NEUROLEPTIC-INDUCED PERFORMANCE DEFICITS: MOTOR OR REWARD DEFICIT?

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A Thesis

in

The Department

of

Psychology

Presented in Partial Fulfillment of the Requirements
for the Degree of Master of Arts at
Concordia University
Montreal, Quebec, Canada

September 1981

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ABSTRACT

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Two contrasting hypotheses exist as to the effects of neuroleptics on operant behavior in animals. The first view suggests that neuroleptics cause an inability to initiate voluntary motor movements. The second view suggests that neuroleptics result in an attenuation of the rewarding value of normally reinforcing stimuli. In order to test these contrasting hypotheses, the present investigation attempts to determine if food given to neuroleptic-treated rats can both sustain and establish a normal response habit, i.e., bar-pressing. Three experiments were conducted with male Sprague Dawley rats as subjects using the neuroleptic pimozide. The effects of repeated pimozide experience on the rate of bar-pressing is examined in order to evaluate the response-sustaining capabilities of food. Examination of the

response-acquiring capacities of food involves measuring the rate of acquisition of bar-pressing in naive, drugged rats. In contrast to the motor deficit hypothesis, pimozide-treated rats demonstrate an ability to execute a series of complex, coordinated motor movements. In accordance with the reward attenuation hypothesis, the maintenance of a normal rate of responding in well-trained rats and the establishment of the bar-pressing in naive rats is influenced by the rewarding properties of food. These findings suggest that one major effect of neuroleptics may be the attenuation of the rewarding properties of primary reinforcing stimuli. The evidence supporting such a theory is discussed.

Acknowledgements

The author wishes to express his sincere thanks and appreciation to Roy Wise for his patience, advice and support concerning the design, execution and reporting of the results of this investigation.

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Introduction

Neuroleptics: Clinical Perspective

A significant advance in the treatment of mental illness has been the use of drugs that are effective in the management of the psychotic patient. Prior to the advent of such antipsychotic drugs, generally referred to as neuroleptics, the treatment of schizophrenia and other psychotic disorders were primarily custodial in nature. Until 1956 (the first year of widespread use of the neuroleptics), the population of psychiatric inpatients in both public and private mental institutions had been increasing yearly. However, since 1957 this statistic has reversed and the inpatient population has declined in each successive year (Kornetsky, 1976). Patients who previously had to be maintained in psychiatric institutions for extended periods of time are now more frequently treated on an outpatient basis and returned to their homes and community, usually to lead a considerably more normal life. This change is directly attributable to the advent of neuroleptic treatment.

Although the practical importance of these drugs is clear, more critical questions remain.

Do these drugs actually reverse the schizophrenia process, or do they merely serve to arrest the symptoms of schizophrenia? If they merely provide symptomatic relief, are their actions specific to schizophrenic symptoms, or do these drugs simply suppress behavior in general? That neuroleptics lessen the burden of the psychiatric staff by making the previously recalcitrant patient more manageable is not a sufficient answer.

Delay, Deniker, Ropert, Beek, Barande and Eurieult (1969) were first to document the effectiveness of neuroleptics in the schizophrenic population. They argued that chlorpromazine and reserpine did indeed have "antipsychotic" effects on their patients without impairing their consciousness. Since both these drugs are known to produce sedation (Denber, 1979; Klein & Davis, 1969), the diminution of agitation in their hyperactive patients was expected. However, withdrawn patients given the identical drug dosage responded by becoming more "activated." This paradoxical effect was considered to be a critical characteristic of a truly anti-schizophrenic drug.

Although it is true that many of the primary and secondary symptoms which are peculiar to

schizophrenia (e.g., thought disorder, abnormal affect and withdrawal) are attenuated and in some cases even eliminated as a result of neuroleptic intervention, the majority of patients do not fully recover. That less than fifty percent of neuroleptic-treated schizophrenics living in the community are deemed well adjusted (Lipton, 1976) is an unfortunate testimony to our lack of understanding of the drugs in use today. Moreover, adverse side effects of prolonged neuroleptic treatment are well known (Iversen, 1975; Jansen & Van Bever, 1978; Klein & Davis, 1969). Kornetsky (1976) suggest that the ideal antipsychotic drug should be able 1) to reduce the agitated state, 2) to reverse the process of the psychotic symptom, 3) to not interfere with any motoric functioning, and 4) to exhibit to extra-pyramidal symptoms. Currently, there exists no drug in production that can satisfy these requirements. One step towards producing such a drug is a more thorough understanding of the actions of the drugs currently in use.

The Dopamine Receptor as the Site of Neuroleptic Action

With the emergence of neuroleptics as the treatment of choice for schizophrenia, a great deal

of attention has been focused on the mechanisms of neuroleptic action. It appears that neuroleptic administration results in a blockade of dopamine receptors in the central nervous system, and that this blockade is primarily responsible for the alleviation of psychotic symptoms (Byck, 1975; Iversen, 1975; Snyder, Banerjee, Yamamura & Greenberg, 1974). Evidence in support of this view comes from numerous studies that have focused on dopaminergic blockade as inferred from a variety of methods and arguments.

First, Horn and Snyder (1971) and Horn, Post and Kennard (1975) have demonstrated that certain neuroleptics are structurally similar to dopamine. Through x-ray analysis, they have shown that dopamine can be almost perfectly superimposed upon a portion of each of the neuroleptics that they tested. The similarity of the dopamine conformation to part of the chemical structure of the neuroleptic suggests that these drugs are likely to interact with dopamine-related receptor sites.

A second line of studies has attempted to identify the dopamine receptor and determine its neuroleptic affinity. With the use of radioactively labelled drugs, specific drug-receptor

binding can be measured in homogenized samples of the brain. Burt, Creese and Snyder (1976) and Creese and Snyder (1978) have demonstrated that (^{3}H) -dopamine and (^{3}H) -haloperidol each bind to brain homogenates. These investigators found that neuroleptics significantly displaced the binding of each other. In addition, dopamine displaced the binding of the neuroleptics to the same degree. These findings led the investigators to conclude that dopamine and neuroleptics compete for the same class of dopamine receptor binding sites.

The conformational similarity between certain portions of the neuroleptic and dopamine molecules and the displacement of radioactive haloperidol by dopamine support the view that neuroleptics block dopamine receptors because of their ability to compete with dopamine to occupy the same receptor sites. However, the fact that neuroleptics may bind to at least some of the same sites as does dopamine does not, by itself, imply that this is the biological site of neuroleptic action. Electrophysiological and behavioral studies are needed to determine whether a drug indeed acts at its various binding sites. It must be determined that a binding site is a site of dopamine action

before it can be inferred that it is a site of pharmacological blockade.

The major dopaminergic pathways in the brain include the nigro-striatal, mesolimbic and mesocortical systems. The cell bodies of these neurons are located in the zona compacta of the substantia nigra and the adjacent ventral tegmental area. These cell bodies innervate the caudate nucleus and the putamen of the striatum, the frontal cortex, the septum, the nucleus accumbens and other limbic structures (Ungerstedt, 1971a). Through the use of extracellular single cell recording techniques, Bunney and Aghajanian (1976) located cells in the prefrontal cortex that are innervated by dopamine-containing cell terminals. In a third major approach, they were therefore able to test the effects of various drugs on cells which are the presumed site of synaptic dopamine action. Dopamine inhibited the firing of these cells. Trifluoperazine, a potent neuroleptic, selectively blocked the dopaminergic inhibition of cell activity. This and similar studies (Bunney & Grace, 1978; Bunney, Walters, Roth & Aghajanian, 1973; Groves, Rebec & Segal, 1974; York, 1972) are direct demonstrations

of the dopamine blocking action of neuroleptics measured within the dopaminergic synapse itself.

A fourth approach to demonstrating the dopamine-blocking action of neuroleptics is behavioral in nature. Bilateral injections of dopamine into the striatum result in stereotypic behavior in the form of sniffing, licking and biting (Fog & Pakkenberg, 1971). Similar injections into the nucleus accumbens produce a pattern of enhanced locomotor activity (Pijnenburg & Van Rossum, 1973). The demonstration of dopamine-induced stereotypic and locomotor activity are behavioral signs of central dopaminergic activity in the rat.

Several related drugs have similar behavioral effects through various molecular mechanisms. Bilateral injections of L-DOPA (the physiological precursor to dopamine and norepinephrine) directly into the striatum result in a production and accumulation of dopamine in that area (Bertler & Rosengren, 1959). On a behavioral level these injections produce stereotypic responses similar to those that occur as a consequence of direct dopamine injections. Thus, it is demonstrated that L-DOPA administration produced dopamine-like behaviors, and it is presumed to do so through

metabolic conversion to dopamine.

The psychomotor stimulant amphetamine activates dopaminergic systems in many ways. First, when it is injected directly into the caudate nucleus, increased amounts of dopamine can be recovered from extracellular space (McKenzie & Szerb, 1968). Similarly, amphetamine locally applied to the caudate nucleus following injections of radioactively labelled dopamine into the same area causes significant amounts of the radioactive neurotransmitter to appear in extracellular spaces (Besson, Cheramy, Glowinski & Gauchy, 1973; Carlsson, 1970; Corrodi, Fuxe & Hokfelt, 1967). Such findings suggest that one of the functions of amphetamine includes a release of dopamine from nerve terminals in the brain.

In addition to causing the release of dopamine, there is considerable evidence to suggest that amphetamine also interferes with the reuptake of dopamine at the cell membrane (Coyle & Snyder, 1969; Ferris, Tang & Maxwell, 1972; Heikkula, Orlansky, Mytilineou & Cohen, 1975). If dopamine is not inactivated through uptake by the presynaptic neuron, then its prolonged presence in the extracellular space generates dopaminergic activity at the postsynpatic receptors. In other words,

blocking the reuptake process has a final consequence similar to dopamine being released into the synaptic cleft by a releasing agent: in each case dopaminergic activity is prolonged because of the extended length of time that dopamine remains in the synaptic space.

That amphetamine both releases and inhibits the reuptake of dopamine in the brain is thought to account for the major pharmacological action of amphetamine. The fact that it potentiates the activity of the neurotransmitter strongly suggests that the effects of amphetamine might be mediated by dopaminergic pathways in the brain. This is consistent with its behavioral effects. When amphetamine is administered directly into the caudate nucleus, stereotypic patterns of behavior are seen similar to the behaviours seen in L-DOPA or dopamine-injected animals (Ellinwood & Balster, 1974; Randrup & Munkvad, 1974). That amphetamine causes behavioral consequences similar to those produced by dopamine injections implicates the involvement of central dopaminergic mechanisms in the mediation of its effects.

Administration of apomorphine, another psychomotor stimulant, is thought to result in the stimulation of dopamine receptors directly

(Andén, Rubenson, Fuxe & Hokfelt, 1967). Behaviorally, the effects of systemic apomorphine injections are consistent with the pattern of behaviors observed following L-DOPA and amphetamine administration (Ernst & Smelik, 1966; Randrup & Munkvad, 1966, 1974; Scheel-Kruger & Randrup, 1967).

As mentioned, bilateral injections of dopamine into the nucleus accumbens result in enhanced locomotor activity. When dopamine is unilaterally injected into this area, asymmetrical locomotor activity in the form of rotational behavior ensues (Ungerstedt, Butcher, Butcher, Andén & Fuxe, 1969). Although the direction is opposite, rotational movements can also be induced by unilateral striatal lesions using the neurotoxin 6-hydroxydopamine. This procedure causes a selective degeneration of nigro-striatal neurons which is thought to be responsible for the specific motoric asymmetries that have been observed (Ungerstedt, 1968, 1971b).

When unilaterally lesioned animals are injected with psychomotor stimulant drugs, their behavioral reactions differ according to the drug. Systemic amphetamine administration results in even more vigorous circular rotations in the same direction (Andén et al., 1967; Kelly & Moore, 1976; Ungerstedt,

1971b). As reported earlier, the effects of amphetamine (i.e., dopamine release) are mediated by nigro-striatal dopaminergic neurons. As a result of the unilateral lesions to this pathway, amphetamine causes a release of dopamine only on the intact side. Therefore yet a further imbalance is created causing more intense rotational movements. When apomorphine or L-DOPA is administered systematically, rotational behavior in the direction of the unoperated (contralateral) side is induced (Kelly & Moore, 1976; Ungerstedt, 1971b; Von Voightlander & Moore, 1973). The rotational behavior in this case is opposite in direction to the circling behavior observed after amphetamine administration. Although apomorphine is known to act directly on the dopamine receptors (Andén et al., 1967) while L-DOPA's actions are presynaptic in origin (Ungerstedt, 1971b), the contralateral rotations observed by both drugs have been attributed to a supersensitivity of the denervated striatal dopamine receptors (Ungerstedt, 1971b).

Thus, it has been demonstrated that psychomotor stimulants mimic the effects of dopamine in the brain. Behavioral and neurochemical studies involving both dopamine and psychomotor stimulants suggest

that the effects of these drugs are mediated by dopaminergic pathways in the brain. Since these drugs potentiate the action of dopamine on nigro-striatal neurons, they can be used as an index of the effects of neuroleptics on dopaminergic activity. The stereotypic behavior and locomotor activity which typically follow stimulant administration are blocked when animals are pretreated with neuroleptics (Fog, Randrup & Pakkenberg, 1968a,b; Lal, Marky & Fielding, 1976; Pijenburg, Honig & Van Rossum, 1975; Schlecter & Butcher, 1972). Neuroleptics have also been demonstrated to block the vigorous rotational movements that are seen in lesioned animals following systemic stimulant administration (Andén et al., 1967; Andén, Butcher, Corrodi, Fuxe & Ungerstedt, 1970; Ungerstedt, 1971b). Since neuroleptics are capable of attenuating both stimulant-induced and lesion-induced behaviors, it follows that neuroleptics inhibit dopaminergic activity in the brain.

A final line of behavioral evidence supporting the notion that neuroleptic administration results in a blockade of dopamine receptors in the central nervous system comes from studies which look at the correlations between the degrees of dopamine binding

and the clinical potency of neuroleptics. It is possible to predict the relative clinical efficacy of a specific neuroleptic from its degree of binding affinity to the dopamine receptor. The more readily the neuroleptic binds to the dopamine receptor, the more effective the drug is in controlling the behavior of the schizophrenic patient (Burt et al, 1976; Creese, Burt & Snyder, 1976; Seeman, 1981; Seeman & Lee, 1975; Seeman, Chau-Wong, Tedesco & Wonk, 1975). Since the affinity of neuroleptics for dopamine receptors but not other brain binding sites is correlated with behavioral effectiveness, it is likely that neuroleptic action is exerted through the blockade of dopamine receptor activity.

To summarize, through radioactive labelling, electrophysiological recording and behavioral measures, it appears that neuroleptics produce a blockade of central dopamine receptors. That these drugs bind to the same receptor sites as does dopamine coupled with the fact that they block the action of the drugs that release and potentiate dopaminergic activity support the speculation that neuroleptics are dopamine antagonists. Moreover, the clinical potency of the neuroleptics is largely

proportional to the degree of binding on the dopamine receptors.

Effects of Neuroleptics in Normal Animals

In addition to the biochemical and physiologicial effects of neuroleptics described above, research has been conducted on the behavioral effects of neuroleptics in an attempt to better understand the general function of dopamine in behavior. There have been two major hypotheses as to the effects of neuroleptics on operant behavior in normal animals. Both are derived from studies which have demonstrated that animals treated with neuroleptics fail to respond as strongly or frequently as in their previous non-drugged state. In the first hypothesis it is suggested that the behavioral deficits observed in neuroleptic-treated animals are due to motoric difficulties, while in the second hypothesis it is suggested that the deficits result from an attenuation of the rewarding value of normally reinforcing stimuli.

Animals will perform a variety of responses in order to obtain such rewards as food, water and brain stimulation (Dunham, 1972; Olds & Milner, 1954; Skinner, 1938). Disruptions in the performance of these responses caused by neuroleptic treatment

have been demonstrated, and proponents of the motor deficit hypothesis have interpreted these disruptions to be due to an incapacity of the animals to perform the responses necessary to obtain the reward in question (Ahlenius, 1979; Ettenberg, Cinsavich & White, 1979; Fibiger, Carter & Phillips, 1976; Rolls, Rolls, Kelly, Shaw, Wood & Dale, 1974). The conclusion that animals are incapable of initiating or sustaining adequate motor responses has been reached as a result of many investigations using different methodological approaches. One such method has been to compare the effects of working for a rewarding stimulus with the effects of allowing free access to the rewarding event. Hungry animals pretreated with neuroleptics show significantly depressed rates of bar pressing for food reward, while animals given the same drug treatment and allowed free access to food eat as much as undrugged controls (Fibiger et al., 1976). Since food consumption in the free-feeding condition was normal, Fibiger et al. (1976) concluded that the decrease in responding observed in the former group could not be a result of a decreased hunger drive or a decrease in the rewarding properties of the food. Rather, these investigators argued that

neuroleptics produced an inability to perform the necessary lever pressing response.

Against this argument it is quite possible that the decreased lever pressing is a consequence of the decreased rewarding impact of food under neuroleptics. If this were the case, then an alternative explanation to the data provided by Fibiger et al. (1976) could be offered. If food is not as rewarding under the influence of neuroleptics, then decrements in rates of responding seen in animals working for food would be expected. If, however, food is presented to the animals in a free feeding situation (that is, with little response cost to the animals), then the primitive cues associated with food and consummatory behavior could be sufficient to maintain feeding behavior even after neuroleptic pretreatment.

Some researchers have suggested that what neuroleptic-treated animals are incapable of coping with is the complexity of particular required motor acts. Indeed, it has been demonstrated that rats failed to perform a complex motor task (pressing a lever) to obtain water under the influence of the neuroleptic spiroperidol, while no decrease in performance was observed when the rats were

required to carry out a simpler motor task such as licking a tube to obtain water reinforcement (Rolls et al., 1974).

Although the sequence of behaviors involved in approaching and pressing the lever and in obtaining reinforcement may be considered complex as suggested by Rolls et al. (1974), such behaviors may also require more effort on the animal's part then simply positioning itself in front of the water dispenser and licking the water. Since the reinforcing value of water may be lessened under the influence of neuroleptics, its acquisition may simply not be worth the extra effort involved in the lever pressing task.

In addition to the possibility that the motivation to perform the licking responses for water reward is attenuated under neuroleptics, there also exists the possibility that licking is more difficult to disrupt because it is more biologically primitive. Consummatory behaviors such as eating and drinking are of direct value to the animal, whereas preparatory responses (e.g., bar pressing and alley running) merely lead to, and make possible, a consummatory response (Woodworth, 1918). Since preparatory responses lead up to the

consummatory act, they are further removed from the direct goal of the organism. Therefore it is likely that neuroleptics may more easily interfere with goal-directed behaviors (i.e., pressing a lever) than with the actual consummatory act (i.e., licking a tube for water) towards which these behaviors are directed.

A third approach which led to the conclusion that neuroleptics produce motor deficts has involved the observation of a response that the animal emits naturally at a high rate. Following injections of the neuroleptic pimozide, Ettenberg et al. (1979) placed animals in a box which had a two centimeter hole in the middle of one of the walls. The latency of the first nosepokes in the test session was recorded. Although no difference was found in the latency of emission of the first nosepoke between drugged and undrugged animals, the ones injected with pimozide emitted fewer nosepokes during the test session than did control animals. Ettenberg et al. (1979) argued that because nosepoking is a behavior which occurs in the absence of primary reinforcement, the decrease in its frequency after neuroleptic administration is indicative of a motoric incapacity induced by the drug.

This argument, too, is open to question. Within the motivation literature, curiosity, the need to explore and the alleviation of boredom have typically been considered primary drives. Given a choice, animals will often prefer to place themselves in novel situations. Perhaps even more striking is the fact that deprived animals, when introduced into a novel situation, will invariably explore the novel features of the environment before settling down to eat or drink (Millenson, 1967). This suggests that the reinforcing value of exploration exceeds that of food or water, at least initially. In view of these findings, it seems possible that animals might naturally poke their noses out of a hole in an experimental chamber for what can be considered "intrinsic" primary reinforcement. If one considers this possibility, then a different light is cast on the findings reported by Ettenberg et al. (1979). The lack of a difference between the drugged and undrugged groups in the latency of the first nosepoke rules out the possibility that pimozide induced a state of gross motor impairment in the animals. Moreover, that the pimozide-treated group emitted fewer total nosepokes may be a function of the

animals' decreased interest in the environmental surroundings. This is significant for under drug-free conditions such interest may maintain responding for a time by serving as a reinforcer. Indeed, monkeys placed in a dimly lit experimental chamber will learn to open a door in a discrimination task in order to receive 30 seconds access to views of the laboratory, the experimenter, other monkeys or moving toy objects such as an electric train (Butler, 1953). Thus, it is quite possible that neuroleptics cause a decrease in the rewarding impact of the environmental surroundings, and this decrease can account for a decrease in their general locomotion.

Another technique which has been used in an attempt to demonstrate that neuroleptics produce motor deficits in animals has been 6-hydroxydopamine lesions to the nigro-striatal pathway. Lesions of this nature have been shown to cause decrements in animals' bar pressing behavior similar to the decrements seen after neuroleptic treatment (Fibiger et al., 1976). Fibiger et al. (1976) argue that in both these instances the animal's ability to initiate and maintain a specific motor response is dramatically impaired.

The conclusion of Fibiger et al. (1976) that both neuroleptics and nigro-striatal lesions produce motor deficits has not been uncontested in the literature. There exist many reports of lesion-induced deficits suggesting that the impairment seen after nigro-striatal damage is not simply motoric in nature. For example, severe deficits in orientation to stimuli were produced in rats whose ascending dopamine-containing neurons were destroyed. Since rats with unilateral lesions to these pathways were capable of turning contralaterally when placed in an open field, it was concluded that the deficit observed was simply more of a sensory nature than a motor one (Marshall, 1978; Marshall, Turner & Teitelbaum, 1971). Furthermore, the sensorimotor dysfunction produced by nigro-striatal lesions has been shown to reverse when the animals are placed in a highly activating situation. Lesioned animals forced to swim underwater to safety, placed in an ice bath or put in other high arousal situations are able to overcome their difficulty in initiating motor movements (Feeney & Weir, 1979; Marshall, 1978; Marshall, Levitan & Stricker, 1976; Marshall et al., 1971; Ranje & Ungerstedt, 1977a, 1977b, 1977c). A motor

deficit hypothesis therefore provides a clearly insufficient explanation of the lesioned animals' behavior because of their demonstrated capacity to locomote albeit only under conditions of extreme stress.

That animals with severe nigro-striatal damage can reverse their akinetic state under certain conditions presents what appears to be an animal analog of a phenomenon which occurs in Parkinson's disease. One pronounced symptom of this debilitating disorder is the difficulty which Parkinsonian patients have in initiating movements (Barbeau, 1974). However, when confronted with an extremely stressful situation (for example, a fire in the house), Parkinsonian patients have been known to overcome their disability and escape from the hazardous environment. When safe, they revert to their previous akinetic state (Schwaub, 1972).

That such "emergency" stimuli as a fire for Parkinsonian patients and underwater mazes for nigro-striatal lesioned animals are required for behavior to be observed, suggests the presence of motivational components in behaviors such as locomotion. Indeed, the fact that lesioned animals or Parkinsonian patients do not show signs

of movement does not mean to say that they are physically incapacitated. Furthermore, the neurons that have been lesioned by 6-hydroxydopamine or that have degenerated as a result of Parkinson's disease are known to have dopamine as their transmitter (Hornykiewicz, 1966, 1974; Thornburg & Moore, 1975). Since it is dopamine which appears to be the critical transmitter that when blocked by neuroleptics attenuates the reward sustaining qualities of brain stimulation (Zarevics, Weidley & Setler, 1977; Zarevics & Setler, 1979), the possibility that dopamine denervation or neuroleptic treatment results in a motivational deficit cannot be overlooked.

Recent studies have revealed deficits in performance where it is nevertheless clear that the animals are capable of performing the required behaviors. Direct evidence from these studies questions the validity of a drug-induced motor impairment hypothesis. Experiments in which the neuroleptic spiroperidol has been bilaterally injected into various sites of monkey brains reveal that self-stimulation at some sites is severely attenuated while self-stimulation at other sites is not affected at all (Mora, Rolls, Burton & Shaw, 1976). Moreover, immediately after the test sessions for

self-stimulation are completed, the monkeys are able to perform the identical motor task to obtain a 20 percent glucose solution, indicating further that the animals are indeed capable of performing motor responses under the influence of neuroleptics.

Along similar lines microinjections of spiroperidol into the nucleus accumbens (a region high in dopamine content) significantly reduce self-stimulation rates. Self-stimulation of the contralateral nucleus accumbens is not altered. Similarly, injections of the neuroleptic into the prefrontal cortex (another region high in dopamine content) cause a decrease in self-stimulation on the ipsilateral but not the contralateral side (Robertson & Mogensen, 1978). These findings rule out the possibility that neuroleptics exert a general bilateral motor impairment.

It is evident that the selective decrements in responding observed by Robertson and Mogenson (1978) and Mora et al. (1976) cannot be explained in terms of a general impairment of motor functioning. Since normal rates of responding have been demonstrated in some situations but not others, a more likely interpretation of the evidence is that the animals are capable of responding but nevertheless fail to

do so. The deficits in responding seen after neuroleptic treatment may be a reflection of an attenuation of the reinforcing properties of the rewarding event (in this case, brain stimulation).

Further evidence of normal performance capacity is provided by studies employing a paradigm in which a number of successive bar presses result in a reduction of the current intensity of the brain stimulation delivered. In addition, a second lever is provided which, when pressed, would reset the current to the original intensity of stimulation. Neuroleptic-treated animals press the reset button sooner than do undrugged controls (Schaefer & Michael, 1980; Zarevics & Setler, 1979). This finding indicates that animals under neuroleptics are still capable of highly coordinated movements (in this case, moving to a lever and pressing it). Moreover, higher current intensities are required in order for neuroleptic-treated animals to maintain levels of responding similar to those of non-drugged controls. This finding suggests that neuroleptics cause an attenuation of the reinforcing properties of rewarding events (in this case, brain stimulation).

One interesting effect that occurs in animals treated with neuroleptics is that normal or near

normal rates of responding are sustained, at least initially. Animals trained to press a lever for food and given the neuroleptic pimozide responded in quite the same fashion in the first test session as do non-rewarded, undrugged controls (Wise, Spindler, De Wit & Gerber, 1978; Wise, Spindler & Legault, 1978). Evidently, pimozide at the dose tested did not interfere with the animals' ability to initiate and to conduct complex motor movements, at least in the first test session. Similarly, neuroleptic-treated animals working for brain stimulation reward typically respond vigorously at the beginning of the test session in a manner similar to undrugged, non-rewarded or vehicle drug control animals (Fouriezos, Hansson & Wise, 1978; Liebman & Butcher, 1973).

Since a performance capacity has been demonstrated in neuroleptic-treated animals, it is evident that a simple motor deficit model is not sufficient to explain the observed deficits in performance. Rather, it may be that neuroleptics exert a much more subtle effect by somehow attenuating the rewarding properties of the primary reinforcing stimuli of food and brain stimulation. If this were the case, then it would be expected

that the behaviors that were previously maintained by these reinforcers would eventually undergo a process that would resemble extinction. Support for this notion is found when the effects of repeated neuroleptic administration are investigated. As reported earlier, animals given the neuroleptic pimozide for the first time under a continuous reinforcement schedule bar press for food reward at approximately the same rate as undrugged or non-rewarded controls. However, subsequent experience in the testing situation with pimozide results in a decrease, across sessions, in the total number of bar presses per session. Furthermore, after four spaced exposures to pimozide and the testing situation, the bar pressing rates of the drug-treated animals become significantly discriminable from the undrugged, but not the non-rewarded, control animals (Wise et al., 1978a, 1978b).

To rule out the possibility that the continued drop in responding is simply a result of pharmacological experience with pimozide, another group of animals was given injections of pimozide in their home cages for each of the first three test sessions and was allowed access to the experimental chamber on the fourth test day. This

group emitted as many responses as the group of animals given pimozide for the first time (Wise et al., 1978b). It appears, then, that repeated experience with pimozide in combination with the testing situation has a cumulative experiential effect. The animals seemingly make the association that on test days when pimozide is in their system, food is not as rewarding. Since the loss of impact of a rewarding stimulus is somewhat similar to the removal of the rewarding stimulus, it is as if the animals undergo an extinction session while under the influence of pimozide. A history of testing with pimozide and normal reward conditions resembles closely the history of testing without drugs and with no reward.

The similarity between the effect of neuroleptics and the impact of non-reward is also demonstrated when pimozide is administered to animals that have been given prior experience with non-reward. From the evidence presented earlier, it would be expected that hungry animals given pimozide for the first time would bar press for food reward at normal or near normal rates across the test session. However, animals subjected to three test sessions of non-reward and then given

pimozide on the fourth test day responded in the same manner as did animals that were given three previous exposures to pimozide and then given the drug again on the fourth test day. The three previous exposures to the non-reward condition together with the effects of the first experience with pimozide produced an extremely low rate of responding across the test session. Since animals undergoing extinction procedures typically respond with decreasing frequency across test sessions (Kling, 1971) and since response rates in the non-reward-pimozide transfer conditions show a progressive decline across test sessions, it is as if pimozide substituted for the fourth exposure to the extinction condition. This "transfer" effect provides perhaps the most striking evidence in support of the reward attenuation hypothesis.

Another demonstration of the similarity between the effect of pimozide and the impact of extinction involves a phenomenon labelled spontaneous recovery. Animals that have extinguished a response to a stimulus that no longer provides reinforcement typically respond to that stimulus (for a short time and to a lesser degree) again in subsequent test sessions (Millenson, 1967). If a lever, which

when pressed provides brain stimulation, is disconnected, animals will soon cease responding to it (Deutsch, 1964; Olds & Milner, 1954). Pimozide-treated animals subjected to this procedure, followed by a period where a bar press provides a rewarding situation again, press the lever at a high rate for a short time (Fouriezos & Wise, 1976; Fouriezos et al., 1978).

Yet another demonstration of the similarity between the effect of pimozide and the impact of non-reward can be found in studies which require animals to run down alleyways for reinforcement. Such studies have shown that pimozide-treated animals are as capable of organizing a complex, coordinated set of behaviors (that is, running down an alleyway and pressing a lever for brain stimulation) as are undrugged, non-rewarded controls in the initial trials of test sessions. It is only in the subsequent trials that an increase in response latencies and a decrease in running speeds is observed in both groups (Fouriezos et al., 1978). That pimozide-treated animals demonstrate an ability to perform these tasks in the initial trials rules out any likelihood that the drug induces an inability to

initiate motor movements. Moreover, the fact that pimozide-treated animals respond in a similar fashion to that of the non-rewarded controls across the entire test session suggests that pimozide somehow interferes with the reinforcing properties of the previously rewarding brain stimulation.

The changes in response latencies and running speeds that are observed in pimozide-treated animals working for brain stimulation are not seen as quickly when food is offered as the rewarding stimulus. Wise et al. (1978b) failed to notice any difference among a drugged but normally rewarded, an undrugged but non-rewarded, and a vehicle control group in either latencies or running speeds across all eight trials in the first test session. However, differences among the groups were observed when the same animals were retested under the same conditions one week later. The pimozide-treated group and the non-rewarded group took progressively longer both in starting to run and in reaching the goal box. Hungry animals given pimozide for a second time seemingly made the association that food is not as rewarding when pimozide is in their system, and their performance may be a reflection of this neuroleptic-induced attenuation of the

rewarding stimulus.

Several examples of the similiarity between the influence of neuroleptics and the impact of non-reward have been cited. A possible explanation for the decrements in performance observed in drug-treated animals could be that neuroleptics make the animals more susceptible to fatigue. A number of investigators (e.g., Phillips & Fibiger, 1979; Ettenberg, personal communication; White, personal communication) have argued that the initial, normal rate of responding and the subsequent drop in response rates across the test session reported by Wise et al. (1978a, 1978b) may be attributable to neuroleptic-induced fatigue. To test this specific possibility, Franklin and McCoy (1979) trained rats in a paradigm that alternated 3 minute periods of Variable Interval (VI15) and Fixed Ratio (FR4) reinforcement. Separating the schedules were 3 minute periods of non-reward. Animals tested included a pimozide-treated and a reduced-current group. Throughout training, half of the animals in each group were exposed to a flashing light, which, when turned on, signified the institution of the FR4 schedule. The light stimulus remained on through a subsequent period of non-reward and was

turned off when the schedule was changed to VI15. Thus the animals were trained to associate (a) the flashing light onset with the recommencement of reward on FR4 following a period of non-reward and, (b) the flashing light offset with the recommencement of the VI15 schedule following non-reward. The pimozide-treated and reduced-current groups produced similar decrements in rates of responding for brain stimulation reward. Of particular interest is the comparison between these two groups. When the pimozide-treated group ceased responding, the effect of the onset of the flashing light stimulus on them was identical to its effect on the reduced brain stimulation group. Both groups responded as vigorously to the light onset as when they began responding at the start of the test session. This led Franklin and McCoy (1979) to conclude that depression of responding seen in the pimozide group could not be the result of any specific motor deficit since they responded at near normal rates in the middle of the test session. That pimozide mimicked the effects of reduced brain stimulation reward suggests that it interfered with the rewarding properties of a previously rewarding stimulus.

Thus, far, the reward-attenuating properties of

neuroleptics have been discussed in relation to food and brain stimulation reward. Recent studies with stimulant drugs such as amphetamine and cocaine also demonstrate that neuroleptics interfere with the rewarding properties of drugs of abuse. Typically, when the dose per injection of amphetamine is either lowered or raised, lever pressing rates for the drug increase or decrease, respectively (Yokel & Pickens, 1973). Thus, when the amount of the reward is decreased (that is, when the dose is lowered), the animals press more often in order to receive essentially the same amount of drug per test session. Pimozide-treated rats show an increase in lever-pressing for amphetamine in comparison to undrugged controls (Yokel & Wise, 1975, 1976), suggesting that more of the drug may be required in the system in order for it to maintain the same reinforcing effect. Interestingly, even high doses of amphetamine and cocaine are not capable of sustaining high levels of responding after the initial segments of the test sessions (de Wit & Wise, 1977; Yokel & Wise, 1975, 1976). Like the brain stimulation paradigm, the normal (and in fact, increased) levels of self-administration of amphetamine and cocaine rule out any possibility of

a pimozide-induced motor deficit. Moreover, the subsequent decrement and cessation of response rates suggest that pimozide interferes with the rewarding impact of drugs of abuse.

The present study. As reported earlier there exist two contrasting hypotheses concerning the effects of neuroleptics in animals. One involves the notion that neuroleptics induce a state of motoric incapacity in animals, while the other involves the notion that neuroleptics attenuate the rewarding properties of the reinforcing stimuli. Although there is strong evidence to suggest that neuroleptic-treated animals are capable of initiating and executing complex motor responses (e.g., Fouriezos et al., 1978; Franklin & McCoy, 1979; Wise et al., 1978a, 1978b) which is in direct contrast to the motor deficit view, more evidence is required to strengthen the alternative position that neuroleptics significantly blunt the rewarding properties of otherwise reinforcing stimuli. The present series of experiments represents a further evaluation of the effects of pimozide on lever-pressing in the normal rat. In the following three investigations, attempts have been made to confirm that animals are indeed capable of

initiating and performing (at least initially) a series of motor movements and to explore the similarities between the impact of pimozide and the impact of the non-reward (extinction) condition. The first experiment is a replication of that conducted by Wise et al. (1978b): both a response capacity and a neuroleptic-induced reward deficit is demonstrated in drug-treated animals. Since it has been argued that neuroleptics produce motor deficits in animals (e.g., Ettenberg et al., 1979; Fibiger et al., 1976), a confirmation of a response capacity and a neuroleptic-induced reward deficit is of particular importance. In the first experiment increased experience with pimozide in the testing situation was expected to lead to a gradual reduction in the rate of responding. Furthermore, it was predicted that the animals' first experience with pimozide after previous repeated exposures to non-reward would be significantly different from the animals' first experience to pimozide without such a history.

The second experiment investigated the effects of pimozide on the acquisition of a particular behavior. The length of time necessary for hungry, naive animals to acquire the standard lever-pressing

response under different doses of pimozide pretreatment is a critical factor in understanding the extent (if any) of pimozide's effects on the rewarding properties of food. It was predicted that the impact of food on hungry, drug-treated animals would be sufficiently blunted by the drug to retard the learning of the lever-pressing habit. Moreover, since different levels of pimozide were administered, it was predicted that the severity of the retardation of acquisition would be related to the dose delivered.

Finally, the third experiment was an attempt to determine if there were residual effects of pimozide. It was postulated that a reason there was a failure to produce a transfer effect from the pimozide condition to the non-reward condition was determined by the pharmacological history of that group of animals. This experiment attempted to determine if animals given pimozide injections for five days would demonstrate an increase in their response rates when placed in the transfer test condition. It was predicted that if animals in the daily pimozide group showed such an increased rate of responding, then the failure to produce a transfer from the pimozide to the

non-reward condition could be attributed to their pharmacological history.

Experiment 1

Wise et al. (1978b) demonstrated a similarity between the attenuated impact of food in animals treated with pimozide and the impact of non-reward in animals tested under extinction conditions. Animals treated with pimozide across four spaced sessions showed a significant decrease in response rates over these sessions. This pattern of responding was also observed in animals in the non-reward (extinction) condition. Furthermore, animals subjected to three sessions of non-reward and then transferred to pimozide for the first time on the fourth test day responded in the same fashion as the group receiving their fourth test under the non-reward condition. In this transfer group, pimozide appeared to have a similar impact as the predicted fourth exposure to non-reward. A motor deficit hypothesis is not sufficient to explain the deficits observed by Wise et al. (1978b). Rather, these findings support a model based on the attenuation of the rewarding propeties of previously reinforcing stimuli.

Essentially, there are two main criteria that an event must meet in order for it to be considered rewarding. The present experiment deals with the

first criterion which demands that the event be able to sustain a well trained or well-established set of behaviors. The present investigation is a replication of that by Wise et al. (1978b), designed to confirm that pimozide does not critically impair performance capacity in animals and that pimozide causes animals to respond in a similar manner to animals undergoing extinction. Here, it was expected that food-deprived, well trained animals would a) respond normally or at least almost normally after their first experience with pimozide (performance capacity); b) demonstrate a significant decrease in responding by the last test session (reward deficit); and c) respond differently, if they were given pimozide after repeated exposure, to non-reward from those animals experiencing pimozide for the first time without this history (transfer effect).

Method

Subjects. The subjects in this experiment were 32 experimentally naive male Sprague-Dawley rats that weighed between 250 and 300 grams each upon delivery from the supplier.

Apparatus. The apparatus consisted of eight conditioning units (Grason Stadler and Company).

Each unit was individually housed in a sound attenuating box. The appropriate relays and counters required for the automatic operation of each box were located in an adjacent room.

Procedure. The animals were randomly assigned to four treatment groups and then individually housed in a temperature and humidity controlled room with a 12 hour light/dark cycle. They were fed ad libitum for a period of 72 hours and then placed on a 22 hour food deprivation schedule. Water was always available in the home cages.

The training sessions began after one day of deprivation. Each session lasted 45 minutes. The initial session consisted of magazine training and was followed by 15 consecutive days of bar pressing under a continuous schedule of reinforcement (CRF).

After the completion of the 15 training days, the experimental sessions began. The four treatment groups were as follows:

1) Pimozide: Animals in this group received 1 mg/kg of pimozide (Janssen Pharmaceuticals, Inc.) every third day for a total of five times. During the 45 minute test sessions they were placed on a CRF schedule.

2) Non-reward: Animals in this group received 1 mg/kg of the drug vehicle tartaric acid rather than pimozide. The feed tube was also disconnected from the food dispenser so that when the animals were placed in the experimental chambers, they did not receive any food pellets but the sounds associated with pellet delivery were still present. Each test session lasted 45 minutes.

3) Pimozide-Non-reward: This group received identical treatment to the Pimozide group except for the last test day (Day 13). On this day instead of being given pimozide as in the previous four injections, they were given .50 mg/kg of tartaric acid. Animals in this group were therefore subjected to their first experience with non-reward on the final test day.

4) Non-reward-Pimozide: This group received identical treatment to the non-reward group except for the last test day. On this day instead of being placed in the non-reward condition as in the previous four test sessions, they were injected with 1.0 mg/kg of pimozide and subjected to their first experience with the drug and normal reward conditions in the experimental chambers.

All animals received their injections four hours prior to testing. The number of lever presses was recorded every five minutes. During the two days between treatments, the animals received 45 minutes of training to bar-press for food under a CRF schedule. These inter-test training days were identical to the initial 15 days of training. One hour after each session ended, the animals were allowed to feed freely in their home cages for two hours.

Results

A two-way (Groups x Treatment Days) Analysis of Variance with repeated measures across days was conducted on the first four test days to determine the cumulative effects of the treatment conditions. No significant difference among the four groups as well as no significant interaction between the groups and treatment days was found. However, the analysis revealed a significant Treatment Days effect, $F(3,84) = 17.40$, $p < .001$. The response rates in all four groups dropped progressively across the first four test days. Figure 1 illustrates the rates of responding for the groups.

A second two-way (Groups x Treatment Days) repeated Analysis of Variance with repeated measures

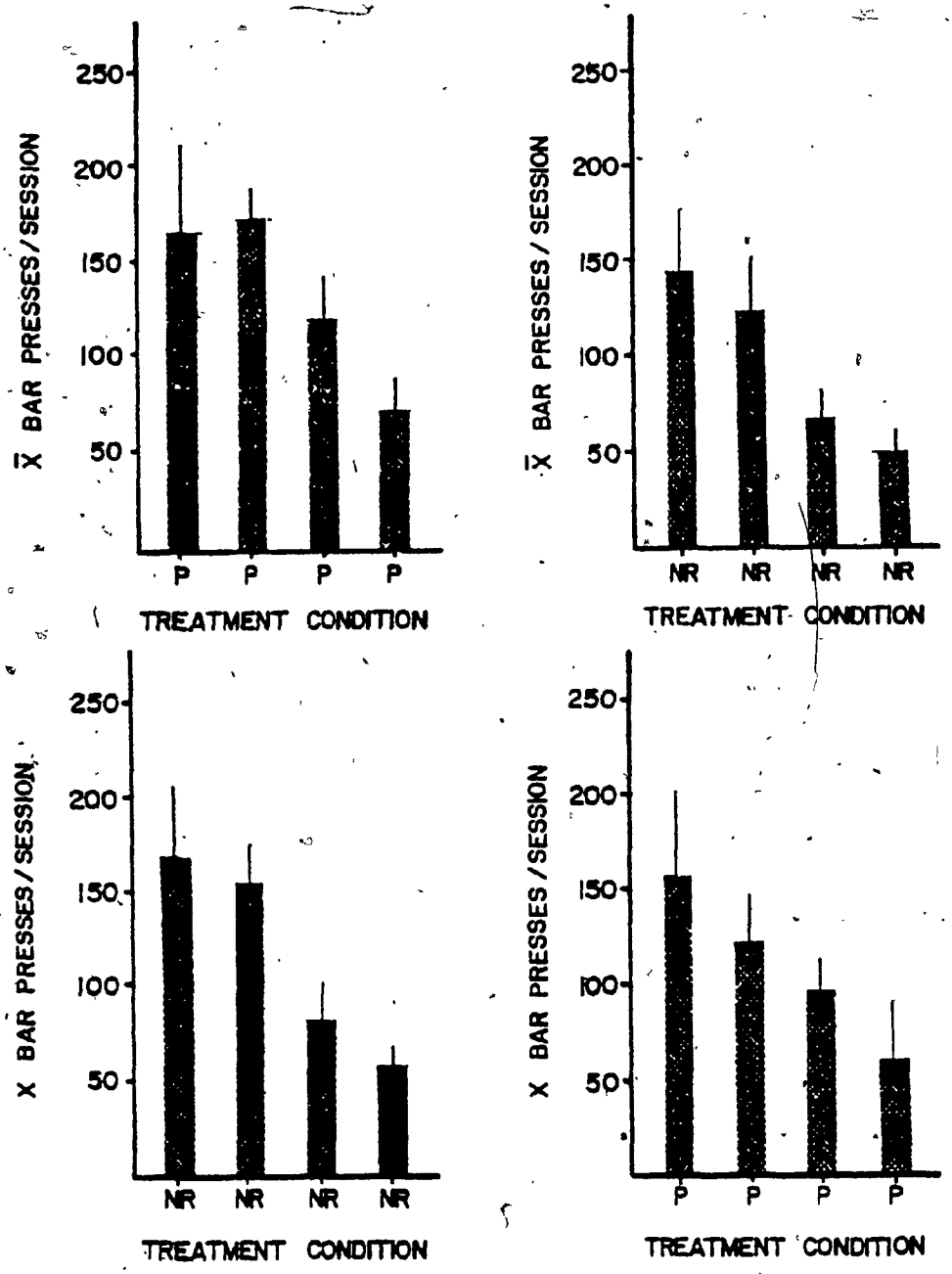

Figure 1. Mean number of bar presses for pimozide and non-reward treatment groups across four test days.

P = Pimozide
NR = Non-reward

across treatment days was conducted to include the effects of the final transfer test day. A significant Groups x Treatment Days effect was found $F(12,112) = 4.12$, $p < .001$.

Post hoc analyses on the first and last test day were conducted for each group. In the Pimozide condition, there was a significant decrease in response rates between Test Day 1 and Test Day 5 ($F(1,7) = 6.27$, $p < .05$). After four repeated experiences with pimozide, the animals responded significantly fewer times in a fifth test session. This occurred despite the two days of retraining between test days to re-establish normal rates of responding.

Similar results were found in the Non-reward group ($F(1,7) = 12.25$, $p < .01$). The fifth experience in the extinction condition significantly reduced the rate of responding to mere token responses, all occurring within the first few minutes of the test session.

Post hoc analysis of the Pimozide-Non-reward transfer group revealed a significant difference between the first and fifth test days ($F(1,7) = 14.08$, $p < .01$). As Figure 2d illustrates, response rates rose dramatically on the transfer test day

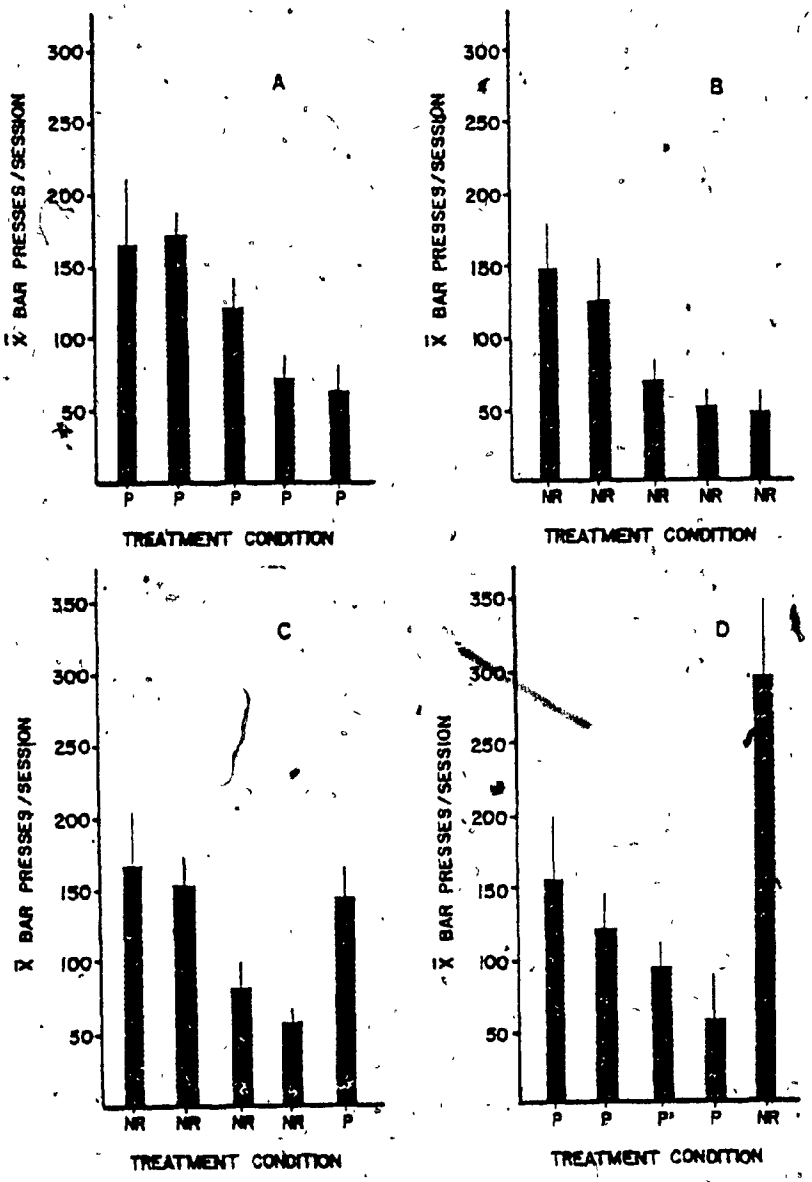

Figure 2. Mean number of bar presses for pimozide and non-reward treatment groups including the transfer test day.

P = Pimozide
NR = Non-reward

when compared to the animals' first experience with pimozide on Test Day 1.

In the Non-reward-Pimozide transfer group, response rates showed a statistically insignificant difference on the transfer test day (see Figure 2c). Prior history (four test sessions) with non-reward did not influence the response rates of the animals given pimozide for the first time on Test Day 5.

A third two-way (Groups x Retraining Days) Analysis of Variance with repeated measures across days revealed no differences between groups in response rates during the inter-test (retraining) days. However, following each test day there was a positive trend in the number of responses made in the subsequent retraining sessions for all groups tested.

Discussion

In accordance with the data of Wise et al. (1978b), animals treated with pimozide responded in a similar fashion to undrugged animals subjected to repeated conditions of non-reward (extinction). In the first test session, these two groups of animals responded at normal or near normal rates and showed a progressive decline in responding across subsequent sessions. That pimozide-treated

animals bar-pressed as often as did non-drugged controls in the first test session confirms the notion that pimozide does not produce any gross motor impairments. Rather, these results provide a demonstration of normal performance capacity while the animals were under the effects of the drug. Furthermore, given that there is the capacity to respond in these animals, the successive decline in response rates across sessions reflects a progressive diminution of the rewarding properties of food itself. Since response rates during the two drug-free retraining days between injections were normal, it appears that an association between pimozide and food was made - the fifth experience with both conditions where food was no longer a rewarding stimulus.

The transfer effect that was demonstrated by Wise et al.(1978b) was not replicated in this study. These investigators found that after three exposures to the non-reward condition animals responded to their first experience with pimozide on the fourth test day in a similar fashion to the undrugged controls during their fourth exposure to non-reward. However in the present study previous experience with non-reward did not have any effect on the

animals' first experience with pimozide. The animals responded at rates similar to undrugged, normally rewarded animals. Although this finding strengthens the view that animals treated with pimozide are capable of responding motorically, it suggests that pimozide effects are not entirely equivalent to the effects of extinction.

A failure to produce a transfer effect was also observed in a second group. Four spaced injections of pimozide did not result in a decrease in response rates when the animals were subjected to their first experience with non-reward. Responding in this group was different (although not significantly) from the pattern of responding in the Non-reward-Pimozide group. Animals given repeated pimozide injections and then subjected to the non-reward condition for the first time showed an enhanced resistance to extinction.

A failure to replicate the transfer effect has also been reported by Mason et al. (1980) and Wise et al. (1978a) using food as the reinforcing stimulus, and by Gerber, Sing and Wise (1981) using water as the reinforcing stimulus. The reliability of this effect is therefore suspect. However, trends in the direction of transfer have been observed by

Gerber et al.(1981) and Wise et al.(1978a). This trend suggests that although the transfer effect is neither robust nor statistically reliable, the transfer of experience from non-reward to the condition of neuroleptic treatment, and vice versa, has not yet been adequately explored.

Although Experiment 1 did not demonstrate a trend toward transfer from non-reward to pimozide, there did appear to be a difference between the response rates of animals in the pimozide to non-reward condition and those animals in the non-reward to pimozide condition. One possible explanation for the discrepancy observed between the two transfer groups might be their different pharmacological histories. If there were residual effects of repeated pimozide treatment, such effects would contribute to one but not the other transfer condition. Thus, it is important to determine if there are any pharmacological carry-over effects of repeated pimozide injections. Experiment 3 was designed to examine this possibility.

The fact that animals treated repeatedly with pimozide showed a progressive decrease in responding across test sessions indicates that food failed to meet the first criterion of a

rewarding event - the ability of a stimulus to sustain a well established set of behaviors. However, in order to strengthen the position that pimozide causes an attenuation of the rewarding properties of food, it must be determined that pimozide can block or at least retard the acquisition of a new response. The following experiment was designed to test this second criterion.

Experiment 2

In Experiment 1, it was observed that food under pimozide failed to meet one criterion of a reward - the maintenance of habitual responding in well trained, food deprived animals. The present experiment was designed to investigate another, more fundamental criterion of a reward - the ability to establish new responding in naive animals. The present experiment investigated the length of time necessary for food deprived animals to acquire the standard lever pressing response for food reward under different degrees of pimozide pre-treatment. It was predicted that the rate of acquisition of the bar-pressing response would be directly related to the dose of pimozide administered. In other words animals receiving the highest dose of pimozide (1.0 mg/kg) would require the greatest number of sessions to acquire the lever-pressing habit. Conversely, animals that received the lowest dose of pimozide (0.25 mg/kg) would be expected to acquire the bar press response in significantly fewer sessions, and their behavior would more closely resemble that of the drug vehicle control group.

Method

Subjects. The subjects were 32 experimentally naive male Sprague Dawley rats, that weighed between 250 and 300 grams each upon arrival from the supplier.

Apparatus. The apparatus used in this experiment was identical to that used in the previous experiment.

Procedure. Upon being received from the supplier, the animals were randomly assigned to four drug treatment groups and then individually housed. They were fed ad libitum for 72 hours and then placed on a daily 22 hour deprivation schedule. Water was always available in the home cages. Training began 24 hours after the animals were placed on the deprivation schedule. One hour after the termination of each session, each animal was given free access to food for two hours in their home cages.

The animals were assigned to the following drug treatment groups: Group 1 received .25 mg/kg of pimozide; Group 2 received .50 mg/kg of pimozide; Group 3 received 1.0 mg/kg of pimozide; and Group 4 received .50 mg/kg of the vehicle drug, tartaric acid. Drugs were injected intraperitoneally four hours before testing.

Each group was tested once a week, with each

session lasting 45 minutes. Four hours after their initial injection, the animals were placed in the experimental chambers for the first time under a continuous reinforcement schedule (CRF). Each animal also received a "free pellet" at variable intervals with an average of one every minute (VI60"). Thus, even if the animal remained motionless for the duration of the session, approximately 45 pellets would be dispensed to the chamber. The number of bar presses was recorded every five minutes.

Each animal received the "free" pellets on a VI60" schedule until a criterion of 150 responses were made in a session. After this criterion level of responding was achieved, the "free" pellets were discontinued for the subsequent sessions. An animal was considered to have acquired the lever-pressing habit if it pressed at least 150 times for each of four consecutive sessions.

Results

A two-way (Groups x Sessions) Analysis of Variance with repeated measures across sessions was performed to determine the rates of acquisition for each group. For the purposes of this analysis, only the first four test sessions were analyzed

together. Results revealed a significant main effect of treatment groups, $F(3,28) = 4.57$, $p < .001$, a significant sessions effect, $F(9,84) = 2.64$, $p < .001$, as well as a significant interaction, $F(9,84) = 7.53$, $p < .01$.

Post hoc tests were computed across groups on both Days 1 and 4. On Day 1 the drug vehicle control group had made significantly more responses than all three pimozide dose groups. Mean bar presses for the first test session exceeded criterion levels of responding and response rates for the control group reached asymptotic levels over the final 3 test sessions. Rate of responding in the low dose pimozide group (.25 mg/kg) was significantly higher than the high dose group (1.0 mg/kg) but not the medium dose group (.5 mg/kg). The low dose group reached the criterion level of bar pressing by the end of the second test day and reached the level of the vehicle control group by the fourth test day. No significant differences were found between the medium and high dose groups on the first test day. However, by the fourth test session, the rate of responding in the medium dose group had significantly surpassed the high dose group's levels. Neither the medium nor the high dose pimozide groups reached

the criterion level of responding in any of the four test sessions. Only in subsequent test sessions did the medium dose group approach the criterion level of responding. Response rates in the highest dose pimozide group remained at low levels throughout all test sessions and did not ever approach criterion levels of responding. Figure 3 illustrates the rates of acquisition for the four treatment groups across all test sessions.

Discussion

The rate of acquisition of the four drug treatment groups shows a typical dose response curve (see Figure 3). As expected, both the drug vehicle control group and the low dose pimozide group learned to press the bar to receive food after one and two sessions, respectively. Even such a low dose of pimozide (.25 mg/kg) delayed somewhat the acquisition of the response set. The medium dose group (.5 mg/kg) required 6 sessions to approach criterion levels of responding. That animals in this group eventually acquired the lever-pressing habit in the later test sessions cannot be well explained in terms of a motor deficit hypothesis. It seems clear that these animals were capable, under drug, of reaching the response criterion of 150 lever presses in 45 minutes. The fact that animals in this group showed delayed,

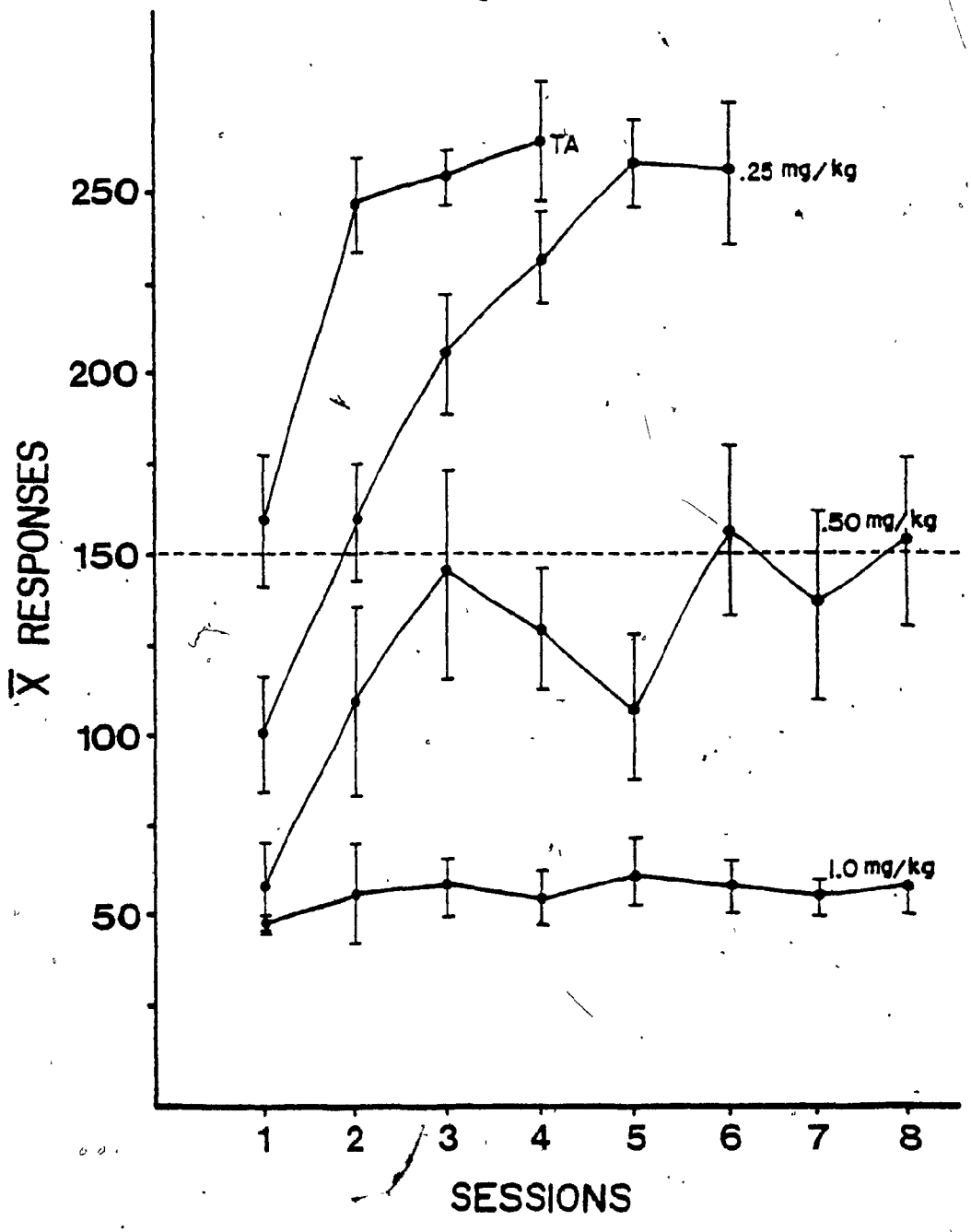

Figure 3. Mean number of responses per session as a function of dose of pimozide. The dotted line represents the criterion level of responding at which learning has taken place.

through clear, signs of learning suggests that pimozide altered either the rewarding properties of the food, the motivational state of the animal or both. The fact that the final performance of the animals was still below that of the low dose and control groups suggests that there may have been some degree of performance deficit as well.

Of particular interest are the results of the high dose pimozide group. As can be seen in Figure 3, the rates of responding in all test sessions did not even approach criterion levels of responding. Animals that did not reach criterion rates continued to receive "free" pellets on the average of one every minute. If pimozide caused an inability in these animals to initiate any voluntary movements, then one would expect to find approximately 45 pellets in the food magazine at the end of each test session. However this was not the case. Following each session, it was noted that all pellets were consumed during the experimental period. Thus the animals were capable of executing the topographical responses necessary to move to the magazine, remove a pellet from it and eat it. Since these animals were capable of performing such motor acts, it appears that pimozide sufficiently reduced the rewarding properties of food

to retard the acquisition of the lever-pressing habit. Thus, food under the influence of pimozide failed to meet the second criterion of a rewarding event - the ability to establish a learned set of behaviors in naive, food-deprived animals. Again, the performance of the high dose group may reflect some degree of performance deficit in addition to any motivational deficit caused by pimozide.

Experiment 3

The presence both of normal performance capacity and of a similarity between the effect of pimozide and the impact of non-reward was confirmed in Experiment 1. However, the transfer effect reported by Wise et al. (1978b) was not replicated. Similar discrepancies have been seen in other studies (e.g. Mason, Beninger, Fibiger & Phillips, 1980; Tombaugh, Tombaugh & Anisman, 1979). The third experiment in this series was therefore designed to test a particular hypothesis about the difficulty in demonstrating the transfer effect reported by Wise et al. (1978b). In their investigation it was found that after three sessions of pimozide administration, animals showed enhanced resistance to extinction when tested under the non-reward condition for the first time. This was in direct contrast to the group of animals subjected to three test sessions of non-reward and then given pimozide for the first time. This latter group showed minimal responding on the transfer test day. Although Experiment 1 demonstrated that repeated pimozide administration and repeated experience with non-reward are behaviorally similar, one possible explanation for the difference in response rates

between the two groups could be the different pharmacological histories of the groups. It is possible that repeated injections of pimozide caused a state of enhanced dopamine receptor sensitivity in the animals. Indeed, receptor supersensitivity has been demonstrated after two daily injections of pimozide over a period of three days (Ettenberg & Milner, 1977) and has also been reported after just one administration (Schaefer & Michael, 1980). Therefore, the following experiment was an attempt to determine the effect of daily pimozide injections on the resistance to extinction in well-trained animals placed in a non-reward condition for the first time. It was predicted that if enhanced resistance to extinction could be demonstrated in animals after several home cage injections of pimozide, then the failure to observe the transfer from pimozide to non-reward could be due to neuroleptic-induced dopamine receptor supersensitivity.

Method

Subjects. The subjects used in this experiment were 32 experimentally naive male Sprague-Dawley rats, ranging in weight from 250 to 300 grams each upon arrival from the supplier.

Apparatus. The apparatus used in this experiment

was identical to that used in the previous two experiments.

Procedure. The animals were randomly assigned to four treatment groups and then were housed individually. They were fed ad libitum for a period of 72 hours, and then were placed on a 22 hour food deprivation schedule. Water was always available in the home cages.

Training sessions began 24 hours after the animals were placed on the deprivation schedule. Each session lasted 45 minutes. The initial session consisted of magazine training and was followed by 15 consecutive days of bar-pressing for food under a continuous schedule of reinforcement (CRF).

Following the 15 days of CRF training, the experimental phase began. The animals were divided into the following groups:

1) Pimozide-Home Cage: Animals in this group received 1.0 mg/kg of pimozide for five consecutive days in their home cages. On the sixth day, they were allowed free access to food for two hours, and on the seventh day they were tested in the experimental chambers.
2) Tartaric Acid-Home Cage: Animals in this group received the identical treatment to those in the

Pimozide-Home Cage condition except that they were injected with .50 mg/kg of tartaric acid, the vehicle control drug.

3) Pimozide-Retraining: Animals in this group received injections of 1.0 mg/kg of pimozide every third day for a total of four treatment days. During the two days between the drug injections days, they received 45 minutes of CRF training identical to the type received in the training phase. Following the fourth series of retraining sessions, the animals were tested in the experimental chambers.

4) Tartaric Acid-Retraining: Animals in this group received the identical treatment to those in the Pimozide-Retraining group with the following exception. Instead of receiving four injections of pimozide, they received injections of .50 mg/kg of the vehicle drug, tartaric acid.

Prior to being tested on the final test day, the pellet dispensers in the experimental chambers were emptied. Thus, each time the animal pressed the lever on this day, the same noise was produced as had been previously associated with food delivery, but no food pellet followed. The number of bar presses was recorded every five minutes.

Results

A one way Analysis of Variance was conducted on the four treatment groups on the non-reward test day. There was no significant group effect. Due to the observed variability in some of the experimental animals, t-tests were also performed between the Pimozide-Retraining and Pimozide-Home Cage groups as well as between the Tartaric Acid-Retraining and Tartaric Acid-Home Cage groups. This analysis also did not reveal any statistical significance between the groups. Figure 4 illustrates the results of the experimental groups on the non-reward test day.

Discussion

Neither the Analysis of Variance nor the subsequent t-test revealed any statistically significant differences between the groups. Thus, it appears that repeated administration of pimozide did not in and of itself, result in a change in the response rate of those animals treated. It seems unlikely, then, that the failure to demonstrate the transfer effect in Experiment 1 was due to the repeated pimozide injections themselves. On the non-reward test day rates of responding in both the Pimozide-Home Cage and Pimozide-Retraining

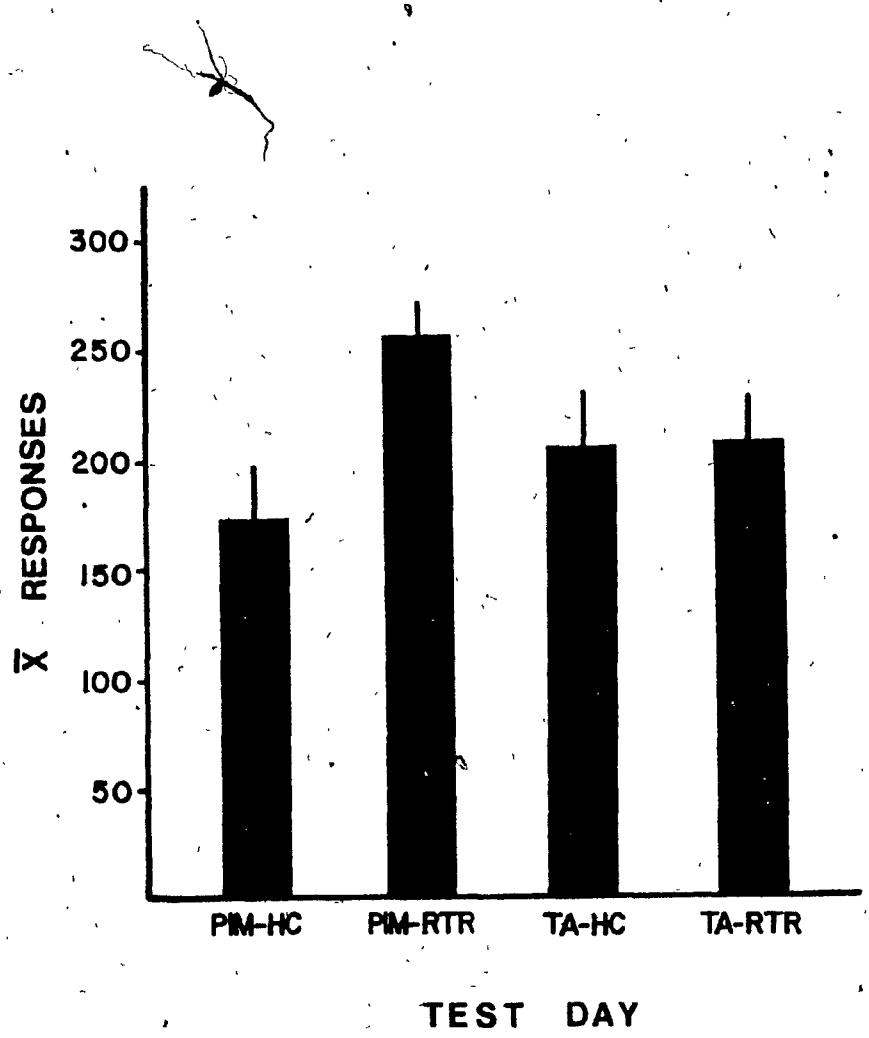

Figure 4. Mean number of responses for the pimozide and the drug vehicle control groups on the non-reward test day.

groups were comparable to the group of undrugged animals' first experience with non-reward in Experiment 1. Thus, an alternative interpretation is needed to explain the failure to produce a transfer effect in Experiment 1. It is possible that more subjects and a significant modification of the design might produce a transfer effect. However, if such modifications are required to produce the transfer effect, then the robustness of the effect reported by Wise et al. (1978b) is in question.

General Discussion

The preceding experiments were conducted to determine the variables responsible for the response deficits seen in animals given neuroleptic drugs. A reduction in response rates within and across sessions was observed in pimozide-treated animals in Experiment 1. Experiment 2 revealed a pimozide-induced retardation of the acquisition of a new response. The results from these investigations appear to be in support of a reward attenuation hypothesis. Under the influence of pimozide, food failed to meet both criteria of a rewarding event - the ability to maintain a well established set of responses in well trained animals and the ability to instate a response habit in naive animals. Furthermore, these experiments provided a distinct demonstration of normal response capabilities of animals under the influence of pimozide. That the animals can perform a series of complex, coordinated acts clearly refutes the notion that pimozide (at the doses used in these investigations) renders the animals incapable of initiating voluntary movements.

Evidence of Response Capability

If pimozide or neuroleptics in general cause

motor deficits in animals, then this must be demonstrated in all situations. If performance capacity can be demonstrated in any situation or under any given set of circumstances, then some other explanation of the observed phenomena must be entertained. In Experiment 1 animals injected with pimozide for the first time bar-pressed for food reward as often as did undrugged animals. Evidently, pimozide did not interfere with their ability to execute the response in question. In Experiment 2 pimozide retarded the acquisition of the bar-pressing habit as a function of the dose administered. Even in the high dose group, animals were nevertheless capable of executing the responses required to consume an average of 45 "free" pellets given to aid in the acquisition of the lever-pressing habit. Performance capacity was demonstrated, therefore, in all pimozide dose groups. The response capabilities that were demonstrated in Experiment 1 and 2 complement the following studies which have employed different reinforcers using a variety of paradigms.

Selective dopamine blockade. Neuroleptic induced decreases in self-stimulation rates have been demonstrated in certain areas of the brain but

not others (Mora et al., 1975). Similarly, ipsilateral injections of neuroleptics do not affect self-stimulation of the contralateral hemisphere (Robertson & Mogenson, 1978). These results suggest that the decrease in self-stimulation in the affected regions does not occur as a result of sedation or motor impairment.

Enhanced responding for stimulant drugs. After injections of neuroleptics, animals significantly increase their lever-pressing rates in order to receive intravenous injections of psychomotor stimulant drugs such as amphetamine (Yokel & Wise, 1975) and cocaine (de Wit & Wise, 1977). Although at high doses this enhancement is short-lived and although the animals may increase their responding in order to overcome any general malaise induced by neuroleptics, it is nevertheless clear that the animals are quite capable of making the necessary motor responses.

Response initiation, latencies and running speeds. Animals pretreated with pimozide have demonstrated normal or near normal rates of bar-pressing, response latencies and running speeds in the initial segments or trials of the test session (Fouriezos et al., 1978; Franklin, 1978; Franklin &

McCoy, 1979; Wise et al., 1978a, 1978b). It is only in the subsequent minutes or trials of the test session that pimozide-treated animals begin to show decrements in responding. That animals under the influence of pimozide can initially respond in a similar fashion to undrugged control animals indicates that these animals do not suffer from a general inability to perform the required motor responses.

Spontaneous recovery. Some proponents of a neuroleptic-induced motor deficit hypothesis argue that the general decline in responding (within the test session) seen in pimozide-treated rats is a result of fatigue which is induced by the drug. This premature "tiredness" falls within the boundaries of a motor deficit model. However, neuroleptic-treated rats have been shown to begin lever-pressing after a period of cessation of responding in a particular test session (Fouriezos et al., 1978; Franklin & McCoy, 1979). In both these investigations, animals pretreated with pimozide ceased bar-pressing at one point in the test session and recommenced responding when placed back in the experimental apparatus or situation. When animals cease to respond or extinguish a response and start again a short time later, then

it is improbable that they are fatigued or sedated. Altering the test situation or environment and observing a spontaneous-like return of response rates even if it is only for a short time suggests that the animals are capable of executing the required motor responses while under the influence of pimozide. It is quite possible that modifying various aspects of the stimulus and environment raises the arousal levels in the animals sufficiently to allow them to respond as vigorously as when they are first exposed to the same situation. This "arousal" hypothesis provides for a better understanding of the spontaneous recovery of responding observed in pimozide-treated animals.

Evidence for a Reward Attenuation Hypothesis

It appears evident from the data just reviewed that a motor deficit hypothesis fails to explain many of the phenomena that occur in animals treated with neuroleptics. The fact that these animals show an eventual decrease in responding to stimuli that in drug-free conditions maintain normal rates suggests that the effects of pimozide are much more subtle. That the observed decline in responding may be due to any pharmacological effects of the drug is ruled out by Wise et al. (1978b). The only

alternative explanation that can be offered at present is that there is a cumulative experiential effect that occurs between the pimozide treatment and the experimental situation. Animals that are treated with pimozide seemingly learn that the food is not as "satisfying" on days when they are injected with the drug. Experiment 1 demonstrated that pimozide seemed to interfere with the rewarding properties of the food to the extent that it failed to sustain a well trained series of responses. This response set was not affected when the animals were tested on inter-test days in drug free conditions. In Experiment 2 animals treated with low and medium doses of pimozide took longer to acquire the lever-pressing habit than controls. Moreover, animals in the high dose group failed to acquire this habit. Thus, some interaction between the drug treatment and the experimental situation causes normally rewarding stimuli to lose its impact on these animals. The following will provide an extensive explanation of the reward attenuation model encompassing its similarity to behavioral extinction, its relation to deficits in learning and the role of secondary cues.

Pimozide and non-reward. The failure to produce

a transfer effect in Experiment 1 appears to confirm the notion that the impact of pimozide is not identical to extinction. Experiment 3 attempted to investigate one of the possibilities why a failure to transfer from the pimozide to non-reward condition and from the non-reward to pimozide condition occurred. The fact that an enhanced resistance to extinction occurred in animals given daily pimozide treatments for five days suggests that a failure to transfer cannot be attributed to residual effects of the drug. Since it is unlikely that drug history is the reason for the failure to produce a transfer, the behavioral dissimilarities between the pimozide to non-reward and non-reward to pimozide transfer groups indicate that the effects of pimozide are not equivalent to extinction. It is nevertheless apparent that these two effects share some important characteristics which support the belief that neuroleptics interfere with the rewarding properties of primary reinforcing stimuli. In Experiment 1 pimozide seemed to mimic the effects of the extinction process. Animals treated with pimozide showed a gradual decline in responding across sessions in much the same way as did undrugged, non-rewarded controls. As food did not sustain the lever-pressing

habit, by definition, it cannot be considered a rewarding event. Thus, it can be argued that the animals were undergoing an extinction-like process across the test sessions.

The data from Experiment 1 complement the extinction-mimicking effects of pimozide seen in studies using brain stimulation as the rewarding stimuli. Pimozide-treated animals demonstrated similar increases in response latencies and running speeds to animals whose currents of rewarding stimulation were reduced (Franklin & McCoy, 1979), or switched off (Fouriezos et al., 1978). Similarly, animals pretreated with pimozide pressed a current reset level as often as did undrugged controls receiving successively lower intensities (Schaefer & Michael, 1980; Zarevics et al. 1977, 1979). In these investigations higher current intensities were required for neuroleptic-treated animals in order to maintain levels of responding similar to those of undrugged controls. Moreover, higher current intensities did not even sustain levels of bar-pressing for the entire test session (Schaefer & Michael, 1980).

The extinction-like pattern of responding observed in pimozide-treated animals seems to

indicate that it is their experience with the rewarding stimuli that causes an eventual cessation in responding. The most common assumption about the ability of stimulus events to change behavior is that these events have consequences that become associated with them. A response, therefore, will soon extinguish if the consequence is not rewarding. The same rewarding event that is capable of sustaining normal response rates in animals under drug-free conditions appears to lose that capability when the animals are injected with pimozide. Thus, the similarity between a pimozide-induced decrement in response rates and a behaviorally-induced extinction pattern of responding suggests that the two processes share some common properties.

Response acquisition and learning deficits. As discussed earlier, the ability of an event to sustain a habitual rate of responding is one way of determining if it is rewarding. The other defining property of a rewarding event is its ability to establish a response habit. In Experiment 2, 0.5 mg/kg of pimozide severely retarded the acquisition of a lever-pressing habit in naive animals, while animals in the high dose group (1.0 mg/kg) failed to learn the response. Since

the "free" pellets that were administered throughout the training sessions were all consumed by the pimozide-treated animals, the failure to acquire the habit cannot be attributed to neuroleptic-induced sedation or overall motor incapacity. Evidently, the animals did respond to some of the cues in the experimental situation by virtue of their consummatory responses. A certain degree of response complexity is required in order to become familiar with the food hopper, to find the pellet, to remove it and to eat it. That pimozide-treated animals did not learn to press the lever to obtain the food as did undrugged controls suggests that pimozide may have a deleterious effect on the process of learning itself. There is some evidence to support this notion. Pimozide has been found to block the strengthening effect of a naturally reinforcing event on associations that under drug-free condition produce changes in behavior (White & Major, 1978). Similarly, animals treated with pimozide show no evidence of conditioned reinforcement in the test session whereas undrugged control animals do (Beninger & Phillips, 1980). Since animals in Experiment 2 and in the investigations of White and Major (1978) and

Beninger and Phillips (1980) showed no evidence of overall motor incapacity, it is likely that the pimozide-induced interference in learning is primarily motivational in nature.

Intermittent reinforcement schedules and secondary cues. The results from Experiments 1 and 2 led to the conclusion that experience with the primary reinforcer (food) under pimozide results in an attenuation of the primary reward itself. The animals tested in these investigations were all placed on a continuous reinforcement schedule. It has been well established that this type of schedule is much less resistant to extinction than are intermittent reinforcement schedules (Skinner, 1953). It would be predicted, therefore, that animals treated with pimozide and tested under an intermittent schedule of reinforcement would require more sessions before a decrease in response rates similar to the one demonstrated in Experiment 1 would be evident. This, however, does not appear to be the case. Immediate decreases in response rates after intermittent schedules of reinforcement have been demonstrated in animals tested with the neuroleptic pimozide (Gray & Wise, 1980; Tombaugh, Anisman & Tombaugh, 1980) and haloperidol

(Phillips & Fibiger, 1979). This immediate suppression effect cannot be explained solely in terms of a simple reward attenuation model as proposed in the earlier investigations of Wise et al. (1978a, 1978b). It is evident from the data reported in Experiments 1 and 2 and other investigations (e.g. Fouriezos et al., 1978; Franklin & McCoy, 1979) that pimozide produces marked deficits in the primary reinforcing properties of otherwise reinforcing stimuli. It is nevertheless clear that something more complex than solely an attenuation of primary rewards is occurring when pimozide-treated animals are placed on intermittent schedules of reinforcement. Some investigators (e.g., Mason et al., 1980; Phillips & Fibiger, 1979; Tombaugh et al., 1980) argue that under intermittent schedules of reinforcement animals do not receive any experience with the primary reward before a decrement in responding is observed. However, it is possible that pimozide also interferes with the secondary cues associated with the primary reinforcers. Such secondary reinforcers would include the clicking of the lever and the smells of the experimental apparatus. Thus, neuroleptic-treated animals placed in the testing situation under an intermittent

schedule of reinforcement would be subjected to cues that have been previously associated with the primary reinforcing event. This experience, under pimozide, may lose its rewarding impact, thereby resulting in an immediate suppression of response rates. The reduced rewarding value of the primary and secondary reinforcing stimuli coupled with the fractional reinforcement experience of intermittent schedule training (Millenson, 1967) may produce an additive effect on the behavior of the organism. This algebraic effect could explain the suppressed responding under an intermittent schedule of reinforcement.

Summary and Implications

Results from Experiments 1 and 2 indicate that one effect of pimozide is an attenuation of food as a rewarding stimulus. Food when offered to pimozide-treated animals failed to meet the two operational criteria of a rewarding event - the maintenance of habitual responding in well trained animals and the acquisition of a lever-pressing habit in naive animals. Evidence from other studies corroborates with these investigations in confirming the notion of a pimozide-induced interference of primary reinforcers. However, it does not appear

that only primary reinforcers lose their ability to control the behavior of neuroleptic-treated animals. Secondary cues that have become associated with these primary reinforcers also appear to lose their effectiveness in maintaining response patterns. These factors combined produce deficits in performance which are seen in animals where motoric dysfunction has evidently been ruled out. This is not to say that pimozide or neuroleptics in general do not produce any motor incapacity whatsoever. It can be argued, perhaps, that pimozide causes an increased difficulty to locomote rather than a total inability. For example, pimozide-treated animals have been shown to take more than three seconds to initiate eating in the testing situation (Beninger & Phillips, 1980). It is difficult to determine whether the latency in performance was due to a difficulty in moving to the food, to a decrease in the rewarding properties of the food or to a combination of both factors. Evidently, further research employing a design which would unequivocally dissociate motor from reward variables would provide a better understanding of the effects of neuroleptics. At present, the results from Experiments 1 and 2 as well as those of other

investigations (e.g., Fouriezos et al., 1978; Franklin & McCoy, 1979; Wise et al., 1978a, 1978b) make it clear that a major effect of pimozide is its capacity to interfere with the rewarding properties of primary reinforcing stimuli. Furthermore, a recent study by Gray and Wise (1980) led these authors to suggest that secondary cues associated with the primary reinforcing events are also attenuated by pimozide. This neuroleptic-induced attenuation of the rewarding qualities of reinforcing events is believed to be a critical factor in disrupting normal response rates in animals.

That both the primary and secondary reinforcing qualities of rewarding stimuli may be attenuated by neuroleptic treatment, independent of any gross motor impairment, may bear important implications to the understanding of human disorders that are directly or indirectly affected by abnormal dopaminergic activity. It may no longer be feasible to consider diseases such as Parkinsonism as simply disorders of brain mechanisms which control motor functioning. It seems that there may be significant motivational components to these diseases which must be considered in their treatment. For example, dysphoria and lack of movement are often reported in

Parkinsonian patients, and flatness of affect is a common diagnostic criterion of schizophrenia. These symptoms may be in part a result of a loss of ability of the environment to maintain its secondary rewarding properties which are related to more basic, primary needs. Evidently, the neuroleptic-induced disruption of normal behavior patterns as evidence in this investigation as well as other studies creates a demand for a more complex understanding of the actions and effects of antipsychotic drugs.

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Appendix 1

ANOVA summary table for pimozide treatment days 1 - 4, Experiment 1.

Source	SS	df	MS	F
Between Subjects	332161.36	31		
Groups	16354.56	3	5451.52	1
Subjects w Groups	315806.80	28	11278.81	
Within Subjects	507437.50	96		
Days	191105.84	3	63201.94	17.40***
Groups x Days	8785.21	9	976.13	1
Days x Sub w Group	307546.45	84	3661.27	

*** $p < .001$

Appendix 2

ANOVA summary table for transfer test day, Experiment 1.

Source	SS	df	MS	F
Between Subjects	458124.64	31		
Groups	69269.90	3		
Subjects w Groups	388854.74	28	23089.97	1.66
Within Subjects	1080841.57	128		
Days	208080.28	4	52020.05	9.62***
Groups x Days	267392.51	12	22282.71	4.12***
Days x Sub w Group	605368.78	112	5405.07	

*** $p < .001$

Appendix 3

ANOVA summary table for inter-test training days, Experiment 1.

Source	SS	df	MS	F
Between Subjects	837698.72	31		
Groups	179232.86	3	59744.28	2.54
Subjects w Groups	658465.86	28	23516.63	
Within Subjects	409505.18	224		
Days	32853.18	7	4693.31	2.54*
Groups x Days	15031.12	21	715.76	1
Days x Sub w Group	361620.88	196	1845.00	

* $p < .05$

Appendix 4

ANOVA summary table for acquisition days, Experiment 2.

Source	SS	df	MS	F
Between Subjects	963846.6	31		
Groups	748643.0	3	2495.48	32.4686***
Subjects w Groups	215203.6	28	7685.81	
Within Subjects	363925.02	96		
Days	206565.60	3	68854.9	66.39***
Groups x Days	70241.70	9	7804.63	7.52***
Days x Sub w Group	87113.72	84	1037.12	

*** $p < .001$

Appendix 5

ANOVA summary table for transfer test day, Experiment 3.

Source	SS	df	MS	F
Total	163928.0	31		
Groups	28185.25	3	9395.08	1.93
Subjects w Group	135742.75	28	4847.95	