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FUDAN LECTURES IN NEUROBIOLOGY

Movement Perception and the Optomotor Feedback Loop in Arthropods

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Introduction

Movement detection is vital for an organism in many respects. The task of extracting movement information from the temporal-spatial intensity distribution on the retina, however, is no trivial one. The problem is to explain how information on the angular velocity of a pattern can be derived from the signals generated by the arrays of retinal photoreceptors. It has turned out that neither in the retina nor in higher centers of vertebrate and arthropod brains the response of motion sensitive neurons is a function of the velocity of a pattern alone. That is to say, these neurons do not "code" for velocity. The strength of the response depends for a given pattern velocity upon many other parameters as well, such as light intensity, contrast, spatial spectral composition, direction of movement or colour.

Several movement detection models have been developed (see review by Borst and Egelhaaf 1989[1]). The most thoroughly investigated type is the so called correlation type of movement detector. It has been worked out on the basis of optomotor experiments in insects[2, 3, 4, 5, 6, 7].

One of the most conspicous properties of this type of movement detector is that it is not angular velocity of a pattern that is decisive for the response but rather angular velocity divided by the spatial wavelength of the pattern, as long as the latter having an intensity profile of a sinewave. This ratio is called "contrast frequency", because it represents the frequency in which the signal in the individual photoreceptors is modulated.

Experiments designed to clarify the question of whether contrast frequency or velocity is the decisive parameter led to controversial results: open loop experiments on different insect species have shown that contrast frequency is the decisive parameter, whereas investigation of honey bees in free flight indicate that velocity perception seems to govern course control in these insects[8].

The following paper presents a concept that in principle can unify these contradictory results. The concept is as follows:

1. Elementary movement detection follows the rules of the correlation scheme of movement detection.
2. Following this first step, however, is a second one, in which the gain in the signals of the movement detectors is adjusted in such a way as to compensate for the movement detectors' texture dependence. In order to work, this gain control unit needs closed loop conditions.

Results and discussion

Walking or flying insects try to follow a stripe pattern, rotating around their vertical body axis(optomotor response)[9, 6]. Similarly, if a stripe pattern is moving up and down in front of a fly, the animal turns its head up and down. Such head movements, as shown in Fig. 1b, c demonstrate that the "gain" of this optomotor response is not constant but variable, depending upon the stimulus paradigm. This can be interpreted as being due to an automatic gain control mechanism in the movement detection system of the fly. Implications for optomotor responses will be discussed.

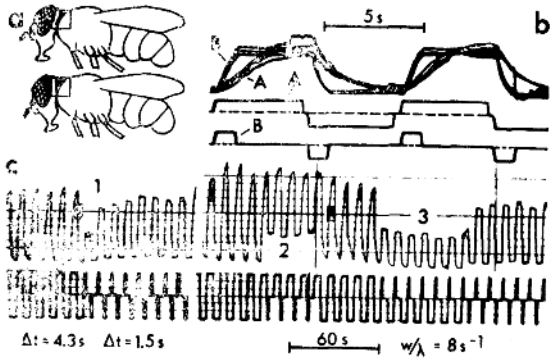
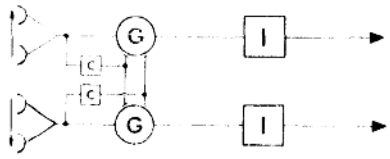


Figure 1

a Alignment of the aperture for monitoring head movement of the fly *Musca*. The light flux, passing the rectangular aperture indicated, chan-ges with the head position and is measured by a photomultiplier. Red light, invisible to the fly, was used.

b, c Upper tracks, head position of *Musca* ♀ (rotation around transverse axis). The maximal amplitudes correspond roughly to 10 to 15° head pitch. This is far from any mechanical stop which occurs only at an angle of ≈30°[21]. Although the head was free to move, the situation corresponds practically to an open loop condition since angular velocity of the head pitch (≈10°/s) is much slower than angular velocity of the pattern movement (≈80°/s).

The two lower tracks in b and the lower track in c indicate the periods of movement of the striped pattern (pattern wavelength λ = 10°). Movement from dorsal to ventral is indicated by the upper position of the line, from ventral to dorsal by the lower position. Qualitatively same results have been found by all 12 flys observed. Quantitatively there was considerable variability in the degree of change of the gain between different flies.



Fsgure 2

Flow diagram with two individual movement detectors, gain control units G, feed forward control element C and filter I that links the output of G to the head position.

At the onset of the experiments illustrated in Fig. lb, a striped pattern was moved upwards and downwards with reversal of direction every 4.3 seconds(Fig. lb, tracks A). Head-bending follows this motion stimulus, as can be seen in the upper tracks, whereby the movement of the head was relatively slow. Headmovement to the onset of the same motion stimulus is much faster if motion of the pattern lasts for only 1.5 sec, followed by a phase in which the pattern is stationary for 3 sec, then moves for 1.5 sec in the opposite direction, etc. As can be seen in the tracks B, the amplitude of the head-bending to this short stimuli has roughly the same amplitude as to the longer lasting stimuli (tracks A). If the duration of a short stimulus (track B) would have been increased, the amplitude of the head tilt transiently would be larger than shown in Fig. lb, upper track B.

The different angular velocities of head movement to the onset of the same motion stimulus indicate that, following onset of the stimulus, an internal signal must be generated, different in amplitude in the two stimulus paradigms. The difference can be interpreted as being due to a gain control element G (Fig. 2). The gain of the unit G is assumed to be modified by the signal of the motion detectors via the filter C. The results in fig. lb can be modelled by assuming that the gain in case B is about twice that of case A. The filter C is a complicated element properties of which will be described in more detail elsewhere(Kirschfeld in prep.). If the contrast frequency of the stimulus is constant as in the example shown, it acts as a low pass filter with a time constant in the order of a few seconds. Furthermore, gain control is "reciprocal", i. e. the gain for the movement upwards is controlled not only by movement detectors sensitive to motion from bottom-to-top, but also by those sensitive to motion from top-to-bottom. This is indicated by the results presented in Fig. lc. In this figure, the head-bending to different stimulus paradigms is shown. Besides the two cases as illustrated in Fig. lb which on a lower time scale are shown at the left of the figure, responses to two more stimulus combinations are shown at the right: if a longer lasting stimulus is applied downwards, it reduces the gain also for motion upwards, with

the outcome that a short stimulus leads only to a weak response (this indicated by number 2 in the figure) and vice versa (number 3). This property of "reciprocal" gain control is also included in the flow diagram of the model (Fig. 2), in which the filter I links the internal signal at the output of unit G to the head position. I has properties of an integrator that acts against an element with restoring force, increasing with angular excursion of the head (cf. Hengsten-berg 1984[10] for roll responses of the head).

The flow diagram as illustrated in Fig. 2 is further supported by data from giant neurons of the lobula plate of the fly. This type of neuron probably mediates optomotor responses[11]. In one type of these neurons, the so-called H_1 neuron, preadaptation to motion in the preferred direction reduces the sensitivity to motion stimuli of these neurons, i.e. their gain is reduced. This phenomenon of "adaptation" has been investigated in some detail by Maddess and Laughlin[12]. We have shown furthermore that also adaptation to motion in the *nonpreferred* direction (which inhibits the activity of this neuron) reduces the sensitivity in the preferred direction in the sense of "reciprocal" gain control as illustrated above. The com-plicated phenomena cannot be interpreted just as transient responses of arrays of elementary movement detectors[13], or to be due to variable time constants of the input filters of elementary movement detectors[14, 15] as will be discussed elsewhere (Kirschfeld and Reitmajer, in prep.).

If the optomotor response in insects in open loop conditions is measured as a function of the contrast frequency, the maximum of the response is found to have a more or less constant, rather low contrast frequency, irrespective of the wavelength of the pattern (in *Musca* and *Drosophila* e. g. ≈ 1 sec^{-1}[16]. This was originally interpreted as a property of elementary movement detectors of the Hassenstein-Reichardt type[9, 5]. If a variable gain, as described above, is a general property in such optomotor systems, it means that this maximum is rather a property of the gain control mechanism; the conspicuous constancy of the response maximum over contrast frequency in this view results from the fact that the gain control depends mainly upon the contrast frequency[12], irrespective of the wavelength of the stimulus pattern, and in this way creates a maximum at a con-stant w/λ. Only contrast frequencies larger $\approx 1s^{-1}$ reduce gain with the result that in steady state the response only to higher contrast frequencies are reduced and the consequence that the response maximum is shifted to shorter wavelengths.

Heisenberg and Wolf[17] have shown that the yaw torque response of *Drosophila* in open loop conditions to a striped pattern is large, if it is presented with constant angular velocity. If fluctuations are superimposed to the constant angular velocity, the mean amplitude of the yaw torque response amplitude is reduced (their Fig. 6a, b). This reduction can be interpreted as being due to a reduction in

gain by the superimposed high frequency fluctuation of the motion detection system.

A modification of gain in optomotor control systems by visual stimuli is not restricted to arthropods. The ocular following system in the monkey exhibits so-called "post-saccadic enhancement"[18]: within a short time(30-70ms) after a saccade, the velocity of ocular following to the movement of a test pattern is *enhanced*, i.e. the gain is increased. A similar increase in gain can also be generated by sac-cade-like movements of a visual scene, which shows that here too the *visual input* is decisive for the gain control.

One of the advantages of such a variable gain in optomotor control systems (Fig.3), besides an adjustment of the dynamic range of the system, may be that it allows for a better compromise between output error signal of the system, velocity and texture of the pattern, and stability: closing of the feed back loop in Fig. 3 results in a reduction of the amplitude of the "slip signal" w(t). Hence the motion stimulus at the eye is reduced, and, via filter C_1 increases the gain of the system. This reduces the output error signal and thus improves the feedback loop performance. As soon as the gain becomes to large the system starts oscillating, gain is reduced and stability regained. A similar argument has been put forward for the visual system of primates[18] and crabs[19].

Optomotor responses in flies have been investigated in flight simulators that can be operated in open as well as in closed loop conditions. A question that has long been discussed is whether flies can discriminate between these two cases, that is whether the torque response a fly generates for the same optical stimulus w(t) (Fig. 3) is different, depending upon whether the simulator is in open or closed loop conditions. Heisenberg and Wolf[17] have shown that the torque response in the two cases is different, indeed. It is weaker in open loop condition than expected from the closed loop results. The question is how the fly can be "aware" of whether the system is closed or open. The authors interpret their results as being due to an interaction between the endogenous yaw torque ("noise") generator and the optomotor controller, and discuss it in the context of von Holst and Mittelstaedt's[20] principle of reafference. According to this principle an interaction via an "efference copy" has to be assumed between endogenous noise generator and optomotor controller (ec, Fig.3).

A simpler solution could be realized if, instead of an efference copy of the noise, the torque T(t), generated by the fly, interacts with the optomotor controller via a filter, called C_2 in Fig.3. If the gain of the optomotor controller is reduced by torque signals of large amplitude, in open loop conditions(ol, Fig.3) the response to a given slip signal could be smaller than in closed loop conditions due to the general properties of the negative feedback system : in such a feedback system

the noise of the endogenous noise generator will be reduced in amplitude by the feedback loop, whereas it remains unaffected by the system in open loop conditions. An increase in torque amplitudes(primarily in the low frequency range) in open loop conditions experimentally has been demonstrated by Heisenberg and Wolf[17]. For the same reasoning as discussed above for C_1 these increased torque amplitudes, via C, could be used to modify the gain in the optomotor controller, improve the performance of the optomotor system and explain the results.

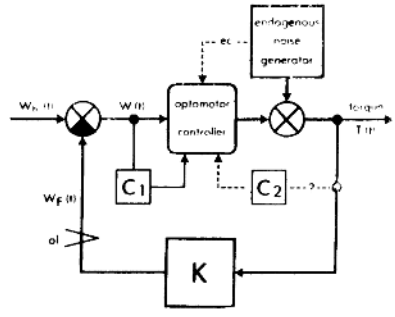


Figure 3

Thick lines: conventional visual feed back loop as proposed for the optomotor response of flies in a "flight simulator" by Poggio and Reichardt[22]. The filter M is a unit linking the fly's yaw torque T(t) to the angular velocity of the fly $W_F(t)$ which feeds back to the angular velocity W_b of the panorama. The torque T(t) generated by the fly does not only depend upon the "slip signal" W(t), but also "noise", generated endogenously by the fly, is added. In analogy to C in Fig. 2, a filter C_1 has been included into the system. An additional filter C_2, also capable of changing the gain of the optomotor controller, is assumed to connect the torque output of the fly with the controller. ol: location where the system can be opened by the experimenter. ec: efference copy. Details discussed in the text.

The concept developed in this paper on how the nervous system is capable to extract information on relative motion from the signals, generated in the retina, has the following characteristics: one element of non perfect function——the movement detector of the correlation type——is followed by a second element that compensates for the deficits of the first one. This way a satisfactory overall-function of the system is guaranteed.

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FUDAN LECTURES IN NEUROBIOLOGY

Dopamine Receptors: Regulation and Role in Schizophrenia

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INTRODUCTION

Schizophrenia has been recorded for centuries with references to this disease appearing in the writings of many societies. Although we no longer attribute the symptoms of schizophrenia to a demonic possession of the individual, the etiology of this syndrome remains unclear. The diagnosis of schizophrenia encom-passes a myriad of symptoms. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSMIII) specifies six criteria for the diagnoses of schizophrenia: (1) At least one critical symptom must be displayed which can include several types of delusions, auditory hallucinations and thought disorders (such as incoherence, poverty of thought); (2) deterioration from a previous level of functioning; (3) onset of illness before age 45; (4) duration of symptoms must be at least 6 months; (5) no preexisting affective disorder(e.g., depression or manic syndrome); (6)not due to organic mental disorder (e.g., concussion) or mental retardation. Schizophrenics may experience one or several of a multiplicity of symptoms in addition to those mentioned above including associational disturbances, bizarre or persecutory delusions, impairment of abstracting ability, flat or inappropriate affect and social withdrawal which are characterized as paranoid, disorganized, undifferentiated, catatonic or residual schizophrenia. The prevalence of this illness is approximately 0.5 percent in all populations studied. There is a genetic predisposition to the disorder with the risk of schizophrenia increasing with the extent of genetic relatedness to another schizophrenic family member. This fact suggests the possibility of a central nervous system (CNS) biochemical or anatomical abnormality.

Several lines of evidence, primarily pharmacological, suggest an association of CNS dopaminergic neuronal systems in the etiology of schizophrenia. Chronic abuse of stimulants such as amphetamine, which are known to enhance dopaminergic activity in the brain, can lead to a paranoid psychosis that is almost indistinguishable from classic paranoid schizophrenia. Furthermore, acute administration of amphetamine will exacerbate the symptomotology of a schizophrenic and initiate a recurrent psychosis in a schizophrenic in remission. On the other hand, schizophrenic symptomotology can be reduced by reserpine, which depletes brain dopamine or by α-methyl para-tyrosine which blocks dopamine's synthesis. The involvement of the various dopaminergic pathways in the CNS in normal and abnormal behavior, especially schizophrenia, is not known. However, it has

been hypothesized that the nigrostriatal pathway, which is part of the extrapyramidal motor system, is involved in the motoric symptoms seen in some forms of schizophrenia (catatonia) and in the parkinsonian side-effects of the neuroleptic drugs which are used to treat schizophrenia. The mesolimbic and mesocortical pathways which innervate brain areas classically associated with intellectual function and emotionality, are probably involved in the more cardinal psychiatric symptoms of the disease.

The nigrostriatal pathway, which accounts for about 70% of the total brain content of dopamine, has become an obvious focus of research. The existence of the nigrostriatal pathway was strongly indicated by the observations of Hornykiewicz who demonstrated that patients with Parkinson's disease displayed a concomitant loss of dopamine in the basal ganglia, along with the degeneration of cells in the substantia nigra, pars compacta. The other major dopamine pathway originates from a group of cells in the ventrotegmental area and innervates limbic and cortical structures. The substantia nigra and ventrotegmental dopamine cell groups are more correctly described as a continuum, with the more laterally situated cells innervating the striatum and the more medial cells predominantly innervating the mesolimbic and mesocortical areas. The striatal projection includes the caudate nucleus, putamen, and globus pallidus, whereas the terminal areas of the mesocortical projection include the medial frontal, anterior cingulate, entorhinal, perirhinal and piriform cortex. More recent studies are suggesting an even wider dopaminergic innervation to other cortical areas in primate and man. The mesolimbic innervation includes the olfactory tubercle, septum, nucleus accumbens, amygdaloid complex and hippocampus. Of the other dopamine pathways, the tuberohypophyseal system has received most attention because of dopamine's role in inhibiting prolactin hormone secretion from the anterior pituitary.

PHARMACOLOGICAL TREATMENT OF SCHIZOPHRENIA

The antipsychotic drugs used in the treatment of schizophrenia are termed neuroleptics. Besides being antipsychotic, these drugs also antagonize the behavioral and biochemical effects induced by dopamine agonists in animals. The biochemical interactions of neuroleptic drugs with CNS dopamine systems have been much researched as they may provide clues to the etiology of schizophrenia. Chlorpromazine was the first synthetic neuroleptic identified and is one of the phenothiazines in widest use. Since its introduction in the early 1950's, many hundreds of other phenothiazines such as fluphenazine and thioridazine have been synthesized in the hope of discovering more potent and specific agents. The other major class of neuroleptics, the butyrophenones, include haloperidol which is about as potent therapeutically as fluphenazine. Another butyrophenone, important

for biochemical experiments, is spiperone or spiroperidol.

Since none of the antipsychotic drugs antagonize dopaminergic activity by depleting dopamine levels or inhibiting dopamine release, it was soon realized that these drugs were most likely dopamine receptor antagonists. The evidence that neuroleptic, antipsychotic drugs act by blocking postsynaptic dopamine receptors was initially circumstantial as neuroleptics increase the release of dopamine as shown by the pioneering research of Carlsson. Much initial data were also gathered in animal studies where the effects of dopaminergic agonists were blocked by the administration of neuroleptic drugs.

RECEPTOR IDENTIFICATION

One mechanism, of many, by which agonist interactions at neurotransmitter receptors are transduced into biochemical signals is by the activation of the enzyme adenylate cyclase which catalyses the conversion of ATP to cyclic AMP (cAMP). In the early 1970's, the dopamine sensitive adenylate cyclase was one of the first CNS receptor systems identified. The regional distribution of dopamine stimulated adenylate cyclase activity corresponds well with the distribution of endogenous dopamine, wherein the greatest activation is observed in the striatum, olfactory tubercle and nucleus accumbens. Greengard's group and later Iversen and colleagues evaluated the effects of neuroleptic drugs on dopamine stimulated adenylate cyclase activity. The phenothiazines were effective competitive inhibitors of the enzyme in keeping with their hypothesized dopamine receptor antagonist property. In studies utilizing an extensive series of phenothiazines general parallels emerged between their pharmacological potencies and their antipsychotic activities in man versus their inhibition of dopamine stimulated adenylate cyclase activity. However, this correlation surprisingly did not extend to the butyrophenones and other neuroleptics. For example, the new benzamide antipsychotic sulpiride, which is from a different structural class altogether, is almost devoid of inhibitory effects on dopamine stimulated adenylate cyclase activity.

These discrepancies ultimately prompted the multiple dopamine receptor hypothesis. The dopamine receptors implicated in the stimulation of adenylate cyclase activity have since been termed D_1 receptors and possess low affinities for butyrophenones and benzamides. The identification of the other dopamine receptor subtype at which the butyrophenones and benzamides are effective antagonists, now termed D_2 receptors, followed a somewhat more circuitous route.

At the same time as it was realized that blockade of D_2 receptor stimulation of adenylate cyclase activity was not predictive of many of the biochemical and behavioral actions of neuroleptics, radiolabeled butyrophenones of high specific activity first became available. These were utilized in receptor binding studies to

pharmacologically characterize the receptor sites to which these butyrophenone radioligands bound. Not surprisingly, given the potent *in vivo* dopamine antagonist profiles of the butyrophenones, ligands such as ^{3}H-haloperidol labeled sites at which dopamine was the most potent neurotransmitter competitor. Furthermore, the distribution of these sites in the brain paralleled the distribution of the terminal fields of dopamine neurons, reinforcing their association with dopamine receptors. The most compelling evidence, however, was the demon-stration that neuroleptics' potencies in competing for these ^{3}H-butyrophenone-labeled sites, was predictive of their *in vivo* activity as dopamine antagonists and their antipsychotic activity. It has now been shown that these D_2 receptors, in many, if not all tissues, inhibit adenylate cyclase activity, an only recently discovered receptor mediated response common to other neurotransmitter and hormone receptors.

Recently, investigators have determined that, for many receptors, adenylate cyclase activity is guanine nucleotide sensitive. Not surprisingly then, GTP is a requirement for D_1 receptor stimulated adenylate cyclase activity and also regulates receptor binding characteristics. Antagonist competition curves for ^{3}H-antagonist binding are uniformly steep suggesting the presence of a single population of D_1 dopamine receptors. Agonist competition curves are extremely shallow sug-gesting the presence of a heterogeneous population of agonist binding states of the D_1 dopamine receptor. Computer-aided analysis of these curves with non linear, least squares curve fitting programs, such as LIGAND clearly resolve agonist competition curves to D_1 receptors into 2 components of high and low affinity. In the presence of GTP, these curves are steepened and shifted rightward due to a reduction in high affinity binding sites. Similarly, agonist competition for ^{3}H-spiperone binding to D_2 receptors is complex and best models to two sites of high and low affinities. GTP will convert most, if not all, of the high affinity binding sites to low affinity binding sites.

The effects of GTP on agonist binding to D_2 receptors were described before its second messenger system had been identified, so it was not unexpected perhaps, that D_2 receptors are coupled to adenylate cyclase, albeit in negative manner. One of the problems in studying D_2 receptor mediated inhibition of adenylate cyclase activity in the striatum is that the degree of inhibition is small ($\sim$20%) and must be amplified for detailed study by increasing basal activity with forskolin.

THE TERNARY COMPLEX MODEL

Guanine nucleotides regulate agonist interactions with ^{3}H-antagonist labeled receptors in many adenylate cyclase-coupled receptor systems, perhaps best

typified by the β-adrenergic receptor. In these systems the effect of guanine nucleotides, such as GTP, is primarily to reduce the overall affinity of agonists for these receptors (i.e. shift curves to the right) by reducing the percent of agonist high affinity binding. A detailed description of the molecular events that underlie these changes in receptor binding affinities of agonists has been developed by complex binding and biochemical studies of other adenylate cyclase linked receptors. Extensive evidence indicates that a guanine nucleotide regulatory protein(now generally termed N_s)represents the functional communicator between agonist occupied receptors and the catalytic subunit of adenylate cyclase (C) in stimulatory linked receptor systems. N_s is also thought to regulate agonist interactions at ^{3}H-antagonist labeled receptors in parallel with adenylate cyclase regulation. Briefly, both agonists (A) and antagonists bind to the receptor recognition site (R) forming a drug/receptor complex. However, only agonists promote or stabilize the interaction between R and N_s. Thus, a ternary complex is formed (ARN_s) representing the R_H state of the receptor which has high affinity (K_H) for agonists. This ternary complex is the precursor to the activated intermediate of N_s which can interact with adenylate cyclase. In this model, the addition of guanine nucleotides promotes the dissociation of R and N_s representing the R_L agonist binding state which has low affinity (K_L) for agonists. A similar model may be used to describe inhibitory adenylate cyclase linked receptors (e.g. D_2 dopamine receptors). Agonist binding in this model is also regulated by an intermediate guanine nucleotide regulatory protein. This guanine nucleotide regulatory subunit has been well characterized in some inhibitory adenylate cyclase linked receptors. It is not completely identical to N_s and for obvious reasons has been termed N_i. N_s and N_i are multisubunit proteins which upon activation, as Gilman has shown, dissociate into a GTP binding moiety and a smaller regulatory unit. The smaller subunits of N_s and N_i are functionally and biochemically indistinguishable from each other.

BEHAVIORAL CORRELATES OF DOPAMINE RECEPTORS

The dopamine agonist most frequently employed in behavioral, biochemical or physiological experiments is (-)apomorphine. This alkaloid of the aporphine family acts a partial agonist of D_1 receptors but it exhibits full agonist activity at D_2 dopamine receptors. The only well characterized, truly selective D_1 agonist available to date is the partial ergoline LY171555 and its racemate LY141865. The benzazepine SKF38393 is the best characterized selective D_1 receptor agonist.

All neuroleptics, commonly used drugs in the treatment of schizophrenia, have been shown to be either mixed D_1/D_2 dopamine receptor antagonists or

selective D_2 dopamine receptor antagonists. Thus, D_2 dopamine receptors have been implicated as the site mediating the antipsychotic and antidopaminergic activity of neuroleptics. By inference, D_2 receptors were initially considered to be the mediators of dopaminergic agonists' behavioral effects. The behaivoral effects of dopamine agonists and antagonists in animals are primarily observed as changes in motor function. Dopaminergic agonists administered to rodents *in vivo* tend to elicit an increase in activity. At low doses of agonists a decrease in locomotor activity, sometimes accompanied by yawning behavior, is observed which is thought to be the result of a decrease in dopamine release mediated via stimulation of dopamine D_2 autoreceptors on dopamine nerve terminals. Higher doses result in increased locomotor activity. Further increase in agonist dose result in the development of stereotyped behaviors characterized by repetitive execution of behavioral patterns such as sniffing, rearing, head movements and, at very high doses, licking and biting. Additionally, dopamine agonists induce emesis in many mammals.

Neuroleptics reduce spontaneous motor behavior and at moderate doses induce catalepsy. Furthermore, dopaminergic antagonists suppress conditioned avoidance responses, and antagonize the hyperactivity and stereotypy responses elicited by dopamine agonists. Neuroleptics are also antiemetic and induce hyperprolactinemia by blocking D_2 dopamine receptors in the anterior pituitary. These behaviors are elicited by selective D_2 receptor antagonists or mixed D_1/D_2 receptor antagonists and are generally predictive of antipsychotic activity in man. Consequently, these behavioral effects have been used by the pharmaceutical industry as screens for potential new neuroleptic drugs

Until recently the functional role of D_1 dopamine receptors had not been clearly defined due to the lack of *selective*, high affinity D_1 dopamine receptor ligands. Recently, a potent and selective D_1 receptor antagonist, SCH23390, was developed and has since been tritiated, making further detailed D_1 dopamine receptor characterization possible. This novel benzazepine exhibits nanomolar potency in inhibiting dopamine stimulation of striatal adenylate cyclase activity and exhibits an apparent K_D value of approximately 0.5 nM for the striatal D_1 dopamine receptor binding sites. In contrast, its affinity for D_2 dopamine receptors is orders of magnitude lower. Whereas SCH23390 is a selective D_1 dopamine receptor antagonist, it surprisingly mimics some of the behavioral effects previously associated with D_2 dopamine receptor antagonists such as blocking conditioned avoidance responding, agonist-induced stereotypy and hyperactivity, as well as inducing catalepsy. That SCH23390 can induce these neuroleptic behavioral effects, without blockade of D_2 dopamine receptors, suggests that it may be a novel antipsychotic agent.