{di}^{bin} is not shown, as its value only indicates presence of bias, which is eliminated in the calculation of R_{ds}^{bin}, R_{ds}^{mon}, and R_{di}^{mon}. Figure 2g gives a representation of the translatory movements of the fly, i.e., how much the fly walked straight forward

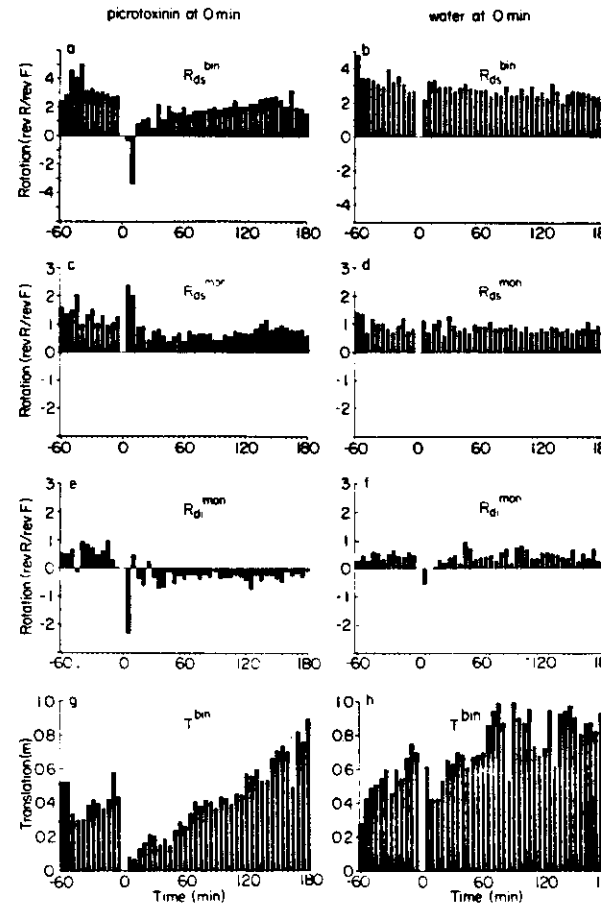

Fig. 2a–h. Mean direction-sensitive (R_{ds}) and direction-insensitive (R_{di}) components of the optomotor turning response of *Drosophila* flies placed in the locomotion recorder and stimulated binocularly (bin) or monocularly (mon) with moving gratings. **a**, **c**, and **e** Responses of 14 flies injected with 20–30 pmol picrotoxinin in 20–30 nl water after a pretest of 60 min. **b**, **d**, and **f** control measurements made with 13 flies which were injected with 30 nl water. **g** and **h** Translatory locomotor activity before and after injection of picrotoxinin (**g**) or water (**h**)

without turning.[1] Here the values for binocular stimulation are given, translatory activity during other types of stimulation being similar. The responses to translatory movements decreases strongly immediately after injection and recover to normal within 130 min (monocular stimulation) to 180 min pi (binocular stimulation) and then increase even further to surpass values measured before injection. This last

[1] The optomotor turning response rev R has been computed once with regard to the translatory activity rev F as rev R/rev F (shown in this figure) and also with regard to the time as rev R/time (not shown). The picrotoxinin-induced modifications of R_{ds} or R_{di} do not appear to be qualitatively different in both types of calculation, but, because of the modified locomotor activity, it is more apparent in rev R/rev F

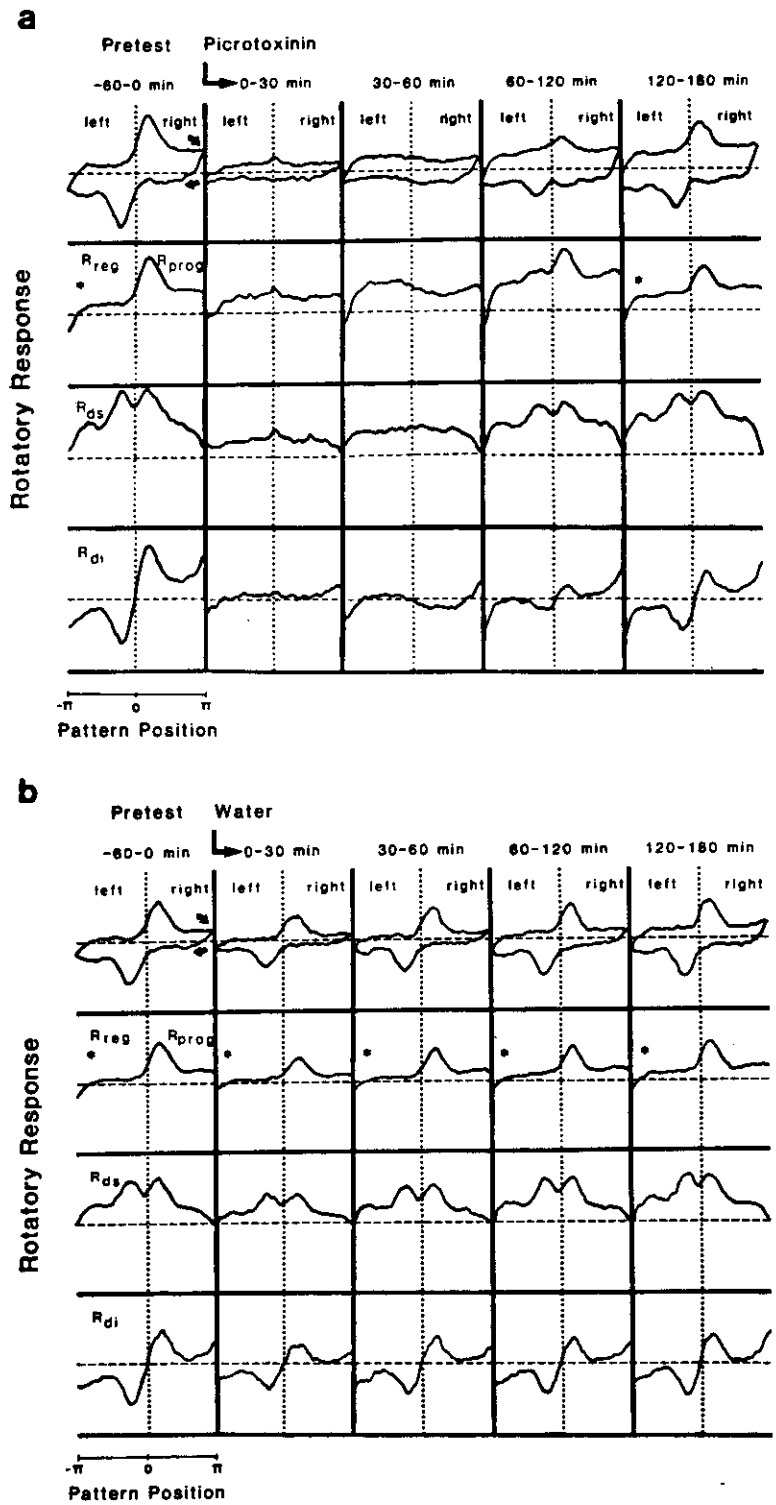

Fig. 3a and b. Transient optomotor response to a small-field stimulus (12° wide black stripe) moving at 10°/s in alternative clockwise and counterclockwise directions. Positive response reflects clockwise turning tendency of the flies. The rotatory responses are rearranged in the three last rows by combining responses to stimulation of the left and right eyes. Each curve represents the average of 25 or 50 sweeps obtained from 13 females which received an injection of picrotoxinin (**a**) after the test period or from 8 females which received water (**b**). ↷ (↶) cw (ccw) rotation of the stripe. • Scale of the ordinate reduced to the half. For more details see text

fact has two possible explanations: (1) non-injected flies have been observed to gradually increase their translatory locomotor activity within the first 8–12 h of testing (Bülthoff 1981), (2) it has been observed that flies which received smaller quantities of picrotoxinin are likely to show an increased translatory locomotor activity (Bülthoff and Bülthoff, unpubl. results). One to three hours after injection, the active picrotoxinin in the flies could have decreased to an amount inducing a similar stimulation of their locomotor activity.

3.1.3 Single-Stripe Stimulation. With that type of stimulation, the fly is monocularly stimulated except when the stripe passes through the binocular frontal field of the fly. In Fig. 3a, the first row shows that after injection of picrotoxinin the optomotor response to the clockwise or counterclockwise moving stripe was reduced. The calculated R^{ds}_{mon} is shown in the third row; it is markedly reduced within the first 60 min pi, and almost back to normal values around 120 min pi. As observed in the previous experiments, no inversion of R^{ds}_{mon} appears with monocular stimulation. In the second row, the monocular responses to the stripe moving progressively or regressively for each eye are combined. In the pretest period R_{prog} is larger than R_{reg}. Between 30 and 60 min pi, R_{prog} is smaller than R_{reg}. Then around 120 min pi, R_{prog} is again larger than R_{reg} as in the pretest period. The picrotoxinin-induced modification of the asymmetry in the optomotor response is best seen in the fourth row where the direction-insensitive component R^{mon}_{di} is calculated by the difference of R_{prog} and R_{reg} ($R^{mon}_{di} = R_{prog} - R_{reg}$).

3.2 Flies Tested in the Flight Recorder

Except after injection of picrotoxinin, one full sequence of stimulation lasted usually 15 ± 2 min (see Fig. 4). After injection of the drug, the flies were less inclined to fly. While most flies were able to walk immediately after injection of picrotoxinin, many flies were flying satisfactorily only around 15 min pi and even then, their flight was often interrupted. R^{bin}_{ds} (Fig. 4a) and R^{mon}_{ds} (Fig. 4c) are both reduced to about 60% after injection of picrotoxinin. They remain reduced for the period of testing (70 min pi). The results obtained with walking flies show that the period of inverted R^{bin}_{ds} for these flies takes place during these first 15 min pi, thereafter R^{bin}_{ds} is reduced, but not negative. Therefore it is unlikely to observe any inversion of R_{ds} in the results obtained with flying flies. R^{mon}_{di} is inverted after injection of picrotoxinin for the first 35 min pi, thereafter it is strongly reduced (first to 16% and then to 33% of the pretest value). Picrotoxinin acts similarly on the optomotor response whatever inclinations the gratings had, this suggests that the motion detection system for other directions uses EMDs similar to those for horizontal movement, only their orientation differs.

3.3 Control Experiments with Injection of Water

As a control, all experiments reported here were repeated with injection of water without picrotoxinin. Injection of water does not modify significantly R^{bin}_{ds} and R^{mon}_{ds} in case of large-field stimulation (Figs. 2b, d, and 3b). However, it induces a small and short inversion of R^{mon}_{di} (Fig. 2f) and a slight reduction of

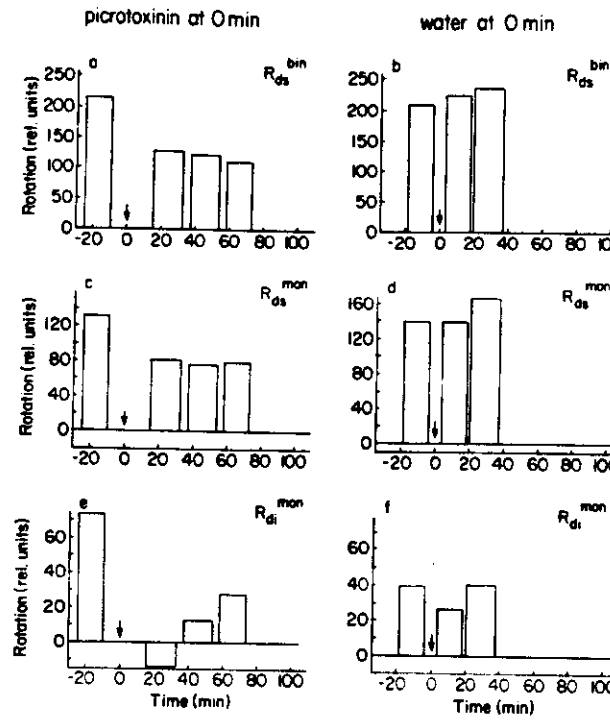

Fig. 4a–f. Mean direction-sensitive (R_{ds}) and direction-insensitive (R_{di}) components of the optomotor turning response of *Drosophila* flies recorded in the flight recorder. The flies were stimulated monocularly (mon) and binocularly (bin) with large-field moving gratings. **a**, **c**, and **e** Responses of 15 flies injected with 10–20 pmol picrotoxinin in 20–30 nl water after one pretest measurement. **b**, **d**, and **f** The same measurements were repeated with 6 flies which received 20–30 nl water after the pretest period

R^{mon}_{ds} in case of small-field stimulation (Fig. 3b). These modifications are much less strong and extended than when picrotoxinin was injected so that one can assume that the inversion of R^{mon}_{di} (Fig. 2e) or the strong reduction of R^{mon}_{ds} (Fig. 3a) observed after injection of picrotoxinin are due mainly to the specific effect of the drug. The behavior of water-injected flies shows that it is picrotoxinin, and not any injection-induced impairment, which is responsible for the difficulties of the flies to fly after injection and for their reduced locomotor activity.

4 Discussion

The inversion of the direction-selective component of the optomotor following response for binocular stimulation is in complete agreement with the picrotoxinin-induced inversion of direction-selectivity observed in a large-field giant neuron (H1-cell) in the fly *Calliphora erythrocephala* (Bülthoff and Schmid 1983; Schmid and Bülthoff, in preparation). This cell is located in the motion computation center for the

optomotor response, i.e. the lobula plate. On one hand, these electrophysiological results show that the picrotoxinin-induced inversion observed at the behavioral level is induced by changes at the level of neuronal processing of motion rather than by modifications of the motor centers themselves. On the other hand, the behavioral results show that the inversion of directional selectivity of the H1-cell is a phenomenon not limited to the very H1-cell being recorded, but that it should concern other large-field integrating neurons, and that it is recognized and transmitted further by the postsynaptic cells down to the motor output. Therefore, the picrotoxinin-induced modifications observed in the H1-neuron should be also present in the direction-selective output cells of the lobula plate, the HS-cells (reviews: Hausen 1981, 1984). Presently, intracellular recordings of the HS-cells in presence or absence of picrotoxinin are in progress (Hausen et al., in preparation).

In our behavioral studies, binocular and monocular stimulations were given alternatively, assuring that each fly was in identical physiological conditions for both types of stimulation. Nevertheless, the inversion of the response after picrotoxinin injection was observed exclusively in flies stimulated binocularly. This is in contrast to our electrophysiological results in which inversion of the directional selectivity of the H1-cell under picrotoxinin had been obtained with monocular as well as binocular stimulation (Schmid and Bülthoff, in preparation). This is not surprising because the H1-cell gets mainly input from its ipsilateral visual field, i.e. a monocular input. On the level of the motor output on the other hand not only the signal from the H1-cell contributes to the optomotor response but also the signals from other motion-sensitive cells which can be also affected by picrotoxinin. That not only the H1-cell is modified by picrotoxinin has been reported by Bülthoff et al. (1984).

The monocular stimulation has given interesting results besides the lack of picrotoxinin-induced inversion of the direction-sensitive response. In Figs. 2e and 3a, the progressive-regressive asymmetry which is given by the values of R_{di}^{mon} is inverted after injection of picrotoxinin. It has been proposed by Reichardt (1973) that the direction-insensitive response R_{di} shown in the last row of Fig. 3a and b is a measure of pattern-attractiveness for the fly and that the object fixation behavior shown by flies under closed-loop conditions (i.e. the flies control their flight direction in order to maintain a small object in their frontal visual field) is based on this progressive-regressive asymmetry. An alternative hypothesis has been proposed by Pick (1974, 1976) who has shown that object position could be computed independently of movement detectors as the position of an object can be detected by position detectors (also called flicker detectors). Both hypotheses have been discussed by Wehrhahn and Hausen (1980), Geiger (1981), and Bülthoff and Wehrhahn (1984), and independent processing of object-induced course control has been reported in experiments with an optomotor-blind mutant (Götz 1983; Heisenberg and Wolf 1984). As picrotoxinin induces an inversion of the direction-insensitive response R_{di}, it should also promote antifixation, i.e. fixation of the stripe behind the fly. In another paper (Bülthoff and Bülthoff 1986), we show that, after injection of picrotoxinin, 50% of the flies tested in the flight recorder perform antifixation, suggesting that object fixation is indeed based on a movement-sensitive, direction-selective visual processing, as originally proposed by Reichardt (1973). Picrotoxinin-induced changes at a later processing stage (e.g. at the motor output level) or influence on a motion independent position system (flicker detectors) are not excluded but the simplest explanation for the inversion in the fixation response (Bülthoff and Bülthoff 1985a, b) is the inversion of the progressive-regressive asymmetry which can be detected not only in the behavior but furthermore in the response of the H1-cell (Bülthoff and Schmid 1983; Schmid and Bülthoff, in preparation).

The combination of injection of neuropharmacological substances and behavioral studies has proved to be a potent tool for unraveling neuronal computation. One limitation of the method is the various ability of the injected substances to cross the blood-brain barrier. Direct injection into the brain is possible, but in the case of *Drosophila*, we do not know to what extent the flies would behave properly after such an operation. In flies, injection of neuropharmacological substances can be combined with either behavioral experiments or with electrophysiology, thereby one can get a broad set of information based both on the observed modifications of the output of the whole system or the changes induced in specific cells.

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