J. exp. Biol. 112, 65–93 (1984)
Printed in Great Britain © *The Company of Biologists Limited 1984*

NEUROGENETICS AND BEHAVIOUR IN INSECTS

BY K. F. FISCHBACH AND M. HEISENBERG

Institut für Genetik und Mikrobiologie, Röntgenring 11, 8700 Würzburg, West Germany

SUMMARY

The importance of the genome for behaviour has been amply demonstrated by the tools of population genetics. A deeper understanding of the relationship between genes and behaviour requires an investigation of how they influence brain development and neuronal function. This is the objective of neurogenetics.

Rigid genetic control of brain structure in insects is indicated by bilateral symmetry and by the similarity of isogenic brains (in locust). In large parts of the brain (e.g. optic lobes) the role of developmental variability seems to be as limited as in nematodes, but at closer inspection, the growth of at least some brain structures (e.g. mushroom bodies) is influenced by experience, similar to the growth of some vertebrate systems.

The role of individual genes for brain development and brain function is being studied in *Drosophila melanogaster*. Here, many single gene mutations affecting the brain and behaviour have been isolated. They either alter the development of neural circuits or modify cellular functions of neurones. Mutations of both categories are often remarkably specific (i.e. they influence only certain functional subsystems, leaving others unaffected). Therefore, functional subsystems are to some degree ontogenetic units under independent genetic control. Telling examples are sexual dimorphisms of behaviour and brain structure. The already peripheral separation of functional pathways in the brain seems to be partially due to the selective advantage of independent genetic modifiability of functions.

INTRODUCTION

Behavioural neurogenetics is an extension of developmental genetics. Its aim is to elucidate the role of genes in brain development, and in the emergence of species-specific behaviour. For decades, the genetics of behaviour has been governed by the concepts and tools of population genetics. The distinction between the two approaches is not clear to everyone and discussions about genes and behaviour tend to confuse the developmental and population genetical point of view. We shall therefore begin this review with a brief outline of the main concepts of these approaches.

The concept of 'heritability'

Population genetics is concerned with the variability of characters in animal populations and its genetic basis. Variability can result from two factors: variations between

Key words: Brain development, genetic control, brain mutants.

individual genomes and between particular environments. If the total variance of a character is assumed to be simply the sum of the genetically and environmentally caused variances, its heritability is defined as that fraction of the total which is caused by genetic variance. It can be measured, for instance, in isogenic populations under normal environmental variability (Fuller & Thompson, 1960). This has been tried for human characters (including intelligence) in studies of twins (e.g. Jensen, 1970).

Heritability describes an important evolutionary parameter. The higher the heritability, the faster selection works. However, because of the way heritability is defined, 'non-heritable' characters might as well be under tight genetic control. For example, the variability of limb number in any animal population is due mainly to environmental factors. The highly invariable genetic control causes a heritability near zero. Furthermore, it follows from the definition that the heritability of characters in a homozygous inbred strain (or in an isogenic clone) is close to zero. For these reasons, the term heritability for the genetically caused variance fraction is not an appropriate choice. It will certainly continue to cause misunderstandings.

Tolman (1924) was the first to show that behavioural variability in animal populations can be due to variation at the genetic level. By selecting strains of fast and slow learners from a population of rats, he also demonstrated that the development of behavioural traits (even of learning performance) is actually influenced by the genome, an inference which was not self-evident at that time.

The heritability of a character tends to be low when it is under a strong stabilizing selection pressure, for example mating behaviour in *Drosophila* (Fulker, 1966) and the reactivity of *Drosophila* to mechanical stimulation (Hay, 1972). Phototactic and geotactic behaviour of *Drosophila* have been most extensively explored by the techniques of population genetics (see Grossfield, 1978). The heritability is generally below 20 % (Michutta, Krause & Köhler, 1981). This is, however, high enough to allow selection for positive or negative taxis in 20–100 generations. As expected, the heritability of the behaviour decreases as selection proceeds (Dobzhansky, Spassky & Sved, 1969), since under most conditions, selection is a reduction of genetic variability.

Selection experiments have certainly provided important insights into evolutionary mechanisms. However, for the developmental geneticist, analysing a particular behaviour, the draw-backs of selective breeding as a starting point are obvious. The results strongly depend upon the genetic variability which happened to occur in the initial population subjected to selection. Thus, the final genetic analysis of selected strains cannot be interpreted as showing that the behaviour is mainly under the control of one or another chromosome. This fact is sometimes neglected. Another major disadvantage of the selection method is that it requires mass screening which excludes the investigation of more sophisticated behaviour.

The concept of 'innate behaviour'

In contrast to population genetics, developmental genetics elucidates the role of the genome in the individual ontogenetic process. In the strict sense, genes do not determine development; outside factors can always interfere with, or stop the process. However, the existence of genetic guidance is obvious. In any given species the outcome of development, beginning with a fertilized egg, is fairly predictable for

many morphological traits as well as for species-specific action patterns. Ethologists had this in mind when they coined the term 'innate behaviour' (Lorenz & Tinbergen, 1938). They observed that the emergence of some behaviour is a normal and predictable outcome of the developmental process, fairly invariant to environmental fluctuations, including social isolation.

At the beginning, ethologists contrasted 'learned' and 'inborn' behaviour, but from our present point of view, this makes little sense (as already recognized by Lehrman, 1953). Genes acquire meaning only in a narrowly defined biological context. Thus it is difficult to exclude from 'innate behaviour' all that is learned. Whenever the contents of what is learned are predictable (due to invariant environmental factors), learning may simply be regarded as one form of epigenetic mechanism. For example, auditory feedback plays an important role in the development of normal species-specific song patterns in isolated canaries (Marler & Maser, 1977). In *Drosophila*, parameters of visual flight control are influenced by experience (Heisenberg & Wolf, 1984). Development of so-called 'fixed action patterns' may therefore involve learning.

We conclude that the development of species-specific features of brain and behaviour may be called 'genetically controlled' (or 'innate'), whenever the outcome is a reliable event. This convention does not refer to the actual developmental mechanisms involved.

CONSTANCY AND VARIABILITY IN ISOGENIC INSECT BRAINS

The introductory remarks show that observation of behaviour alone is not sufficient to provide a thorough understanding of its genetic basis. It is also essential to investigate the genetic control of brain development. Due to the bilateral symmetry of insect brains, comparison of the two halves may yield information about the extent of genetic control of brain structure. Genetically, both halves are identical, and environmental factors are also likely to be very similar. Deviations from symmetry are therefore an upper estimate of the effect of developmental noise. At the level of the light microscope, these differences are strikingly small. However, symmetry is strongly influenced by the state of the genome (see below).

Intra- and interclonal comparison of isogenic animals is another way of estimating the relative importance of genetic and non-genetic factors on brain development. Macagno, Lopresti & Levinthal (1973) investigated the visual system of isogenic *Daphnia* by serial ultrathin sections and found that the overall structural pattern was highly invariant; however, the positions of cell bodies and major branching points of axons were variable within a range of a few micrometers. Similar results were obtained by Ward, Thomson, White & Brenner (1975) for *Caenorhabditis*.

In insects, Goodman (1976, 1977, 1979) reported the occurrence of duplications and deletions of large and small identified ocellar interneurones in the locust. Typically, extra cells were indistinguishable, morphologically, from their siblings. Comparison of different clones of isogenic grasshoppers indicated a high specificity of the genetic control of cell number. The occurrence of duplications or deletions in one cluster of cells in a given clone was not correlated with their occurrence in other cell clusters.

The expression of a new phenotype with an increased tendency towards duplications or deletions, was never as stable as the wild-type phenotype in other clones. A random bilateral asymmetry was observed that indicates a substantial contribution of noise to the developmental process. In wild-type animals this is obviously smaller, presumably due to a better concordance of the whole genotype. A similar phenomenon of unstable new phenotypes is observed in some structural brain mutants of *Drosophila* (Heisenberg & Böhl, 1979; Heisenberg, 1980).

The existence of genetically controlled duplications and deletions of neurones is of vital importance for an understanding of brain evolution. One main theme of this review is the parallel organization of brain functions. Duplications of existing neuronal pathways may provide the substrate for later functional differentiation.

Not only number, but also neuronal shape is under tight genetic control. One example is the HS neurones of the dipteran lobula plate (Fig. 1). Hausen (1982) reported that although the dendritic branching pattern may vary considerably between HS neurones (of the left and of the right lobula plates within individual *Calliphora erythrocephala*), the dendritic fields of homologous horizontal neurones are nearly identical, even when neurones of different animals are compared. In addition, the density of dendritic branching seems to be constant. Fig. 1 demonstrates that these parameters are also similar for HS neurones of different species. Furthermore, in *Drosophila*, the similarity of major branching patterns between homologous HS neurones of different animals is conspicuous.

Goodman (1979), using the large ocellar interneurones in different isogenic clones of grasshoppers, found that most clones did not show any morphological abnormality. One clone, however, produced abnormal morphologies in a particular pair of neurones in 88% of all individuals.

Goodman & Heitler (1977) described the effects of genetic variability on the physiology of identified neurones. The spike threshold of the fast extensor tibiae motor neurone (FETi) decreases with increasing temperature (Heitler, Goodman & Rowell, 1977), a factor that correlates with the increase in jumping frequency. Among 30 parthenogenic clones of locust, two showed altered behaviour. In one of these, a low probability of jumping and lack of temperature dependence was accompanied by an abnormal increase with temperature of the spike threshold of the FETi motor neurone. Intraclonal variability was low.

To summarize, we can conclude that number, morphology and physiology of neurones are under genetic control.

STRUCTURAL PLASTICITY OF INSECT BRAINS

In the preceding section, variability in the brain which is not due to genetic factors was classified as 'developmental noise'. In this section, some factors contributing to this component of variability are briefly discussed.

Developmental plasticity

Regulatory cell death is a well-known phenomenon, occurring, for example, in the developing optic lobes of insects (Nordlander & Edwards, 1968; Fischbach & Technau, 1984). It has been assumed that there is an overproduction of neurones which

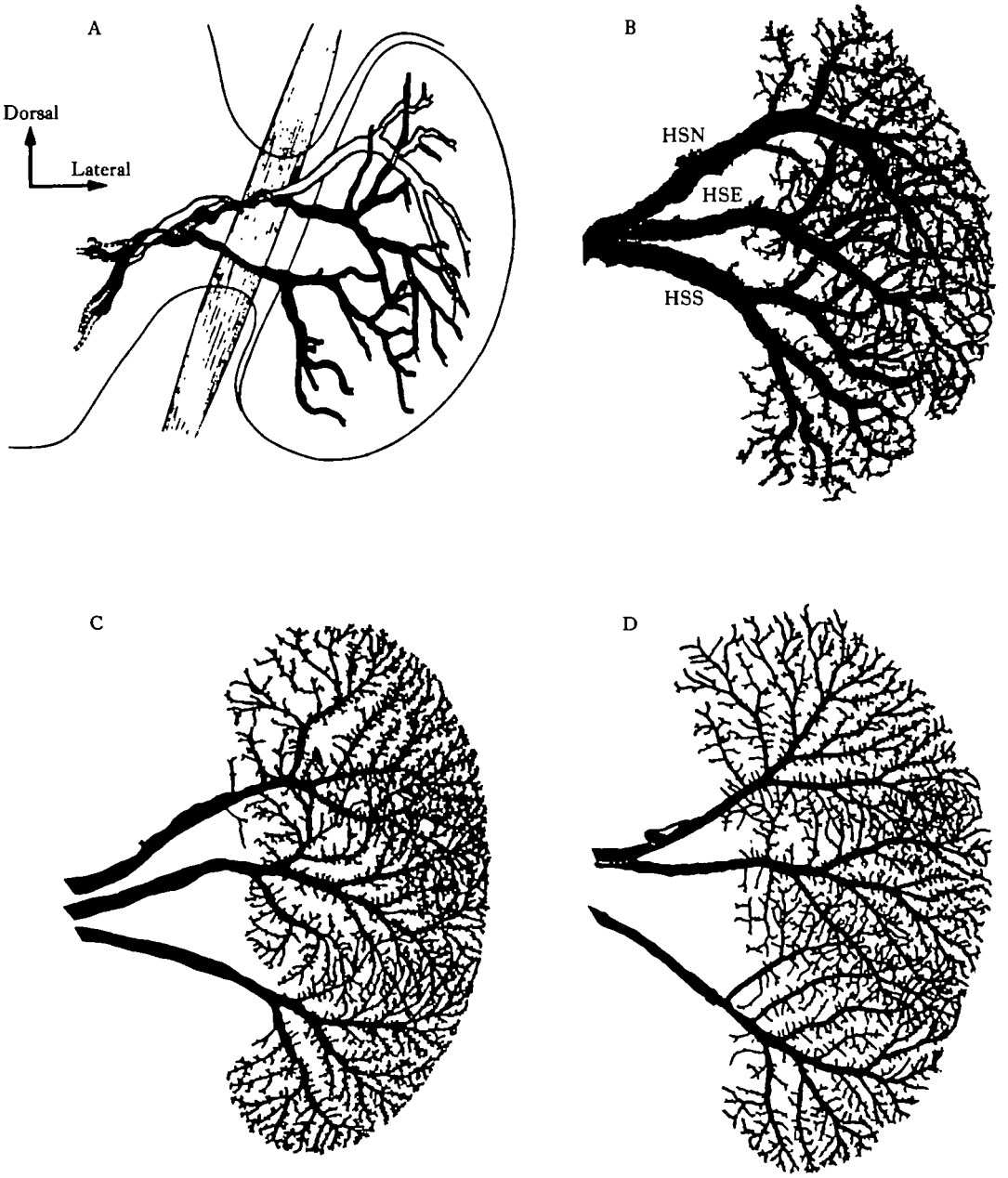


Fig. 1. Dendritic arborizations of the giant horizontal neurones (HS) of the lobula plate of *Drosophila melanogaster* (A,B), *Musca domestica* (C) and *Calliphora erythrocephala* (D) adjusted to about the same size. The two sets of *Drosophila* HS neurones are from different wild-type strains. It is seen that in all three, only distantly related species the number of HS neurones is the same. Furthermore, the north, equatorial and south horizontal cells (HSN, HSE, HSS) have a comparable receptive field organization in all species. Together their dendrites occupy the most frontal layer of the lobula plate. (A) Reconstruction of main dendrites of HS neurones from semithin sections stained with methylene blue (from Heisenberg, Wonneberger & Wolf, 1978). (B) *Camera lucida* drawing of Golgi-stained HS neurones (from Fischbach, 1983*a*). (C),(D) Reconstructions of cobalt-stained HS neurones. (K. Hausen, unpublished and Hausen, 1982).

compete for a limited number of functional contacts. Neurones that lose the competition eventually die. This process (as opposed to programmed cell death) can be regarded as a probabilistic process. This implies that the final outcome (i.e. which cells survive and which die) is not determined by genetic information in the zygote and is not essential for proper functioning of the optic lobes.

Path finding in fibre growth is thought of as a similar probabilistic mechanism. The outgrowth of filopodia from the growth cone is a trial-and-error process (e.g. Johnston & Wessels, 1980), so some minor deviations in axonal projections between isogenic animals can be expected.

Sprouting of neurones in response to experimental (Schneider, 1973; Cotman & Lynch, 1976) or congenital synaptic deprivation (Fischbach, 1983*a*,*b*) reveals epigenetic regulation of the number of functional contacts. The resulting irregular shapes of neurones suggest that the establishment and elimination of new contacts is a selective trial-and-error process.

Experience-dependent structural plasticity

Technau (1984) has shown that the number of axons in the peduncle of the mushroom bodies of *Drosophila melanogaster* changes during adult life. Furthermore, he found that axon number is relatively low after sensory deprivation of adult flies (see Fig. 2). In honey bees, morphological changes of Kenyon cell spines occur during the first orientation flight (Coss & Brandon, 1983). In the coleopteran *Aleochara curtula* (Bieber & Fuldner, 1979) considerable growth of the mushroom bodies occurs during the life-time of the imago. Whether some of these structural changes are related to long-term memory is an open question.

Genetic control of learning ability will be discussed below.

SINGLE GENE ANALYSIS OF NON-SEXUAL BEHAVIOUR

Genetic analysis of brain and behaviour requires the investigation of individual genes. In the last 20 years, a large number of single gene mutations have been isolated in *Drosophila melanogaster* that affect nervous tissue and behaviour. These have recently been comprehensively reviewed by Hall (1982), so that our task here will be to demonstrate, using selected examples, the scope and perspective of single gene analysis.

Jumping behaviour

We begin with a simple motor pattern, the jumping response. This is driven by a pair of giant fibres (GF) which project from the brain through the cervical connective and terminate ipsilaterally in the ventral part of the mesothoracic neuromere (Koto *et al.* 1981). They form an electrical synapse with a motor neurone (TTMm) of the tergotrochanteral jump muscle (TTM; King & Wyman, 1980). Thomas & Wyman (1982) have isolated several X-linked non-jumping mutants with altered physiology and morphology of neurones. One of those, *bendless* (*ben*), lacks the electrical synapse between the GF and the TTMm as seen with anatomical and physiological techniques. In wild-type flies, intracellular stimulation of the GF leads to a TTM

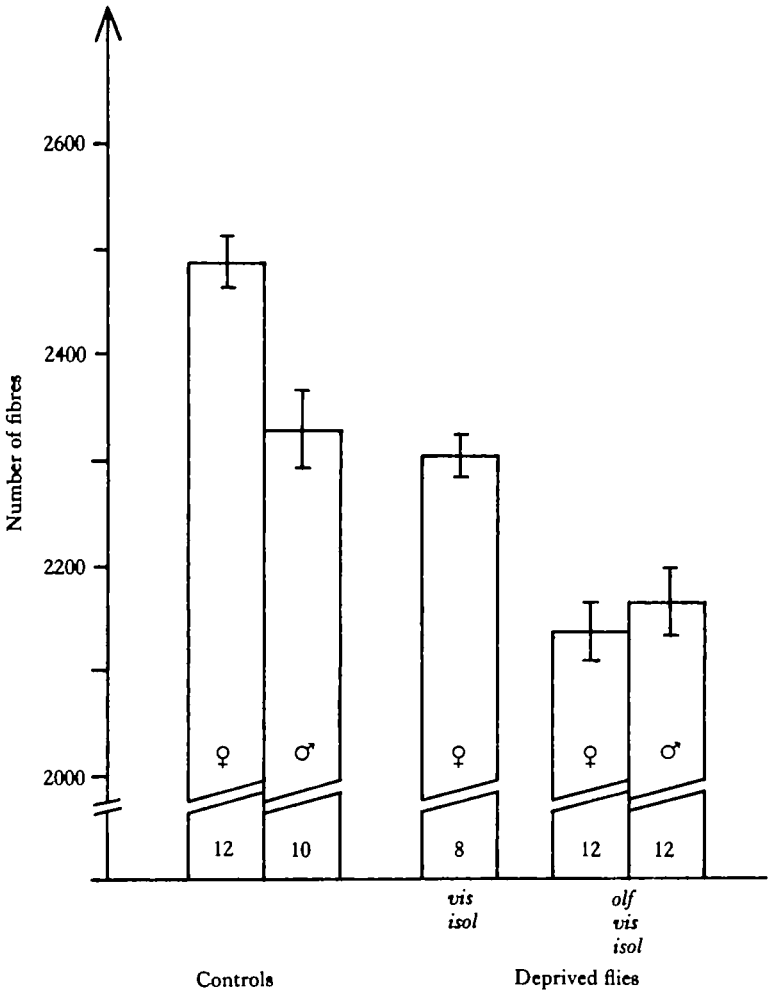


Fig. 2. Fibre counts in cross-sections of the caudal peduncle of adult flies (*Drosophila melanogaster*, wild type '*Berlin*') exposed to environments of different complexity. Flies were kept for 21 days after eclosion either in large cages containing plants and natural odours (Controls) or in social isolation (*isol*) and darkness (*vis*). Some flies were in addition deprived of olfactory and mechanosensory information by amputation of the funiculi and aristae of the antennae (*olf*). The error bars denote the standard deviation of the mean. The numbers refer to the number of flies evaluated respectively (from Technau, 1984). Using a different wild-type strain, Technau (1984) showed that visual deprivation alone has no effect.

response after only 0·8 ms, but in the *ben* mutant the latency is 2·2 ms. The response latencies of other muscles driven by the GF are not different in mutant and wild-type flies.

The specificity of this mutational effect is remarkable. However, it certainly should not reanimate the 'one gene – one synapse' hypothesis. Thomas & Wyman (1982) suggest that the mutation may affect some molecule necessary for recognition between the GF and TTMm. Genetic mosaic analysis should tell whether or not the wild-type

ben gene product is required in the GF or TTMm for proper synapse formation. Obviously, the search for genes specifying parameters for the establishment of connectivity is an exciting prospect.

Visual behaviour

The visual system has been a favourite subject for single gene analysis over the last two decades, and as a result a host of mutations affecting it at different levels has accumulated (66 genes are listed by Hall, 1982, and many additional ones have been isolated since). Recent reviews (Hall & Greenspan, 1979; Heisenberg, 1979; Pak, 1979; Hall, 1982; Heisenberg & Wolf, 1984) have emphasized the value of mutants as tools in vision research. Our main objective here is to extract relevant information about the way the genome instructs the organization of visual functions.

The main anatomical constituents of the 'visual system' are shown in Fig. 3: compound eye, lamina, medulla, lobula, lobula plate and optic foci in the central brain. Not depicted are the ocelli which interact with the processing of visual information mediated by the compound eyes (Fischbach & Reichert, 1978; Miller, Hansen & Stark, 1981). A more detailed account of the cellular structure of the visual system is available (see Fischbach, 1983*a* for *Drosophila* and Strausfeld, 1976 for *Musca*.

Mutations causing total blindness

Total blindness can be caused by disrupting the visual system at different levels. Some mutations interfere with the formation of the compound eyes (e.g. *eyeless, sine oculis*; Power, 1943; Fischbach, 1983*b*; Fischbach & Technau, 1984); others prevent the establishment of connections between the compound eyes and the central brain (*disconnected*; K. F. Fischbach, unpublished; Fig. 11). Blindness also results when mutations disrupt the function or formation of the photoreceptor cells. The normal product of the *no-receptor potential A* (*norpA*) gene is essential for photoreceptor function (Pak & Grabowsky, 1978; Pak, 1979). Some alleles cause a failure to transduce the conformational change of xanthopsin (Vogt, 1983) into a receptor potential.

Mutations in the X-chromosomal gene, *retina degeneration A* (*rdgA*), induce blindness by degeneration of photoreceptors during the first week of adult life. Degeneration seems to be due to a phototransduction defect caused by a block in the synthesis of phosphatidic acid (Hotta, 1984). Alleles may differ in the degree to which they affect receptors R1–6, R7/8 and the ocelli (Harris & Stark, 1977; Homyk, Pye & Pak, 1981; Johnson, Frayer & Stark, 1982).

Mutations causing total blindness are often highly specific insofar as other sensory modalities are not affected.

What follows is a description of some mutants suffering from partial blindness. The point is made that, in most cases 'partial blindness', does not involve attenuation of all functions, but rather elimination or attenuation of specific functions.

Receptor mutants

The ommatidium of a dipteran compound eye contains eight receptor cells which are arranged in a typical pattern. Six receptor cells (R1–6) are situated peripherally, forming unfused rhabdomeres of large diameter which extend from the crystalline

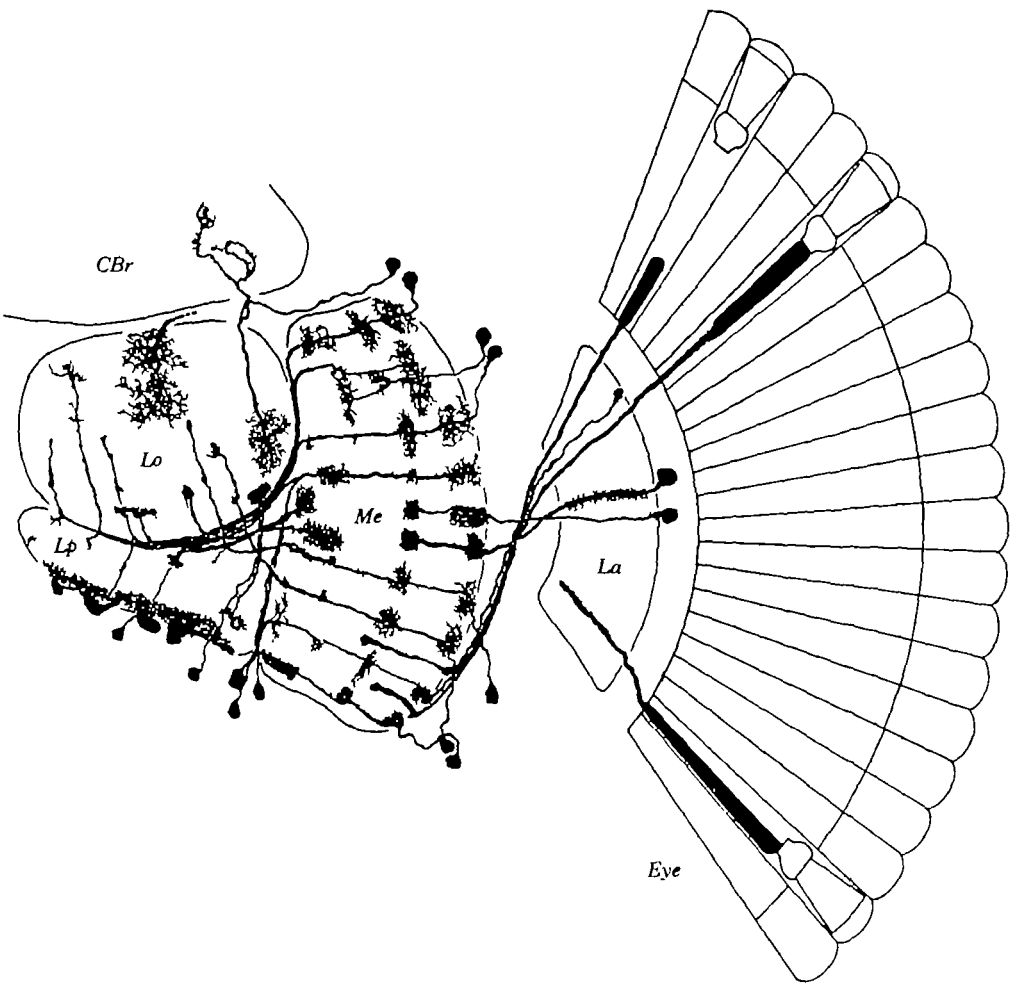


Fig. 3. Eye and optic lobe of *Drosophila melanogaster* with examples of columnar neurones. Retinula cells project from the retina (*Eye*) either into the lamina (*La*) or into the medulla (*Me*). A single medulla column contains many cell types which project in parallel into the lobula (*Lo*) or the lobula plate (*Lp*) or into both. The arborizations of most neurones contribute to only certain layers of medulla, lobula and lobula plate. *CBr*, central brain.

cone to the basal membrane. The central rhabdomere (which is smaller in diameter) is formed distally by receptor R7 and, proximally, by receptor R8. The three receptor types (R1–6, R7, R8) differ in spectral sensitivity (Harris, Stark & Walker, 1976). In the lamina, axons from receptors with identical optical axes converge on so-called 'cartridges' (Braitenberg, 1967; Kirschfeld, 1973). The axons of retinula cells R1–6 terminate in the lamina, while R7 and R8 project into the neuropile of the distal medulla (see Fig. 3).

Several gene mutations specifically affect the different types of receptor cells. The *sevenless*^{LY3} (*sev*) mutation causes non-formation of the R7 retinula cells (Harris *et al.* 1976). It is cell autonomous, i.e. genetically wild-type R7 precursor cells develop normally in otherwise *sev* flies (Campos-Ortega, 1980). The absence of the R7 rhabdomere impairs visual input to retinula cell R8 since the distal end of its rhabdomere lies beyond the focal plane of the corneal lens. The absence of retinula cell R7 should cause a decrease in sensitivity and acuity in visual functions normally mediated by the central rhabdomeres, but Heisenberg & Buchner (1977) have shown that in several responses to visual motion, the *sev* mutant performs as well as the wild-type. Thus retinula cells R7 and R8 do not seem to play any role in movement detection. This observation is corroborated by the behaviour of mutants with defective receptors R1–6.

Outer rhabdomeres absent (*ora*) is probably a structural gene for R1–6 opsin (Schinz, Lo, Larrivee & Pak, 1982). The mutation acts autonomously in receptors R1–6 (Stark, Srygley & Greenberg, 1981) and prevents formation of normal rhabdomeres in receptors 1–6 (Harris *et al.* 1976). The small distal rudiments are depleted of membrane particles (Schinz *et al.* 1982). Accordingly the optomotor yaw responses of *ora* are severely reduced (Heisenberg & Buchner, 1977).

Mutations in the *receptor degeneration B* (*rdgB*) gene cause degeneration of R1–6 receptor cells in response to illumination. The normal gene product is required for phototransduction (Harris & Stark, 1977). Retinula cells R7 and R8 are not affected (Stark, Chen, Johnson & Frayer, 1983). Some *rdgB* flies show no optomotor yaw response, others do (Heisenberg & Buchner, 1977). This behavioural heterogeneity is probably due to variable expression of the mutant defect in individual flies (it should be noted that these behavioural tests are more sensitive than electrophysiological tests for judging the extent of degeneration).

In summary, the observations on receptor mutants strongly support the hypothesis that, in wild-type flies, responses to motion are mainly mediated by receptors R1–6. The mutant analysis also suggests that the central receptor types R7 and R8 function in phototaxis and in colour discrimination (Harris *et al.* 1976; Hu & Stark, 1977; Heisenberg & Buchner, 1977; Fischbach, 1979; Miller *et al.* 1981).

This example of a structural separation of different functions at the level of the retina in *Drosophila* is not an isolated case. Optomotor responses of *Phormia regina* (Kaiser, 1968) and bees (Kaiser & Liske, 1974) are not elicited by moving patterns without intensity contrast. In bees, the spectral sensitivity of the optomotor yaw response corresponds to that of the green receptors, and even in man, colour blindness of certain visual subsystems has been demonstrated (Wolfe, 1983).

Behavioural mutants of the optomotor pathway

Heisenberg (1972) and Heisenberg & Götz (1975) categorized several visual

mutants according to their selective defects in the optomotor yaw response. This behavioural element has been systematically studied over the last three decades (e.g. Reichardt, 1970; Götz, 1968; Heisenberg & Wolf, 1984). The mutants were impaired either in their turning response to movement of narrow stripes in bright light, or to movement of broad stripes in dim light. This observation fitted the notions of a 'low-sensitivity, high-acuity' (HAS) and a 'high-sensitivity, low-acuity' (HSS) system (Eckert, 1971). Later, Heisenberg & Buchner (1977) showed that the optomotor response in dim and bright light is mediated by receptors R1–6 alone (see above); the HAS and HSS systems therefore represent two adaptational states of the R1–6 pathway. Support for this conclusion comes from the observation that in both types of mutants, defects of the lamina potential of the ERG can be observed. Furthermore, in *Musca domestica*, Pick & Buchner (1979) discovered that the distance between the two sampling points of elementary movement detectors increases in dim light, and so at different light intensities different sets of neurones seem to be involved. This may explain the specific defects in the HAS and HSS mutant types.

Structural mutants of the optic lobes

Five examples of structural mutants of the optic lobes will be briefly described below. In these mutants, different, and partially overlapping, sets of visual neurones are defective.

Vacuolar medulla (Vam)

Vacuolar medulla^{KS74} (*Vam*), at present studied by P. Coombe (in preparation), is an X-chromosomal dominant mutation causing degeneration of laminar and medullar cell types. This process begins at eclosion and continues throughout adult life to produce a densely packed array of vacuoles in the distal medulla. In hemizygous males and homozygous females, degeneration becomes apparent during the first few minutes after eclosion, but in heterozygous females, degenerating cell bodies are not visible until at least 1 day after eclosion. With progressing degeneration, the lamina potential in the electroretinogram disappears, as does the optomotor response. However, degeneration obviously does not affect all functional pathways, because certain behaviour patterns persist. The orientation of freely walking *Vam*-flies towards a black vertical stripe (width = 20°) is almost normal. The mutants *ora* and *rdgB* fail in this test. Thus, the orientation response in *Vam* may still be mediated by retinula cells R1–6 *via* a set of non-degenerating lamina interneurones. Electron microscopy of the mutant's lamina should reveal their identity.

Small optic lobes (sol)

While in *Vam*, the optomotor pathway is disrupted, in the mutant *small optic lobes*^{KS58} (*sol*; see Fig. 6) it operates normally (Fischbach & Heisenberg, 1981), although the number of neurones in the medulla and in the lobula complex is reduced to about 50 % by tissue autonomous degeneration of ganglion cells during the first half of pupal development (Fischbach & Technau, 1984). In *sol*, visual acuity is not affected and colour discrimination persists (Fischbach, 1981*a*). For the optomotor yaw response, the light intensity threshold and the upper and lower threshold for contrast

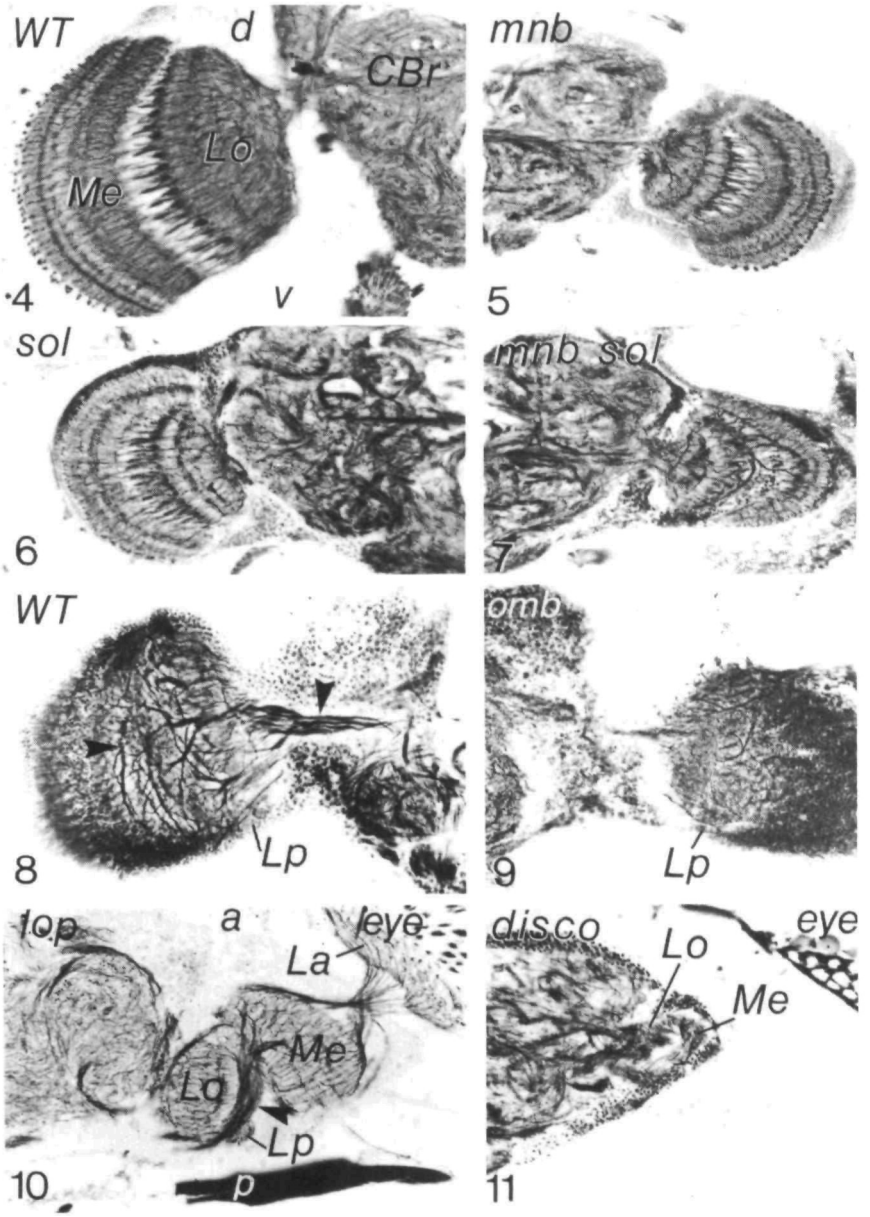
frequency are about normal. Thus, the neuronal network responsible for the optomotor yaw response must be intact in *sol* flies (Fischbach & Heisenberg, 1981). Strong evidence for this conclusion also comes from the relatively normal pattern of radioactive labelling with 2-deoxyglucose (Buchner & Buchner, 1983) in the medulla during responses to movement (Nicod, 1983). The *sol* mutant may, therefore, be of help in identifying the neurones of the optomotor pathway. However, the number of neuronal types in the medulla is very high; in *Musca* it is probably of the order of 120 (Campos-Ortega & Strausfeld, 1972), and in *Drosophila* wild-type 64 types have already been described (Fischbach, 1983*a*). An understanding of this complex structure is facilitated by its organization in columns and layers (see Fig. 3). Evidence for the existence of multiple parallel pathways comes from the distribution of the branching pattern of Golgi-stained neurones; for example, one pathway seems to involve two layers of L1 arborizations in the distal and the most proximal medulla layer. These layers share a large number of interneurones (Fischbach, 1983*a*) and the most proximal medulla layer is the one which is most intimately connected to the lobula plate (e.g. *via* T4 neurones; Fischbach, 1983*a*). In *sol* flies, the 'L1-subsystem' is probably retained. The drastic reduction of cell number per medullar column is mainly explained by the absence of neurones normally participating in the formation of other layers; for example, layer 3 of the medulla, which is closely connected *via* Tm-neurones to deep layers of the lobula, is most reduced in adult *sol* flies (Fischbach, 1983*a*). *sol* flies are impaired in the evaluation of patterns and show a low specificity in the releasing mechanism for landing (Fischbach, 1981*a*). In addition, they are deficient in an object-background discrimination task (Heisenberg & Wolf, 1984) and in several types of visual learning (see below).

Minibrain (mnb) *and the double mutant* mnb sol

The complexity of the optic lobes can be further diminished with the *minibrain mutation* (*mnb*; Fig. 5). This reduces brain volume, including the optic neuropiles (an exception is the lamina), by about 40–50% with a drastic reduction of cell number. As in *sol*, the number of columns in the optic lobes is normal (Heidenreich, 1982) and *mnb* flies still show optomotor yaw and landing responses.

Mutations in different genes often act additively. This may be expected if they act specifically on different subsystems. Examples of such additive effects are given by the double mutants *sev ora* and *rdgB sev* (Harris *et al.* 1976) at the receptor level, and at the level of the optic lobes by *sol so* (Fischbach & Lyly-Hünerberg, 1983) and possibly by *mnb sol* (Fig. 7). The latter double mutant has normal sized eyes and normal sized laminae. Golgi studies have shown that every columnar neurone of the lamina is retained, including C2, C3 and T1, but the volume of the medulla and lobula complex neuropiles is drastically reduced, although still well structured. The lobula plate, especially, is very thin and seems to consist of little more than giant fibres. The extensive sprouting of these giant neurones into the medulla of the double mutant is not seen in *mnb* and *sol* to such an extent. In *mnb sol*, the reduction in the number of input neurones may have reached a threshold which triggers this additional growth. At this level of resolution, the effects of *sol* and *mnb* are synergistic.

Optomotor yaw responses of the double mutant are reduced, but not abolished. Possibly, new functional contacts of the lobula plate giant neurones partially compensate for the loss of normal input neurones.


WT
d
CBr
Lo
Me
v
4
mnb
5
sol
6
mnb sol
7
WT
Lp
8
omb
Lp
9
lop
a
eye
La
Me
Lo
Lp
p
10
disco
Lo
eye
Me
11

Other mutants with reduced optic lobes are being crossed with the double mutant. We hope to end up with an even smaller optic lobe containing a minimal number of cell types. However, sprouting will distort their normal shape.

Optomotor blind (omb)

The HS neurones of the lobula plate (see Fig. 1; Pierantoni, 1973) are part of the optomotor pathway. This hypothesis relies on electrophysiological studies with *Calliphoridae* (review: Hausen, 1981) and on the finding that the behavioural *Drosophila* mutant *optomotor-blind*^{H31} (*omb*) lacks the giant neurones of the lobula plate (compare Figs 8, 9; Heisenberg, Wonneberger & Wolf, 1978; Blondeau & Heisenberg, 1982). It has also been supported by laser ablation experiments with *Musca* (Geiger & Nässel, 1981, 1982) and surgery in *Calliphora* (Hausen & Wehrhahn, 1983). However, a closer inspection of the responses of the *omb* mutant revealed that only the roll response is reduced to zero. Yaw responses in flight range from 20–60 %, depending on the stimulus parameters (Heisenberg & Wolf, 1984). This result is puzzling, since in most mutant flies no anatomical trace of the three HS neurones can be found. Is the loss of these neurones compensated by some developmental mechanism, or is the contribution of a second functional pathway to the turning response revealed by the *omb* defect? The latter seems to be the case for recent advances in the fine analysis of flight control in *Drosophila* (Bülthoff, 1980; Heisenberg & Wolf, 1984) have shown that in wild-type flies two separate functional subsystems contribute to the yaw response. One, the 'classical' optomotor yaw response system, is a large field course control system concerned with flight stabilization against 'involuntary' rotation. It enables a fly to fly straight. It responds equally well to front-to-back and back-to-front motion. The other system responds only to front-to-back movement. In free flight, this movement results from the fly's forward motion in the vicinity of an object. It is called an 'object response' system.

The two systems can be separated in the wild-type under appropriate stimulus conditions. A single vertical black stripe rotating around the fly specifically elicits strong object responses, whereas a homogeneously textured rotating background

---

Fig. 4. Vertical section showing wild-type (*WT*) optic lobe and part of the central brain (*CBr*). *d*, dorsal; *v*, ventral; *Me*, medulla; *Lo*, lobulla. Magnification 140×.

Fig. 5. Same view of a *minibrain* (*mnb*) fly.

Fig. 6. Same view of a *small optic lobes*^{KS58} (*sol*) fly.

Fig. 7. Same view of a *mnb sol* double mutant fly.

Fig. 8. Vertical section showing a wild-type (*WT*) lobula plate (*Lp*) with giant neurones (arrowheads). Magnification 160×.

Fig. 9. Vertical section showing the lobula plate of an *optomotor-blind*^{H31} (*omb*) mutant fly missing the giant neurones. *Lp*, lobula plate. Magnification 160×.

Fig. 10. Horizontal section through compound eye and optic lobe of a *lobula plate-less*^{N684} (*lop*) mutant fly. The lobula plate (*Lp*) is drastically reduced and an ectopic bundle of giant fibres (arrowhead) projects through the inner optic chiasma into the medulla. *a*, anterior; *p*, posterior; *Lo*, lobula; *Me*, medulla; *La*, lamina. Magnification 140×.

Fig. 11. Vertical section through the head of a *disconnected*^{HK2472} (*disco*) mutant fly showing tiny rudiments of medulla (*Me*) and lobula (*Lo*) which still contain tangential neurones. All columnar cell types are missing. Maybe as a consequence, the retinula cell axons make no contact with the rudiment. (K. F. Fischbach, in preparation). Magnification 140×.

stimulates the large field course control system only (Heisenberg & Wolf, 1984). In the mutant *omb*, large field course control is blocked, but the object response is close to normal (Heisenberg & Wolf, 1984). Therefore, the remaining yaw responses are not due to compensatory mechanisms, but to a different functional pathway. The object response does not require the HS neurones, it even uses other elementary movement detectors than the large field course control system (Bausenwein, 1984).

Lobula plate-less (lop)

The above conclusions are supported by results from a second mutant with a defective lobula plate which is called *lobula plate-less*^{N684} (*lop*; Fig. 10). In this mutant, most columnar neurones of the lobula plate are missing due to their selective degeneration in the first half of pupal life. As a result, only a small rudiment of the lobula plate is present in the adult, but it still contains TmY-cell terminals and a few T4 and T5 neurones (Fischbach, 1983*a*). The shortage of presynaptic columnar neurones in the lobula plate has a dramatic effect on what presumably are the VS cells and some other neurones of large diameter. They project in a thick bundle through the second optic chiasma into the upper frontal medulla (Fischbach, 1983*a*; see Fig. 10).

In *lop* there is no response to roll and pitch (Paschma, 1982). The abnormal growth of the VS neurones, which are thought to mediate the roll response in the wild-type, probably does not compensate for the lack of a normal input. However, *lop* flies still show significant optomotor yaw responses (Paschma, 1982). The object response does not account for all of it. Large field course control is reduced, but still operates. This may be explained by the presence of the small lobula plate rudiment which still contains the main HS dendrites (Paschma, 1982).

Chemosensory behaviour

Single gene analysis of chemosensory behaviour has been hampered by the limited knowledge about the general organization of olfaction and taste in insects. The naive concept of such behaviour being a press-button mechanism (sugar-reception – proboscis extension), ignores the problems in evaluating quality and quantity in mixtures of chemicals. Thus, progress from the genetic point of view has largely been confined to the receptor level.

Taste

The problem of how to obtain taste mutants has been elegantly solved. Differential feeding on two food sources is conveniently monitored with food-dyes which after ingestion can be seen in living flies (Falk & Atidia, 1975; Tanimura & Shimada, 1981). Again we will not give a detailed description of the various mutants and their phenotypes, but will instead mention two examples which highlight the manner in which differential gene expression specifies neural cell types.

It has been learned from mutant analysis in *Drosophila* that every sugar receptor cell in the labellar setae contains at least three different sugar receptor molecules. Two mutants have been found in which the sugar cells have reduced sensitivity to pyranose sugars (e.g. sucrose, glucose) while responding normally to fructose, trehalose and

other sugars (Isono & Kikuchi, 1974; Siddiqi & Rodrigues, 1980). A putative structural gene for the second receptor, trehalose, has recently been isolated by Tanimura (1984). The third receptor, the one for fructose, can be specifically eliminated by treatment with papain or trypsin. Obviously, *Drosophila* would be able to distinguish between these sugars, if the genes for the three receptors were expressed in different cells. Such a distinction, however, seems to be of no particular advantage for the fly.

The mutant *gust B* originally was thought to have a reduced salt sensitivity (Rodrigues & Siddiqi, 1978), but recently *gust B* flies have been shown to be attracted by salt (instead of being repelled as is wild-type). In a search for an explanation, Arora & Rodrigues (1983) found that in the setae of this mutant both the salt and the sugar receptor cells show sensitivity to salt. This observation suggests that in *gust* B the gene responsible for salt sensitivity is expressed in the wrong cell type. This emphasizes the importance of differential gene expression for behaviour.

Olfaction

Olfactory neurogenetics of *Drosophila* has recently been summarized by Siddiqi (1984). Mutants with specific anosmias have been reported, but so far none of them have been shown to be affected in the structural gene of a receptor protein. The closest may be the mutant *olf C*. In flies of this strain, there is a reduced response to acetate esters, but normal responses to alcohols or aldehydes. However, it remains to be determined whether this reflects the presence of several genetically independent acetate receptors in the wild-type, as has been proposed by Siddiqi (1984) on the basis of single unit recording in the antenna, or whether the *olf C* allele is a hypomorph. A broad screen for specific anosmias combined with more refined genetic and physiological tests (e.g. Borst, 1984; Siddiqi, 1984) could determine the number of receptor cell types, the number of different receptor molecules, and their distribution in the sensory cells. This information would be valuable for investigating olfactory behaviour.

Biological oscillations

The most interesting result emerging from the mutant analysis of biological oscillations is that the mechanisms of long- (e.g. circadian rhythms) and short-term oscillations (e.g. courtship song) share certain components. By now five genes are known which influence the period length of both.

Konopka & Benzer (1971) isolated three alleles of the *period* (*per*) gene which either shorten (per^s), lengthen (per^l) or abolish (per^o) the oscillation period. Homozygous per^o animals have a reduced synthesis of octopamine due to a decreased concentration of tyrosine decarboxylase (Livingstone, 1981). The concentration of this enzyme in per^o, however, is not zero. This and the fact that heterozygous $per^o/+$ females have wild-type enzyme levels is taken as evidence against tyrosine decarboxylase being the gene product of per^+. One hypothesis is that the *per* gene may interfere with the development of octopamine synthesizing neurones. per^o flies show scattering of certain neurosecretory cells in ectopic positions (Konopka & Wells, 1980). An involvement of neurosecretion is also suggested by transplantation experiments (Handler & Konopka, 1979). Implantation of per^s brains into the abdomen of per^o adults sometimes leads to the establishment of a periodicity characteristic of the donor.

Kyriacou & Hall (1980) discovered that the period of the short-term oscillations in the courtship song of male flies is affected by the *per* locus in much the same way as the circadian rhythm. Preliminary results from mosaic studies indicate that expression of the per^+ allele in the brain is required for the normal circadian rhythm, while expression in the thoracic ganglion is required for the normal courtship song to occur (Hall, 1984).

Genetic coupling of the period of the song and circadian rhythm is also revealed by mutations in the *phase-angle-2* (*psi-2*), *phase-angle-3* (*psi-3*) and *gat* genes (Jackson, 1983; Kyriacou & Jackson as cited in Hall, 1984) and in the *CLK* gene (Konopka, 1984). However, at least one gene (*Andante*; Konopka, 1984) is known to affect the period length of the circadian rhythm, but not the song cycle (Zehring & Hall as cited in Hall, 1984). This important finding shows that the overlap in the set of molecular components between the circadian rhythm and the song cycle is not complete.

It should be noted that parameters of biological oscillations can be changed without serious pleiotropic effects in other functions of the organism, e.g. deletions of the *per* gene are not lethal (Young & Judd, 1978; Smith & Konopka, 1981).

Learning

Single gene mutations affecting learning in *Drosophila melanogaster* are now numerous and may be categorized as 'biochemical' or 'structural'.

'Biochemical' learning mutants

Associative and non-associative learning (the latter comprising habituation and sensitization) probably use common biochemical mechanisms (Hawkins & Kandel, 1984). The work of Kandel and co-workers with the mollusc *Aplysia* has shown that habituation is correlated with a decrease of transmitter release of the habituating synapse. Such a synapse can be sensitized by a heterosynaptic pathway which may use serotonin as a transmitter. Serotonin activates the serotonin receptor which in turn stimulates adenylate cyclase. The subsequent increase in the level of cAMP activates a protein kinase which closes a K^+ channel by phosphorylation. The decrease in the number of K^+ channels results in a broadening of action potentials which in turn allows more Ca^{2+} to enter. The resulting high Ca^{2+} concentration causes more transmitter to be released per action potential.

According to Hawkins & Kandel (1984), classical conditioning is an extension of sensitization (conditioned sensitization). This requires that the adenylate cyclase is not only activated *via* the serotonin receptor, but also by Ca^{2+}. If this is the case, simultaneous stimulation of the heterosynaptic sensitizing pathway and the primary pathway would result in a synergistic effect yielding high amounts of cAMP. This then causes long-lasting changes in membrane properties.

The isolation of learning and memory mutants in *Drosophila* (Dudai *et al.* 1976; Quinn, Sziber & Booker, 1979; Aceves-Pina & Quinn, 1979; Tempel & Quinn, 1980) and the finding that several of them show defects of enzymes playing a role in the basic '*Aplysia*-model' of learning (Byers, Davis & Kiger, 1981; Shotwell & Konopka, 1982; Livingstone, Sziber & Quinn, 1982; Uzzan & Dudai, 1982) has strengthened the hypothesis that basic learning mechanisms may be the same throughout the animal kingdom (Quinn, 1984). Furthermore, mutants in *Drosophila* may be used

to demonstrate coupling between non-associative learning and associative learning mechanisms, and to answer the question whether different molecular mechanisms may coexist for a given form of learning.

Duerr & Quinn (1982) tested habituation and sensitization of the proboscis extension reflex to tarsal stimulation in the mutants *dunce, turnip, rutabaga* and *amnesiac*. *dunce* is the structural gene for the phosphodiesterase II which normally degrades cAMP (Kauvar, 1982); *turnip* blocks the serotonin receptor (Smith as cited in Quinn, 1984), whereas *rutabaga* shows decreased adenylate cyclase activity (Livingstone *et al.* 1982). In *amnesiac* flies the level of adenylate cyclase activity in membrane fractions is higher than normal (Uzzan & Dudai, 1982). The results of Duerr & Quinn (1982) suggest that these mutants, which were selected in associative olfactory learning paradigms, also tend to be defective in habituation and sensitization of the proboscis extension reflex. The mutants *dunce, turnip* and *rutabaga* habituate more slowly than wild-type, while sensitization wanes much more rapidly in *dunce* and *rutabaga* flies. In *amnesiac* flies there is an increased threshold for elicitation of the proboscis extension reflex.

Kyriacou & Hall (1984) report that *dunce* and *rutabaga* mutants are deficient in what is probably an acoustic sensitization: receptivity of wild-type females is enhanced for some minutes by artificial courtship songs. This does not occur in mutant females. Sensitization wanes much faster than in wild-type. The genetic connection between associative and non-associative learning and the possible applicability of the '*Aplysia*-model' in *Drosophila* is exciting, but is the basic molecular mechanism of learning really as general as suggested by these experiments?

A comparison of the mutants in olfactory and visual learning behaviour seems to indicate a qualitative difference. While learning of *dunce* mutants in the original olfactory learning paradigm (Dudai *et al.* 1976) is close to zero, the $dunce^1$ and $dunce^2$ mutants have been found to learn normally in a visual learning paradigm (Dudai & Bicker, 1978). Folkers (1982) reports a decreased, but still highly significant learning of $dunce^1$ in the same visual paradigm. She also tested *amnesiac, turnip* and *rutabaga*, and found them all able to learn, although not as well as the wild type *Canton-S*. In addition, *amnesiac*, originally characterized as a 'memory mutant' (Quinn *et al.* 1979), remembers in the visual test as well as the wild-type (Folkers, 1982).

The 'biochemical' learning and memory mutants have also been tested in a visual paradigm for habituation and sensitization. The landing response of stationary flying *Drosophila* to visual stimuli habituates readily and can be sensitized, e.g. by actual landing (Fischbach, 1981*b*). The landing response to unilateral front-to-back motion is also sensitized for some seconds by contralateral stimuli ('contralateral sensitization'; Fischbach, 1981*b*). The most apparent effect of the *amnesiac, dunce* and *rutabaga* mutations (*turnip* flies did not fly) on the landing response is a dramatic, stimulus specific decrease in excitability (Fig. 12), not a change in its plasticity. Habituation is about normal in the mutants and contralateral sensitization in *rutabaga* and *dunce* flies is neither impaired in its amplitude nor in its time course, although the basic level of responsiveness to front-to-back motion is low in these strains. *amnesiac* flies could not be tested due to their low overall responsiveness (Fischbach, 1983*a*).

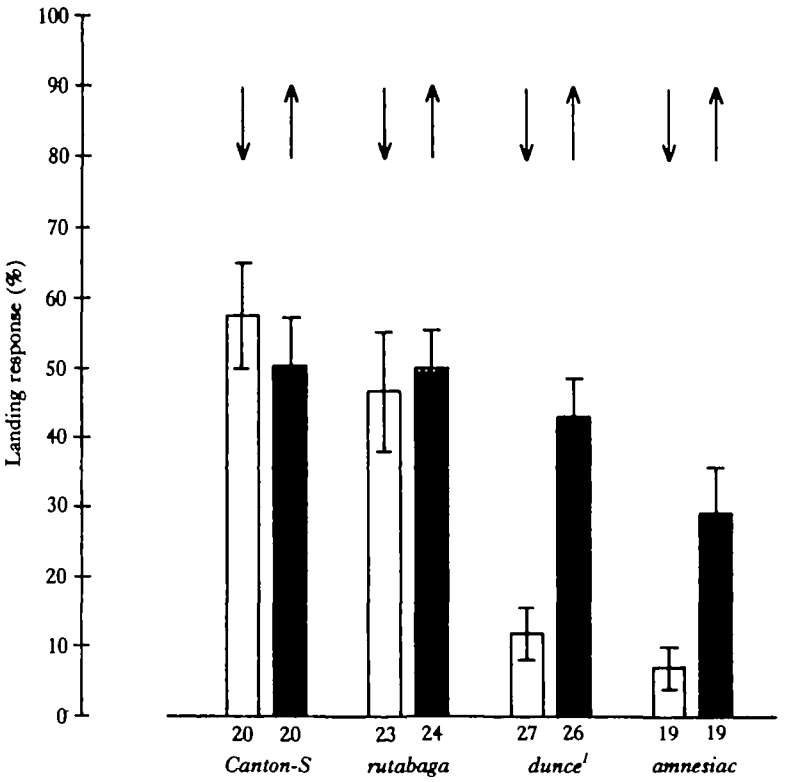


Fig. 12. Mean frequency of landing response of stationary flying flies to the first 16 stimuli presented on the screen of an oscilloscope (upward or downward movement of a dark horizontal stripe as indicated by the arrows). Wild-type *Canton-S* and *rutabaga* flies do not show a significant difference between the two modes of stimulation. However, the response frequency to downward movement is specifically decreased in flies carrying the *dunce*^{1} or the *amnesiac* mutation (Fischbach, 1983*a*). Error bars denote the standard deviation of the mean of the responses of *N* flies (number given at the bottom of each bar).

These results suggest that visual associative and non-associative conditioning may use special mechanisms. 'Contralateral sensitization', for instance, may not change the 'central excitatory state' (Dethier, 1976). It rather may be a property of the detector system for relative retinal expansion signalling the 'time to collision' with an object (Wagner, 1982). The low excitability of the mutants in only certain visual pathways might indicate biochemical differentiation of separate channels of visual information processing.

'Structural' learning mutants

Irrespective of whether one or several molecular mechanisms will be found to underly learning and short-term memory, it is apparent from the work on molluscs and flies that learning and memory are properties of specific behaviour patterns. This point is clearly made by structural brain mutants. Mutants with different structural impairments in the brain have specific learning defects in different behavioural tasks.

Mutants with reduced mushroom bodies are all deficient in olfactory discrimination learning (M. Heisenberg, in preparation). One of them, the mutant *mushroom bodies*

deranged^{KS65} (*mbd*) has normal colour discrimination learning and normal visuo-motor coordination learning (Heisenberg & Wolf, 1984). The structural learning mutants are not insensitive to the conditioned (odours) and unconditioned stimuli (sugar, electric shock). The mutants, *mbd* and *mushroom body miniature*^{N337} (*mbm*) for instance, are able to perceive and distinguish the odours in the same situations in which they fail to learn. Thus, odour perception and evaluation can be genetically separated from learning of the same odours. Mushroom bodies are not necessary for the first task but are required for the second. These functions, therefore, also seem to be structurally separated. A conspicuous anatomical feature of the olfactory system is that the output fibres of the antennal lobes, which project through the antenno-glomerular tract, bifurcate in the dorsal brain sending terminals into the calyx of the mushroom bodies and into the lateral protocerebrum (Heisenberg, 1980; A. Borst & K. F. Fischbach, in preparation). The first projection area may be involved in learning, the latter in immediate evaluation and behaviour.

Mutants with structural defects in the visual system perform well in the olfactory learning paradigm. For instance, the *sol* mutant (see above) learns almost as well as the wild-type in the olfactory tasks, but is severely impaired in visuo-motor coordination learning (Götz, 1983; Heisenberg & Wolf, 1984) and in habituation and sensitization of the landing response. While habituation is slowed down, sensitization wanes unusually quickly (Fischbach, 1983*a*). This is comparable to the effects of the *dunce* and *rutabaga* mutations on habituation and sensitization of the proboscis extension reflex (see above).

The mutants indicate that behavioural plasticity needs to be understood not only at the biochemical level but also at the structural level. Several questions remain to be answered; for example, what is the relationship of the missing neurones to learning performance? What is the extent of the structural separation of 'learning' from primary information processing of sensory information?

SEXUAL DIMORPHISM OF BRAIN STRUCTURE AND BEHAVIOUR

The two genders of a species normally show genetically determined differences in behaviour and often also in brain structure. Striking examples are known in a variety of insects, but only in *Drosophila* is the underlying genetic control beginning to emerge. Aside from courtship, copulation and egg-laying, behavioural differences between males and females in *Drosophila* are small. A large variety of laboratory tests for visual, olfactory and learning performance, some of which have been mentioned above, give very similar results for males and females. Accordingly, the vast majority of known genes of neurological interest are expressed in both genders. Thus, concerning only a subset of genes and a few items of the behavioural repertoire, sexual differentiation may be of particular interest for studying the relation between genes and behaviour.

Neural representation of sex-specific behaviour

Is sex-specific behaviour mediated by specified neural pathways or is it mainly due to (e.g. neurohumoral) modulation of brain function? Extending the view beyond

Drosophila one finds ample evidence for the first proposal. Sexual dimorphisms in sensory organs, brain structure and musculature are very common. A thoroughly investigated example is the visual system of some flies. Male *Musca* and *Calliphora* catch their mates in flight. They exhibit a special chasing behaviour in which they follow small dark objects from below (Wehrhahn, Poggio & Bülthoff, 1982). This male-specific behaviour has a structural correlate. Female and most of the male ommatidia contain the typical pattern of large peripheral and small central rhabdomeres as explained above for *Drosophila*. In the dorso-frontal region of the male eye, the ommatidia are different: R7 rhabdomeres are of similar diameter and have the same spectral sensitivity as R1–6 (Hardie, Franceschini, Ribi & Kirschfeld, 1981; Franceschini, Hardie, Ribi & Kirschfeld, 1981).

Apart from this specialization in the eye, there is also a male-specific differentiation in the visual neuropile. The R7 axons of the male-specific region terminate in the lamina (Franceschini *et al.* 1981; Hardie, 1983) rather than in the medulla. Furthermore, in the lobula, certain giant neurones covering the projection area of the dorso-frontal eye region are found in males and not in females (Strausfeld, 1980; Hausen & Strausfeld, 1980). Thus chasing behaviour of males probably is mediated by a special circuitry in the optic lobes. Apparently, colour vision in the dorso-frontal part of the visual field is sacrificed for optimal contrast sensitivity so that the distance at which a female can be detected is increased. Whether this network is a modification of a homologous network in the female, or whether it uses additional neurones is not known.

In *Bibionidae*, the sexual dimorphism in the visual system is carried to an extreme. Males have large dorsal compound eyes which are not present in females. These eyes do not mediate visual course control (as the ventral eyes do) but seem to be specialized for the detection of small dark objects in the sky (Zeil, 1983*a*,*b*).

Another example of sexually dimorphic circuitry in the central nervous system is the antennal lobes of male moths. The antennae of many male moths have a large number of pheromone receptors which send their axons to one large glomerulus (macroglomerular complex, MGC; e.g. Rospars, 1983). Several male-specific neurone types innervating the MGC have been identified (Boeckh & Boeckh, 1979; Matsumoto & Hildebrand, 1981). As in the dipteran eye, these antennal and neural specializations of the male serve to detect the female at the largest possible distance (for review see Bell & Tobin, 1982). A male antenna can grow in an otherwise female organism, if a male imaginal disk is transplanted into a female larva. The transplant induces growth of an MGC and of identified male-specific interneurones innervating it (Schneidermann, Matsumoto & Hildebrand, 1982). What is even more surprising is that in adult moths, the transplant gives rise to the male-specific up-wind flight response elicited by female pheromones (J. G. Hildebrand, personal communication).

In the central brain, sexual dimorphisms are expressed in the size of particular structural subunits. For instance, the mushroom bodies of worker bees are considerably larger than those of the drones. The behavioural correlate of this particular difference is not obvious but may involve learning (Menzel, Erber & Masuhr, 1974). The sexual dimorphism of mushroom bodies in *Drosophila* is not as obvious as in bees, but it can be uncovered by certain mutations (see below).

Genes affecting sexual differentiation

It has long been known that sex in *Drosophila* ultimately depends upon the X: autosome (X: A) ratio. In recent years a set of at least five regulatory genes which are controlled by the X: A ratio have been described. Like a complicated switch, these genes in turn control the whole battery of genes responsible for the expression of male or female traits (Baker & Ridge, 1980). For example, three female-specific genes that code for yoke proteins are regulated at the transcriptional level (Baker, 1984). With respect to behaviour and brain structure, only few, if any, of these effector genes have been studied (Hall, 1981) and their mode of regulation is not known.

J. M. Belote & B. S. Baker (personal communication) observed that the whole male courtship sequence in *Drosophila* can be induced by a temperature shift in adult flies carrying a temperature-sensitive allele of one of the regulatory genes (*transformer-2^{ts1}*; Belote & Baker, 1982). Chromosomally female (XX) *tra-2^{ts1}* flies grown at low temperature (16 °C) emerge from the pupa as male-like intersexes which, however, do not display male courtship. After 1 week at high temperature (29 °C), 30 % of the flies begin to behave like males. It is possible that in these flies the ventral ganglion was structurally reorganized. Alternatively, a pre-existing circuitry may merely have been switched on by the lack of functional *tra-2* gene product.

The identification of genes responsible for the expression of sexual dimorphisms in the central nervous system (CNS) would be most valuable. Unfortunately, in *Drosophila* the only known structural difference in the CNS between the two genders is the size of the mushroom bodies, which in the female contains about 8 % more Kenyon cell fibres than in the male (see Fig. 2). However, in the mutant *mbm* (see above) most of the female mushroom body degenerates in late second- or early third-instar larvae. Thus, in *mbm*, the male flies have mushroom bodies which appear to be normal whereas in females this structure is missing or unusually small (M. Heisenberg, in preparation). This finding suggests that the degree of sexual dimorphism of mushroom bodies in *Drosophila* is higher than apparent from their gross structural appearance and that the *mbm* gene is essential for their female expression. It is not clear whether *mbm* is expressed in one gender only or in both, nor is it known in which cells and at which time of development the gene is expressed. In principle such questions can now be answered with the help of molecular genetics.

BASTARDIZATION EXPERIMENTS

An intriguing problem in neurogenetics is the question of how presumably homologous, but recognizably different behavioural subroutines and neuronal networks of different species are expressed in their hybrid offspring. Rarely will the interspecific differences under study be due to differences in only one or a few genes (one such case seems to be the difference in courtship songs of *Drosophila melanogaster* and *D. simulans*, which map solely to the X-chromosome, Kyriacou & Hall, as cited in Hall, 1984). But bastardization experiments may illuminate aspects of the genotype-phenotype relationship not assessed by the single gene approach. An interesting example is the acoustic communication system of grasshoppers (von Helversen, 1975*a,b*): The courtship songs of two species, *Chorthippus biguttulus* and

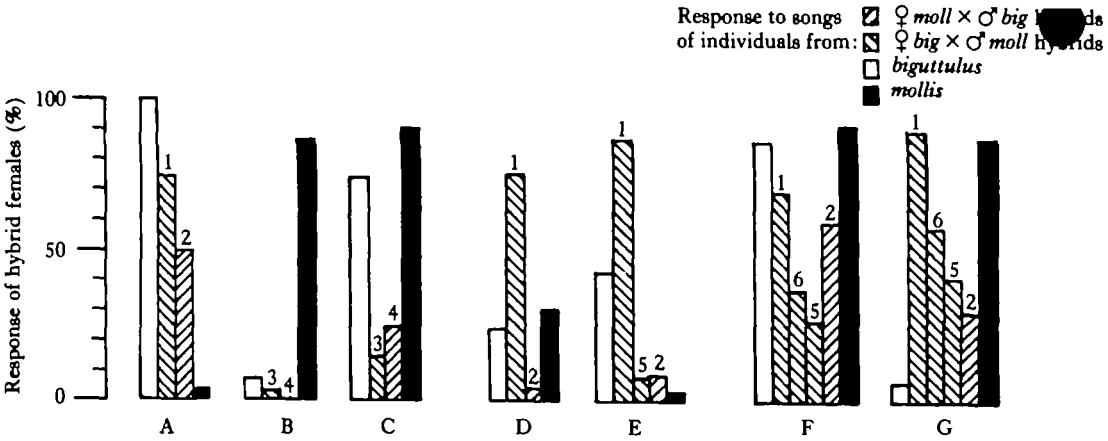


Fig. 13. Response frequency of individual female hybrid grasshoppers (A–G) to songs of different hybrid males (1–6) and males of the parental species (redrawn from von Helversen, 1975*b*). Note the variability between male hybrid songs which is displayed in the response pattern of single hybrid females. The latter as well varies between females.

Ch. mollis, are distinguished by number, length and sequence of pattern elements. The songs and their recognition by females normally prevent bastardization, but mating under laboratory condition can produce vital hybrids. Analysis of the song pattern of individual hybrids showed that some pattern elements were intermediate between the parental ones, whilst others were more-or-less independently superimposed. The authors proposed that to 'some extent independent pattern-generating neuronal networks may be formed during ontogeny, corresponding to the species-specific information of the two parental genomes' (von Helversen, 1975*a*). A similar result was obtained with the song-specific innate releasing mechanism of females. Hybrid females normally answer only weakly to the song of their hybrid brothers, preferring both or one parental song (Fig. 13). Therefore, their innate releasing mechanism is not intermediate. In some hybrid females both parental releasing mechanisms seem to exist in parallel.

Hybrid female individuals differ in their preference for the parental songs and also in their own song pattern. Interestingly, there is no correlation between their own song pattern and their song preference. Therefore, a functional coupling between song pattern and innate releasing mechanism does not exist in grasshoppers (von Helversen, 1975*b*).

However, Hoy (1974) and Hoy, Hahn & Paul (1977) report that in hybrids of *Teleogryllus commodus* and *T. oceanicus*, the F1 females respond best to the hybrid song of F1 males. They therefore postulate a genetic coupling between sender and receiver.

It would be fascinating to complement the results of such bastardization experiments with neurostructural and physiological data.

CONCLUSIONS

It is generally agreed that genetics provides useful tools for the analysis of neurobiological and developmental problems. However, the genetic guidance of brain

development has not been as generally accepted. For example, G. Stent (in Gerhard *et al.* 1982) states: '. . . the genetic approach to development resembles the quantum mechanical approach to genetics that had some vogue in the 1930s and 1940s'. It seems necessary to point to the simple fact that diversification of phenotypes during evolution is achieved by modifications at the genomic level. This implies that the state of the genome controls the invariances of the developmental process. One aim of developmental biology is to understand how the genetic information is used at different stages of epigenesis.

The present paper has reviewed studies about genetic control of brain structure and function in insects. Two general principles emerging will now be discussed.

Peripheral splitting of functional pathways and independent genetic modification of functions

The organization of brains does not only reflect functional aspects. Severe constraints are imposed by evolutionary change. For example, often modification of only certain functions is of selective advantage. Therefore, functional subsystems are – at least to some degree – under independent genetic control. This – besides function – limits the number of possible solutions for the design of a brain. It favours a parallel organization.

The notion of a genetic and structural separation of functional subsystems seems to be trivial as far as different sensory modalities are considered. Therefore, we may concentrate our discussion on the extent of the parallel organization of the visual system of insects. 'Parallel organization' in our context does not refer to the multiplicity of receptor inputs and the retinotopic organization of the optic ganglia. 'Parallel organization of functions' means peripheral separation of information processing channels, and is reflected in the multiplicity of neurones inside single visual columns and is related to the formation of layers in the optic ganglia (Fischbach, 1983*a*; Buchner & Buchner, 1984). Structural separation of visual functions begins at the receptor level. Trivial examples are those where different regions of the visual field serve different functions, e.g. the dorsal eye region of many insects is specialized for the perception of u.v. light (reviewed by Wehner, 1981), or chasing behaviour of male *Musca* relies on its specialized dorso-frontal eye region (Franceschini *et al.* 1981). But separation of functions can also take place at the receptor level when the functions subserve the same part of the visual field. We have seen, for example, that movement detection in bees and flies uses only one receptor type, while colour vision uses all.

Mutants of *Drosophila* have also shown that different visual functions relying on movement detection are separated at the neuronal level (e.g. landing response, large field course control and object response). In this context it is of interest to mention that the large field course control system is in principle able to mediate a response towards objects (Poggio, Reichart & Hausen, 1981), and *vice versa*, the object response system is not blind to large field movements (Heisenberg & Wolf, 1984). The formation of apparently redundant parallel subsystems probably secures optimal genetic modulation of the respective functions. The visual system is not a single 'parallel computer' with different context dependent states. It consists of several, structurally distinct information processing subsystems which are retinotopically organized.

This emerging picture of the organization of the visual system is partly derived from studies of visual mutants. In many cases, these have indicated for the first time a separation of certain functional pathways. Retrospectively, we notice that it is the parallel organization of functions which enables specific mutations.

Differential gene expression and specification of cell types

The insect nervous system and its organization into functional pathways requires an abundance of neuronal cell types characterized by their connectivity and physiology. The differentiation of neurones involves gene regulation. Different sets of genes are expressed in different neurones. This is obvious for sensory neurones (e.g. the trehalose receptor molecule in the sugar receptor or the opsin in retinula cells) and for neurone-specific transmitter metabolism (not discussed in this review, but see for instance Hall, 1982). Impairment of certain neurone types can be due to mutations in the structural gene specifying a certain (neuronal) function and in regulatory genes which specify the 'tissue address' for a structural gene. A possible example for the latter case is the *gust B* mutation which causes salt sensitivity to be expressed in sugar receptors (see above).

So far, in none of the structural brain mutants discussed has the primary gene product of the wild-type allele and its role in brain development been identified. Many of them lead to degeneration of ganglion cells, a process which in the case of the *sol* mutant has been shown to be tissue- (most probably cell-) autonomous (Fischbach & Technau, 1984). Here, the final differentiation of neuronal types seems to be affected. Other mutants (e.g. *omb*) are presumably cell lineage mutants similar to those isolated in *Caenorhabditis* (Sulston & Horvitz, 1981). They may help to identify the genetic basis of the progressive determination of cell types during development.

Genetic control of behaviour?

This review has emphasized that brain development and neuronal functions are under tight genetic control. It may thus be justifiable to speak of genetic control of behaviour. However, we propose not to use this term, as it is easily misunderstood. In any behavioural situation, organisms are not puppets on genetic strings. Genes do not control actual behaviour. Once a brain has developed, it generates behaviour. Genetic functions are still required, but now control is rather the other way around: expression of certain genes may well depend on what is perceived and learned or done by the organism.

We are grateful to Drs A. Borst, E. Buchner, P. Coombe and H. Mariath for discussions and critical reading of the manuscript. C. R. Götz and A. Dittrich prepared the figures and contributed much to the working atmosphere. We also thank H. Karwath, G. Kruschel, C. R. Götz, M. Weltner, D. Richter and G. Schäflein for participating in our screens for structural brain mutants. The reconstructions of the HS cells of *Musca* and *Calliphora* are a kind gift of Dr K. Hausen. The work of the authors was supported by the DFG Grants Fi 336/1-3 and He 986/5-3.

REFERENCES

ACEVES-PINA, E. O. & QUINN, W. G. (1979). Learning in normal and mutant *Drosophila* larvae. *Science, N.Y.* **206**, 93–96.

ARORA, K. & RODRIGUES, V. (1983). Reversal of chemosensory response in a mutant of *Drosophila* attracted by salts. In *Abstracts of Contributed Papers*, Part I. XV International Congress of Genetics, New Delhi India 1983, (ed. M. S. Swaminathan), pp. 71. New Delhi, Bombay, Calcutta: Oxford & IBH Publishing Co.

BAKER, B. S. (1984). Sex determination in *Drosophila*. In *Plenary Symposia and Symposia Sessions*, XV International Congress of Genetics, New Delhi India 1983. *Proceedings* (ed. M. S. Swaminathan). New Delhi, Bombay, Calcutta: Oxford & IBH Publishing Co.

BAKER, B. S. & RIDGE, K. (1980). Sex and the single cell: on the action of major loci affecting sex determination in *Drosophila melanogaster*. *Genetics* **94**, 383–423.

BAUSEWEIN, B. (1984). Eigenschaften der Objektreaktion von *Drosophila melanogaster*. Diplomthesis, University of Würzburg.

BELL, W. J. & TOBIN, T. R. (1982). Chemo-orientation. *Biol. Rev.* **57**, 219–260.

BELOTE, J. M. & BAKER, B. S. (1982). Sex determination in *Drosophila melanogaster*: analysis of *transformer-2*, a sex-transforming locus. *Proc. natn. Acad. Sci. U.S.A.* **79**, 1568–1572.

BIEBER, M. & FULDNER, D. (1979). Brain growth during the adult stage of a holometabolous insect. *Naturwissenschaften* **66**, 426.

BLONDEAU, J. & HEISENBERG, M. (1982). The 3-dimensional optomotor torque system of *Drosophila melanogaster*. Studies on wildtype and the mutant optomotor-blind (H 31). *J. comp. Physiol.* **145**, 321–329.

BOECKH, J. & BOECKH, V. (1979). Threshold and odor specificity of pheromone-sensitive neurons in the deutocerebrum of *Antheraea pernyi* and *A. polyphemus* (Saturnidae). *J. comp. Physiol.* **132**, 235–242.

BORST, A. (1984). Identification of different chemoreceptors by electroantennogram-recording. *J. Insect Physiol.* **30**, 507–510.

BRAITENBERG, V. (1967). Patterns of projections in the visual system of the fly. I. Retina lamina projections. *Expl Brain Res.* **3**, 271–298.

BUCHNER, E. & BUCHNER, S. (1984). Neuroanatomical mapping of visually induced nervous activity in insects by ^{3}H-deoxyglucose. In *Photoreception and Vision in Invertebrates*, (ed. M. A. Ali). New York: Plenum Press.

BÜLTHOFF, H. (1980). Orientation behaviour in *Drosophila melanogaster*. Doctoral thesis, University of Tübingen.

BYERS, D., DAVIS, R. & KIGER, J. A., JR. (1981). Defect in cyclic AMP phosphodiesterase due to the *dunce* mutation of learning in *Drosophila melanogaster*. *Nature, Lond.* **289**, 79–81.

CAMPOS-ORTEGA, J. A. (1980). On compound eye development in *Drosophila melanogaster*. *Curr. Top. dev. Biol.* **15**, 347–371.

CAMPOS-ORTEGA, J. A. & STRAUSFELD, N. J. (1972). Columns and layers in the second synaptic region of the fly's visual system. The case for two superimposed neuronal architectures. In *Information Processing in the Visual System of Arthropods*, (ed. R. Wehner). Berlin, Heidelberg, New York: Springer-Verlag.

COSS, R. G. & BRANDON, J. G. (1983). Rapid changes in drendritic spine morphology during honey-bees first orientation flight. In *The Biology of Social Insects*, (eds M. D. Bread, Ch. D. Michener & H. E. Evans). Colerado: West-View Press.

COTMAN, C. W. & LYNCH, G. S. (1976). Reactive synaptogenesis in the adult nervous system. The effects of partial deafferentiation on new synapse formation. In *Neuronal Recognition*, (ed. S. H. Barondes), pp. 69–108. London: Chapman & Hall.

DETHIER, V. G. (1976). *The Hungry Fly*. Cambridge, Mass.: Harvard University Press.

DOBZHANSKY, TH., SPASSKY, B. & SVED, J. (1969). Effects of selection and migration on geotactic and phototactic behaviour of *Drosophila*. II. *Proc. R. Soc. B* **173**, 191–207.

DUDAI, Y. & BICKER, G. (1978). Comparison of visual and olfactory learning in *Drosophila*. *Naturwissenschaften* **65**, 494–495.

DUDAI, Y., JAN, Y.-N., BYERS, D., QUINN, W. G. & BENZER, S. (1976). *dunce*, a mutant of *Drosophila* deficient in learning. *Proc. natn. Acad. Sci. U.S.A.* **73**, 1684–1688.

DUERR, J. S. & QUINN, W. G. (1982). Three *Drosophila* mutations which block associative learning also affect habituation and sensitization. *Proc. natn. Acad. Sci. U.S.A.* **79**, 3646–3650.

ECKERT, H. (1971). Die spektrale Empfindlichkeit des Komplexauges von *Musca* (Bestimmung aus Messungen der optomotorischen Reaktionen). *Kybernetik* **9**, 145–156.

FALK, R. & ATIDIA, J. (1975). Mutations affecting taste perception in *Drosophila melanogaster*. *Nature, Lond.* **254**, 325–326.

FISCHBACH, K. F. (1979). Simultaneous and successive colour contrast expressed in 'slow' phototactic behaviour of walking *Drosophila melanogaster*. *J. comp. Physiol.* **130**, 161–171.

FISCHBACH, K. F. (1981*a*). Simplified visual behavior of the small optic lobes mutant of *Drosophila melanogaster*. Abstracts 3rd ESCPB Congress Pergamon Press. pp. 229–230.

FISCHBACH, K. F. (1981*b*). Habituation and sensitization of the landing response of *Drosophila melanogaster*. *Naturwissenschaften* **68**, 332.

FISCHBACH, K. F. (1983*a*). Neurogenetik am Beispiel des visuellen Systems von *Drosophila melanogaster*. Habilitationsschrift, Würzburg.

FISCHBACH, K. F. (1983*b*). Neural cell types surviving congenital sensory deprivation in the optic lobes of *Drosophila melanogaster*. *Devl Biol.* **95**, 1–18.

FISCHBACH, K. F. & HEISENBERG, M. (1981). Structural brain mutants of *Drosophila melanogaster* with reduced cell number in the medulla cortex and with normal optomotor yaw response. *Proc. natn. Acad. Sci. U.S.A.* **78**, 1105–1109.

FISCHBACH, K. F. & LYLY-HÜNERBERG, I. (1983). Genetic dissection of anterior optic tract. *Cell Tiss. Res.* **231**, 551–563.

FISCHBACH, K. F. & REICHERT, H. (1978). Interactions of visual subsystems in *Drosophila melanogaster*. A behavioural genetic analysis. *Biology of Behaviour* **3**, 305–317.

FISCHBACH, K. F. & TECHNAU, G. (1984). Cell degeneration in the developing optic lobes of the *sine oculis* and *small optic lobes* mutants of *Drosophila melanogaster*. *Devl Biol.* (in press).

FOLKERS, E. (1982). Visual learning and memory of *Drosophila melanogaster* wild type C-S and the mutants *dunce, amnesiac, turnip* and *rutabaga*. *J. Insect Physiol.* **28**, 535–539.

FRANCESCHINI, N., HARDIE, R., RIBI, W. & KIRSCHFELD, K. (1981). Sexual dimorphism in a photoreceptor. *Nature, Lond.* **291**, 241–244.

FULLER, J. C. & THOMPSON, W. R. (1960). *Behavior Genetics*. London: John Wiley & Sons.

FULKER, D. W. (1966). Mating speed in male *Drosophila melanogaster*: a psychogenetic analysis. *Science, N.Y.* **153**, 203–205.

GEIGER, G. & NÄSSEL, D. R. (1981). Visual orientation behaviour of flies after selective laser beam ablation of interneurons. *Nature, Lond.* **293**, 398–399.

GEIGER, G. & NÄSSEL, D. R. (1982). Visual processing of moving single objects and wide-field patterns in flies. Behavioural analysis after laser-surgical removal of interneurons. *Biol. Cybernetics* **44**, 141–150.

GERHARD, J. C., BERKING, S., COOKE, J., FREEMAN, G. L., HILDEBRANDT, A., JOKUSCH, H., LAWRENCE, P. A., NÜSSLEIN-VOLHARD, C., OSTER, G. F., SANDER, K., SAUER, H. W., STENT, G., WESSELLS, N. K. & WOLPERT, L. (1982). The Cellular Basis of Morphogenetic Change. In *Evolution and Development*, (ed. J. T. Bonner). Berlin, Heidelberg, New York: Springer-Verlag.

GOODMAN, C. S. (1976). Constancy and uniqueness in a large population of small interneurons. *Science, N.Y.* **193**, 502–504.

GOODMAN, C. S. (1977). Neuron duplications and deletions in locust clones and clutches. *Science, N.Y.* **197**, 1384–1386.

GOODMAN, C. S. (1979). Isogenic grasshoppers: genetic variability and development of identified neurons. In *Neurogenetics: Genetic Approaches to the Nervous System*, (ed. X. O. Breakefield), pp. 101–151. New York, Oxford: Elsevier.

GOODMAN, C. S. & HEITLER, W. J. (1977). Isogenic locusts and genetic variability in the effects of temperature on neuronal threshold. *J. comp. Physiol. Psychol.* **117**, 183–200.

GÖTZ, K. G. (1968). Flight control in *Drosophila* by visual perception of motion. *Kybernetik* **4**, 199–208.

GÖTZ, K. G. (1983). Genetics and ontogeny of behaviour. Genetic defects of visual orientation in *Drosophila*. *Verh. dt. zool. Ges.* **1983**, 83–99.

GROSSFIELD, J. (1978). Non-sexual behavior. In *The Genetics and Biology of* Drosophila, Vol. 2b, (eds M. Ashburner & T. R. F. Wright), pp. 1–126. London: Academic Press.

HALL, J. C. (1981). Sex behavior mutants in *Drosophila*. *Bio. Science* **31**, 125–130.

HALL, J. C. (1982). Genetics of the nervous system in *Drosophila*. *Q. Rev. Biophys.* **15**, 223–479.

HALL, J. C. (1984). Mutants of biological rhythms and conditioned behavior in *Drosophila* courtship. In *Evolutionary Genetics of Invertebrate Behavior*, (ed. M. Huettel). New York: Plenum Press (in press).

HALL, J. C. & GREENSPAN, R. J. (1979). Genetic analysis of *Drosophila* neurobiology. *A. Rev. Genetics* **13**, 127–195.

HANDLER, A. N. & KONOPKA, R. J. (1979). Transplantation of a circadian pacemaker in *Drosophila*. *Nature, Lond.* **279**, 236–238.

HARDIE, R. C. (1983). Projection and connectivity of sex-specific photoreceptors in the compound eye of the male housefly (*Musca domestica*). *Cell Tissue Res.* **233**, 1–21.

HARDIE, R. C., FRANCESCHINI, N., RIBI, W. & KIRSCHFELD, K. (1981). Distribution and properties of sex-specific photoreceptors in the fly *Musca domestica*. *J. comp. Physiol.* **145**, 139–152.

HARRIS, W. A. & STARK, W. S. (1977). Hereditary retinal degeneration in *Drosophila melanogaster*. A mutant defect associated with the phototransduction process. *J. gen. Physiol.* **69**, 261–291.

HARRIS, W. A., STARK, W. S. & WALKER, J. A. (1976). Genetic dissection of the photoreceptor system in the compound eye of *Drosophila melanogaster*. *J. Physiol., Lond.* **256**, 415–439.

HAUSEN, K. (1981). Monocular and binocular computation of motion in the lobula plate of the fly. *Verh. dt. zool. Ges.* pp. 49–70. Stuttgart: Gustav Fischer.

HAUSEN, K. (1982). Motion sensitive interneurons in the optomotor system of the fly. I. The horizontal cells structure and signals. *Biol. Cybernetics* **45**, 143–156.

HAUSEN, K. & STRAUSFELD, N. J. (1980). Sexually dimorphic interneuron arrangements in the fly visual system. *Proc. R. Soc. B* **208**, 57–71.

HAUSEN, K. & WEHRHAHN, C. (1983). Microsurgical lesion of horizontal cells changes optomotor yaw responses in the blowfly. *Proc. R. Soc. B* **219**, 211–216.

HAWKINS, R. D. & KANDEL, E. R. (1984). Is there a cell biological alphabet for learning? *Psychobiol. Rev.* (in press).

HAY, D. A. (1972). Genetical and maternal determinants of the activity and preening behaviour of *Drosophila melanogaster* reared in different environments. *Heredity* **28**, 311–336.

HEIDENREICH, D. (1982). Die Genetik der Mutante minibrain (*mnb*) von *Drosophila melanogaster*. Diplomthesis, University of Würzburg.

HEISENBERG, M. (1979). Comparative behavioural studies on two visual mutants of *Drosophila*. *J. comp. Physiol.* **80**, 119–136.

HEISENBERG, M. (1979). Genetic approach to a visual system. In *Handbook of Sensory Physiology*, Vol. VII/6A, (ed. H. Autrum), pp. 665–679. Berlin: Springer-Verlag.

HEISENBERG, M. (1980). Mutants of brain structure and function: what is the significance of the mushroom bodies for behavior? In *Development and Neurobiology of* Drosophila, (eds O. Siddiqi, P. Babu, L. M. Hall & J. C. Hall), pp. 373–390. New York: Plenum Press.

HEISENBERG, M. & BÖHL, K. (1979). Isolation of anatomical brain mutants of *Drosophila* by histological means. *Z. Naturf.* **34**, 143–147.

HEISENBERG, M. & BUCHNER, E. (1977). The role of retinula cell types in visual behavior of *Drosophila melanogaster*. *J. comp. Physiol.* **117**, 127–162.

HEISENBERG, M. & GÖTZ, K. G. (1975). The use of mutations for the partial degradation of vision in *Drosophila melanogaster*. *J. comp. Physiol.* **98**, 217–241.

HEISENBERG, M. & WOLF, R. (1984). Vision in *Drosophila*. Genetics of microbehavior. Berlin, Heidelberg, New York: Springer-Verlag.

HEISENBERG, M., WONNEBERGER, R. & WOLF, R. (1978). *Optomotorblind H31* – a *Drosophila* mutant of the lobula plate giant neurons. *J. comp. Physiol.* **124**, 287–296.

HEITLER, W. J., GOODMAN, C. S. & ROWELL, C. H. F. (1977). The effects of temperature on the threshold of identified neurons in the locust. *J. comp. Physiol. Psychol.* **117**, 163–182.

HELVERSEN, VON D. & O. (1975*a*). Verhaltensgenetische Untersuchungen am akustischen Kommunikationssystem der Feldheuschrecken (Orthoptera, Acrididae) I. Der Gesang von Artbastarden zwischen *Chorthippus biguttulus* und *Ch. mollis*. *J. comp. Physiol.* **104**, 273–299.

HELVERSEN, VON D. & O. (1975*b*). Verhaltensgenetische Untersuchungen am akustischen Kommunikationssystem der Feldheuschrecken (Orthoptera, Acrididae) II. Das Lautschema von Artbastarden zwischen *Chorthippus biguttulus* and *Ch. mollis*. *J. comp. Physiol.* **104**, 301–323.

HOMYK, T. JR., PYE, Q. & PAK, W. L. (1981). Visual defective mutants in *Drosophila*. *Genetics* **97**, 50.

HOTTA, Y. (1984). Genetic and biochemical analysis of the photoreceptor membrane in *Drosophila*. In *Plenary Symposia and Symposia Sessions*, XV International Congress of Genetics, New Delhi, India 1983, (ed. M. S. Swaminathan), pp. 39–40. New Delhi, Bombay, Calcutta: Oxford & IBH Publishing Co.

HOY, R. R. (1974). Genetic control of acoustic behavior in crickets. *Am. Zool.* **14**, 1067–1080.

HOY, R. R., HAHN, J. & PAUL, R. C. (1977). Hybrid cricket auditory behavior: evidence for genetic coupling in animal communication. *Science, N.Y.* **195**, 82–84.

HU, K. G. & STARK, W. S. (1977). Specific receptor input into spectral preference in *Drosophila*. *J. comp. Physiol.* **121**, 241–252.

ISONO, K. & KIKUCHI, T. (1974). Autosomal recessive mutation in sugar response of *Drosophila*. *Nature, Lond.* **248**, 243–244.

JACKSON, F. R. (1983). The isolation of biological rhythm mutations on the autosomes of *Drosophila melanogaster*. *J. Neurogenetics* **1**, 3–15.

JENSEN, A. (1970). IQ's of identical twins reared apart. *Behav. Genet.* **1**, 133–148.

JOHNSON, M. A., FRAYER, K. L. & STARK, W. S. (1982). Characteristics of *rdgA*. Mutants with retinal degeneration in *Drosophila*. *J. Insect Physiol.* **28**, 233–242.

JOHNSTON, R. N. & WESSELS, N. K. (1980). Regulation of the elongating nerve fiber. *Curr. Topics devl Biol.* **16**, 165–206.

KAISER, W. (1968). Zur Frage des Unterscheidungsvermögens für Spektralfarben. Eine Untersuchung der königlichen Glanzfliege *Phormia regina* meig. *Z. vergl. Physiol.* **61**, 71–102.

KAISER, W. & LISKE, E. (1974). Die optomotorischen Reaktionen von fixiert fliegenden Bienen bei Reizung mit Spektrallichtern. *J. comp. Physiol.* **89**, 391–408.

KAUVAR, L. M. (1982). Defective cAMP phosphodiesterase in the *Drosophila* memory mutant *dunce*. *J. Neurosci.* **2**, 1347.

KING, D. G. & WYMAN, R. J. (1980). Anatomy of the giant fibre system in *Drospohila*. I. Three thoracic components of the pathway. *J. Neurocytol.* **9**, 753–770.

KIRSCHFELD, K. (1973). Das neuronale Superpositionsauge. *Fortschr. Zool.* **21**, 229–257.

KONOPKA, R. J. (1984). Neurogenetics of *Drosophila* circadian rhythms. In *Evolutionary Genetics of Invertebrate Behavior*, (ed. M. Huettel). New York: Plenum Press (in press).

KONOPKA, R. J. & BENZER, S. (1971). Clock mutants of *Drosophila melanogaster*. *Proc. natn. Acad. Sci. U.S.A.* **68**, 2112–2116.

KONOPKA, R. J. & WELLS, S. (1980). *Drosophila* clock mutations affect the morphology of a brain neurosecretory cell group. *J. Neurobiol.* **11**, 411–415.

KOTO, M., TANOUYE, M. A., FERRUS, A., THOMAS, J. B. & WYMAN, R. J. (1981). The morphology of the cervical giant fiber neuron of *Drosophila*. *Brain Res.* **221**, 213–217.

KYRIACOU, C. P. & HALL, J. C. (1980). Circadian rhythm mutations in *Drosophila melanogaster* affect short-term fluctuations in the male's courtship song. *Proc. natn. Acad. Sci. U.S.A.* **77**, 6729–6733.

KYRIACOU, C. P. & HALL, J. C. (1984). Learning and memory mutations impair acoustic priming of mating behaviour in *Drosophila*. *Nature, Lond.* **308**, 62–64.

LEHRMAN, D. S. (1953). A critique of Konrad Lorenz's theory of instinctive behavior. *Q. Rev. Biol.* **28**, 337–363.

LIVINGSTONE, M. S. (1981). Two mutations in *Drosophila* affect the synthesis of octopamine, dopamine and serotonin by altering the activities of two different amino-acid decarboxylases. *Neurosci. Abstr.* **7**, 351.

LIVINGSTONE, M. S., SZIBER, P. P. & QUINN, W. G. (1982). Defective adenylate cyclase in the *Drosophila* learning mutant *rutabaga*. *Soc. Neurosci. Abstr.* **8**, 384.

LORENZ, K. & TINBERGEN, N. (1938). Taxis und Instinkthandlung in der Eirollbewegung der Graugans. *I. Z. Tierpsychol.* **2**, 1–29.

MACAGNO, E. R., LOPRESTI, V. & LEVINTHAL, C. (1973). Structure and development of neuronal connections in isogenic organisms: variations and similarities in the optic system of *Daphnia magna*. *Proc. natn. Acad. Sci. U.S.A.* **70**, 47–61.

MARLER, P. & MASER, M. S. (1977). The role of auditory feedback in canary song development. *J. comp. Physiol. Psychol.* **91**, 8–16.

MATSUMOTO, S. G. & HILDEBRAND, J. G. (1981). Olfactory mechanisms in the moth *Manduca sexta*: response characteristics and morphology of central neurons in the antennal lobes. *Proc. R. Soc. B* **213**, 249–277.

MENZEL, R., ERBER, J. & MASUHR, T. (1974). Learning and memory in the honeybee. In *Experimental Analysis of Insect Behaviour*, (ed. L. Barton Browne), pp. 195–217. Berlin, Heidelberg, New York: Springer-Verlag.

MICHUTTA, A., KRAUSE, J. & KÖHLER, W. (1981). Genetische Analyse einer Verhaltensweise. Das phototaktische Verhalten von *Drosophila*. *Naturwissenschaften* **34**, 143–151.

MILLER, G. V., HANSEN, K. N. & STARK, W. S. (1981). Phototaxis in *Drosophila*. R1–6 input and interaction among ocellar and compound eye receptors. *J. Insect Physiol.* **27**, 813–819.

NICOD, I. (1983). Visual mutants of *Drosophila melanogaster*, functional neuroanatomical mapping of nervous activity by ^{3}H-deoxyglucose. Doctoral thesis, University of Tübingen.

NORLANDER, R. H. & EDWARDS, J. S. (1968). Morphological cell death in the post-embryonic development of the insect optic lobes. *Nature, Lond.* **218**, 780–781.

PAK, W. L. (1979). Study of photoreceptor function using *Drosophila* mutants. In *Neurogenetics. Genetic Approaches to the Nervous System*, (ed. X. Breakefield), pp. 67–99. New York: Elsevier, North Holland.

PAK, W. L. & GRABOWSKY, S. R. (1978). Physiology of the visual and flight systems. In *The Genetics and Biology of* Drosophila, Vol. 2a, (eds M. Ashburner & T. R. F. Wright), pp. 553–604. London: Academic Press.

PASCHMA, R. (1982). Strukturelle und funktionelle Defekte der Drosophilamutante *lobula plate-less* (*N684*). Diplomthesis. Würzburg.

PICK, B. & BUCHNER, E. (1979). Visual movement detection under light- and dark-adaptation in the fly *Musca domestica*. *J. comp. Physiol.* **134**, 45–54.

PIERANTONI, R. (1973). Su un tratto nervoso nel cervello della mosca. In *Atti della Prima Riuniore Scientifica Plenaria*, pp. 231–249. Soc. Ital. Biofis. Pura e Applicata.

POGGIO, T., REICHARDT, W. & HAUSEN, K. (1981). A neuronal circuitry for relative movement discrimination by the visual system of the fly. *Naturwissenschaften* **68**, 443–446.

POWER, M. E. (1943). The effect of reduction in numbers of ommatidia upon the brain of *Drosophila melanogaster*. *J. exp. Zool.* **94**, 33–71.

QUINN, W. G., SZIBER, P. P. & BOOKER, R. (1979). The *Drosophila* memory mutant *amnesiac*. *Nature, Lond.* **277**, 212–214.

QUINN, W. G. (1984). Work in invertebrates on the mechanisms underlying learning. In *The Biology of Learning*, (eds P. Mahler & H. S. Terrace). Berlin: Dahlem Conferences (in press).

REICHARDT, W. (1970). The insect eye as a model of uptake transduction and processing of optical data in the nervous system. In *The Neurosciences Second Study Program*, (ed. F. O. Schmitt), pp. 494–511. New York: Rockefeller University Press.

RODRIGUES, V. & SIDDIQI, O. (1978). Genetic analysis of chemosensory pathway. *Proc. Indian Acad. Sci.* **87B**, 147–160.

ROSPARS, J. P. (1983). Invariance and sex-specific variations of the glomerular organisation in the antennal lobes of a moth, *Mamestra brassicae*, and a butterfly, *Pieris brassicae*. *J. comp. Neurol.* **220**, 80–96.

SCHINZ, R. H., LO, M. C., LARRIVEE, D. C. & PAK, W. L. (1982). Freeze-fracture study of the *Drosophila* photoreceptor membrane. Mutations affecting membrane particle density. *J. Cell Biol.* **93**, 961–969.

CHNEIDER, G. E. (1973). Early lesions of superior colliculus. Factors affecting the formation of abnormal retinal projections. *Brain Behav. Evol.* **8**, 73–109.

SCHNEIDERMAN, A. M., MATSUMOTO, S. G. & HILDEBRAND, J. G. (1982). Trans-sexually grafted antennae influence development of sexually dimorphic neurones in moth brain. *Nature, Lond.* **298**, 844–846.

SHOTWELL, S. L. & KONOPKA, R. J. (1982). Hormonal regulation of cyclic nucleotide phosphodiesterase activity in clonal *Drosophila* cell lines. *Caltech Biol. A. Report*, pp. 164.

SIDDIQI, O. (1984). Olfactory neurogenetics of *Drosophila*. In *Plenary Symposia and Symposia Sessions*, XV International Congress of Genetics, New Delhi, 1983. *Proceedings*, (ed. M. S. Swaminathan). New Delhi, Bombay, Calcutta: Oxford & IBH Publishing Co. (in press).

SIDDIQI, O. & RODRIGUES, V. (1980). Genetic analysis of a complex chemoreceptor. In *Development and Neurobiology of* Drosophila, (ed. A. Hollaender), pp. 347–359. New York, London: Plenum Press.

SMITH, R. F. & KONOPKA, R. J. (1981). Circadian clock phenotypes of chromosome aberrations with a breakpoint at *per* locus. *Mol. gen. Genet.* **183**, 243–251.

STARK, W. S., SRYGLEY, R. G. & GREENBERG, R. M. (1981). Analysis of a compound eye mosaic of outer rhabdomeres absent marked with cardinal. *Drosoph. Inf. Serv.* **56**, 132–133.

STARK, W. S., CHEN, D.-M., JOHNSON, M. A. & FRAYER, K. L. (1983). The *rdgB* gene in *Drosophila*: retinal degeneration in different mutant alleles and inhibition of degeneration by *norp A*. *J. Insect Physiol.* **29**, 123–131.

STRAUSFELD, N. J. (1976). *Atlas of an Insect Brain*. Berlin, Heidelberg, New York: Springer-Verlag.

STRAUSFELD, N. J. (1980). Male and female visual neurons in dipterous insects. *Nature, Lond.* **283**, 381–383.

SULSTON, J. E. & HORVITZ, R. (1981). Abnormal cell lineages in mutants of the nematode *Caenorhabditis elegans*. *Devl Biol.* **82**, 41–55.

TANIMURA, T. (1984). Genetic alteration of taste mechanisms in *Drosophila*. In *Animal Behavior: Neurophysiological and Ethological Approaches*, (eds K. Aoki), pp. 61–69. Tokyo: Japan Sci. Soc. Press; Berlin: Springer-Verlag.

TANIMURA, T. & SHIMADA, I. (1981). Multiple receptor proteins for sweet taste in *Drosophila* discriminated by papain treatment. *J. comp. Physiol.* **141**, 265–269.

TECHNAU, G. (1984). Fibre number in the mushroom bodies of adult *Drosophila melanogaster* depends on age, sex and experience. *J. Neurogenetics* **2**, 113–126.

TEMPEL, B. L. & QUINN, W. G. (1980). Reward learning in *Drosophila melanogaster*. *Neurosci. Abstr.* **6**, 589.

THOMAS, J. B. & WYMAN, R. J. (1982). A mutation in *Drosophila* alters normal connectivity between two identified neurones. *Nature, Lond.* **298**, 650–651.

TOLMAN, E. C. (1924). The inheritance of maze learning ability in rats. *J. comp. Psychol.* **4**, 1–18.

UZZAN, A. & DUDAI, Y. (1982). Aminergic receptors in *Drosophila melanogaster*: responsiveness of adenylate cyclase to putative neurotransmitters. *J. Neurochem.* **38**, 1542–1550.

VOGT, K. (1983). Is the fly visual pigment a rhodopsin. *Z. Naturforsch.* **38**C, 329–333.

WAGNER, H. (1982). Flow-field variables trigger landing in flies. *Nature, Lond.* **297**, 147–148.

WALKER, J., STARK, W. & HARRIS, W. (1975). Genetic dissection of the *Drosophila* retina. *Genetics* **80** (suppl.), 82–83.

WARD, S., THOMSON, N., WHITE, J. G. & BRENNER, S. (1975). Electron microscopical reconstruction of the anterior sensory anatomy of the nematode *Caenorhabditis elegans*. *J. comp. Neurol.* **160**, 313–338.

WEHNER, R. (1981). Spatial vision in arthropods. In *Handbook of Sensory Physiology*, Vol. VII/6C, (ed. H. Autrum). Berlin, Heidelberg, New York: Springer-Verlag.

WEHRHAHN, C., POGGIO, T. & BÜLTHOFF, H. (1982). Tracking and chasing in houseflies (*Musca*). *Biol. Cybernetics* **45**, 123–130.

WOLFE, J. M. (1983). Hidden visual processes. *Scient. Am.* **248**, 72–85.

YOUNG, M. W. & JUDD, B. H. (1978). Nonessential sequences, genes, and the polytene chromosome bands of *Drosophila melanogaster*. *Genetics* **88**, 723–742.

ZEIL, J. (1983*a*). Sexual dimorphism in the visual system of flies: the compound eyes and neural superposition in Bibionidae (Diptera). *J. comp. Physiol.* **150**, 379–393.

ZEIL, J. (1983*b*). Sexual dimorphism in the visual system of flies: the free flight behaviour of male Bibionidae (Diptera). *J. comp. Physiol.* **150**, 395–412.