AMPHETAMINE-PRODUCED STEREOTYPED BEHAVIOR IN THE RAT

DETERMINANTS OF AMPHETAMINE-PRODUCED STEREOTYPED BEHAVIOR IN THE RAT

by

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ABSTRACT

Six experiments were designed to determine whether stereotyped behavior produced by amphetamine-injection (AMP-SB) is influenced by factors known to affect the stereotypies of mentally retarded and mentally ill persons. Three experiments demonstrated that the incidence of stereotyped behavior was a monotonic increasing function of amphetamine dose. The interpretation of these studies emphasized the importance of the Ss' arousal levels in determining stereotyped behavior. Two studies examined the relationship between environmental novelty and AMP-SB. AMP-SB was lower among Ss placed into novel environments than among Ss placed into familiar environments. The ability of novel stimuli to evoke exploratory responses incompatable with stereotypy was suggested as the basis for this effect. This interpretation was supported in a final experiment, which observed exploratory behavior and general activity, as well as AMP-SB, in Ss exposed to a novel stimulus in an otherwise familiar environment. All 6 experiments were interpreted as supporting a unified conception of amphetamine-produced and pathological stereotyped behaviors.

Résumé

Six expériences furent effectuées afin de déterminer si le comportement stéréotypé produit par l'injection d'amphétamine (CS-AMP) est influencé par des facteurs connus pour modifier les comportements stéréotypés chez les retardés et les malades mentaux. Trois expériences ont démontré que la présence de comportements stéréotypés était fonction monotone croissante de la dose d'amphétamine. Les expériences ont été interpretées en insistant sur l'importance du niveau d'activation dans la détermination des comportements stéréotypés. Deux études ont examiné les relations possibles entre la nouveauté de l'environnement et le CS-AMP. Les résultats ont montré qu'il y avait moins de CS-AMP chez les rats placés dans de nouveaux environnements que chez les rats placés dans des environnements familiers: Il fut suggéré que cet effet est du à la capacité des stimuli nouveaux d'évoquer des réponses exploratrices incompatibles avec les comportements stéréotypés. Cette interprétation fut supportée par une dernière expérience, où furent observés le comportement exploratoire, l'activité générale, et le CS-AMP chez des rats exposés à un stimulus nouveau dans un environnement familier. Les 6 expériences furent interpretées en support d'une conception unifiée des comportements produits par l'amphétamine et des comportement pathologiques stéréotypés.

Preface

Stereotyped motor acts dominate the behavior of persons suffering from many types of psychopathological conditions. Although several factors known to affect the incidence of stereotyped behaviors have been identified, the underlying organizational principles and the physiological mechanisms involved remain unclear. Stereotyped behavior of similar appearance is seen in normal organisms following amphetamine injection. Despite progress in clarifying the means by which amphetamine influences brain processes, little is presently understood about the relationship among amphetamine dosage, environmental variables, and the resulting stereotyped behavior. The work reported in this thesis represents an effort to determine the effects of amphetamine dosage and of environmental novelty on amphetamine-produced stereotyped behaviors. Both the incidence and form of stereotyped behaviors were found to be influenced by amphetamine dosage in several rat strains. In addition, the exploratory behavior evoked by novel stimuli effectively reduced the incidence of stereotyped behaviors. Because similar effects have been found in studies of pathological stereotyped behavior, the present findings were interpreted as supporting a unified conception of pathological and amphetamine-produced stereotyped behaviors.

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INTRODUCTION

Pathological stereotyped motor acts are a common characteristic of many clinical conditions in man. Stereotyped complex hand movements, repetitive self manipulation or mutilation, repetitive rocking or head rolling, and the assumption of bizarre limb or body postures have been frequently described by those working with mentally deficient persons (Berkson, 1967), disturbed children (Lovaas, 1967), and psychotic adults (Itil, 1969). Because these behaviors are so striking in their extreme manifestations and because they are seen in such a wide variety of clinical conditions, they have elicited a certain amount of interest. Early clinical reports of stereotypy yielded suggestions that these behaviors were caused by such varied factors as genital masturbation (Potter, 1927), maternal deprivation (Spitz & Wolf, 1949), a need for kinesthetic stimulation (Kulka, Fry & Goldstein, 1960; Casler, 1961), a need for tension reduction (Lourie, 1949), movement restraint (Levy, 1944), or a need for stimulation in an unstimulating environment (Levy, 1944; Kaufman, 1963).

More recent studies of stereotyped behavior have concentrated mainly upon discovering conditions or experimental procedures which influence the incidence or intensity of stereotypies. While such studies have successfully isolated a number of the factors which influence pathological stereotyped behavior, they have contributed little more than their predecessors did to our understanding of the origins of stereotyped behavior or of its possible significance (Berkson, 1967).

The discovery that stereotyped behavior can be produced in normal humans and many animal species by high doses of amphetamines (Randrup & Munkvad, 1967) has lead to a number of psychopharmacological studies whose aim has been to discover the mechanisms by which amphetamine produces this behavior. While much work remains to be done on this problem, much progress has been made in learning the characteristics of drugs which produce stereotypies (Biel, 1970), and their modes and sites of action (Randrup & Munkvad, 1972).

The common characteristics of pathological and amphetamine-produced stereotypy have given rise to speculation that they may share some common mechanisms (Ellinwood, 1970). There is hope that the investigation of these amphetamine-produced stereotypies will aid our understanding and treatment of individuals whose behavior is dominated by stereotyped behavior, but the degree to which amphetamine-produced stereotyped behaviors will prove to be a useful model of pathological stereotypy has yet to be determined.

This thesis addresses itself to one part of this question. The work described attempts to assess the degree to which the variables known to influence the incidence or intensity of pathological stereotyped behavior are also capable of influencing amphetamine-produced stereotypy.

Stereotyped Behavior in Pathological Conditions

Pathological stereotyped motor acts are observed in approximately two-thirds of severely or profoundly retarded persons (Berkson & Davenport, 1962; Kaufman & Levitt, 1965). Most of the stereotyped behaviors emitted by these persons take the form of complex hand movements, body and limb posturing, and repetitive movements of the whole body (rocking, swaying, twirling) or of part of it (head rolling or banging). Digit sucking, self biting, eye poking and gouging, repetitive object manipulation, and the repetitive uttering of meaningless sounds are also common (Davenport & Berkson, 1963; Berkson, 1967).

Similar behaviors are frequently seen in severely disturbed children, and are especially prominent in children whose prognosis is poor. Lovaas (1967) has described the behaviors of these children. Their repertoires include repetitive rocking and twirling, gyrating of the head in a jerky manner, and flapping or shaking of the hands and arms. These patients also grind their teeth, cross their eyes, grimace, and fondle or mutilate themselves in a fixed, stereotyped manner. Complex behavior sequences such as the repetition of rhymes or lists of names, or the repetitive manipulation of light switches, faucets, and the flushing of toilets have also been reported (Eisenberg & Kanner, 1956).

Behavior patterns which are strikingly similar to those described above have been reported in primates raised in conditions of social isolation. Davenport and Menzel (1963) have described the stereotyped behaviors emitted by chimpanzees isolated from two months to approximately two years of age. These subjects spent many of their waking hours engaged in rhythmic rocking and swaying of the entire body or movement of a body part, especially the head or hands. Self clasping, digit sucking, self biting, eye poking, limb posturing, and stereotyped object manipulation were also seen frequently. These behaviors developed as soon as the chimpanzees appeared maturationally able to emit them, and were present even in those Ss which had been reared with objects to play with and with the opportunity to see, but not to touch, other chimpanzees. These behaviors still persisted with undiminished vigor 3 years after release from isolation. Mason and Green (1962) report similar behaviors in a group of Rhesus monkeys reared in isolation. These subjects emitted stereotyped behaviors continuously during their waking hours. Feral-reared rhesus monkeys kept in social isolation in adulthood never developed any stereotyped behavior.

Stereotypy can sometimes be seen in apparently normal organisms. Body rocking, head banging, and thumb sucking have been described in some normal human infants (Levy, 1944; Lourie, 1949; Kravitz, Rosenthal, Teplitz, Murphy & Lesser, 1960). Hediger (1950) has discussed the stereotyped pacing and fixed stereotyped movements which sometimes develop in zoo animals, and Levy (1944) has reported upon the repetitive stereotyped head movements of hens and horses deprived of the normal opportunities for movement. Even human infants or children who do not emit abnormal stereotypies in normal surroundings may begin to do so if forced to remain in an environment containing few interesting stimuli (Levy, 1944; Lovaas, Litrownik & Mann, 1971).

Several investigators (Levy, 1944; Berkson, 1967; Lovaas, et al., 1971) have discussed the similar appearance and shared characteristics of the stereotyped behaviors seen in these diverse contexts. In labeling the behavior as "stereotyped" they are making reference to its lack of variability (Randrup & Munkvad, 1967), which is reflected both in the restricted range of acts emitted and in the restrictions of the spatial and temporal flow of these acts to a few endlessly repeated sequences. While the similarities of these behaviors should not be emphasized to the point of excluding from consideration their many differences, their shared characteristics encourage those who would account for them in terms of common mechanisms.

Further suggestion that diverse forms of stereotyped behavior share a common basis is based upon evidence that a few factors influence their incidence or rates similarly. Systematic study of variables which influence stereotyped behavior has not been completed for all types of stereotypy, but the evidence which does exist indicates that most types of stereotypy are similarly influenced by a number of internal states and environmental events. The most important of these are the arousal level of the organism and the presence of environmental stimuli capable of eliciting non-stereotyped responses.

Numerous studies of retarded or disturbed children, of isolation-reared chimpanzees and monkeys, and of caged animals, have shown that many environmental manipulations which can reasonably be interpreted as producing stress, discomfort, or increased arousal will increase the incidence of most types of stereotypy. Specifically, physical confinement, restriction of motor activity, frustration, anticipation of mealtime, loud noise, environmental novelty and complexity, and the presence of other patients, have all been demonstrated to increase the incidence of stereotyped behavior.

Physical confinement or the restraint of movement have been found to produce or exacerbate stereotypy in a number of settings. Confinement to a small, novel room has been found to increase the incidence of stereotyped behavior in retarded children (Berkson & Mason, 1963) and in isolation-reared chimpanzees (Berkson, Mason, & Saxon, 1963). Forehand and Baumeister (1970) found that an 18-minute period during which stereotyped rocking and hand movements were prevented produced a subsequent increase in rocking, as compared to a prerestriction baseline period. Both Levy (1944) and Hediger (1950) have commented upon the stereotyped activities of humans and animals who are prevented from performing species-specific acts.

Various forms of frustration also appear to increase stereotypy. Both the prevention (Forehand & Baumeister, 1971) and extinction (Baumeister & Forehand, 1971) of a reinforced lever pulling response provoked a rate of stereotyped rocking which was higher than the pre-training rate in the same situation. In the former experiment, the degree of increase in rocking was found to be a function of the number of previously reinforced responses.

A variety of stimulus conditions have been found to influence the incidence of stereotypy. High levels of white noise have been found to increase the incidence of stereotyped behaviors in mentally defective individuals (Levitt & Kaufman, 1965; Sineets, 1972) and in restriction-reared chimpanzees (Berkson & Mason, 1964b). Fitz-Gerald (1964) found that a loud buzzer produced a similar effect.

Environmental complexity and novelty have also been found to increase the incidence of stereotypy. Several studies with restriction-reared monkeys and chimpanzees revealed that exposing them to unfamiliar complex, or "frightening" stimuli produced increases in stereotyped behavior (Bernstein & Mason, 1962; Berkson & Mason, 1963; Berkson, Mason, & Saxon, 1963). Hutt and Hutt (1965) exposed disturbed children to three environments of increasing complexity, and found that the increase of stereotyped behavior which resulted was a positive function of the complexity of the environment.

A number of social variables have been reported to influence stereotypies. Forehand and Baumeister (1971) reported that the presence of both rocking and non-rocking patients facilitated rocking in mental defectives. Klaber and Butterfield (1968) reported that the rate of stereotyped rocking increased dramatically during two fights which occurred on the ward.

There is also evidence that hunger increases the incidence of stereotypies. In their study of institutionalized defectives Kaufman and Levitt (1965) found that the number of patients emitting stereotyped behaviors reached a peak shortly before mealtimes. This finding had been replicated at another institution by Klaber and Butterfield (1968).

Several researchers have studied the effects of arousal-altering drugs on stereotypies. Chlorpromazine and other phenothiazine derivatives have been reported to decrease or eliminate stereotypy, while leaving other behavior relatively intact (Hollis, 1968; Davis, Sprague,& Werry, 1969). Barbiturates appear to have no selective effect on stereotyped behavior, but may suppress all behavior at high doses (Berkson, 1965; Hollis, 1968). Amphetamines in doses less than 0.5 mg/kg have had no demonstrable effect on stereotyped behavior in children (Berkson, 1965; Anton & Greer, 1969; Davis, et al., 1969). A somewhat higher dose (1.0 mg/kg) have increased it in isolation-reared chimpanzees (Fitz-Gerald, 1964).

It has occurred to several theorists (e.g. Hutt & Hutt, 1965; Berkson, 1967) that the concept of arousal level may be of considerable use in unifying the rather diverse factors which have been found to increase stereotyped behaviors. As set forth principally by Hebb (1955), Duffy (1957) and Malmo (1959), the term "arousal" or "activation" has been used to refer to the general energizing component or intensity dimension underlying behavior and serving as a common basis for motivation and emotion. Such factors as intensity of auditory stimulation, approach of mealtime, frustration, confinement, and environmental novelty and complexity can all be seen to possess arousal-producing properties in most circumstances. Supporting evidence exists in that children who exhibit stereotyped behavior have been found to have "aroused" EEGs (Hutt & Hutt, 1965) and that drugs which are effective in reducing stereotypies (Hollis, 1968; Davis, et al., 1969) are known to influence the level of reticular formation activity (Randrup & Munkvad, 1972).

The close temporal association of increases in the incidence of stereotyped behaviors and the presence of arousing stimuli has led to a number of suggestions that these repetitive acts may serve the purpose of discharging tension or reducing arousal (Lourie, 1949; Kravitz, et al., 1960; DeLissavoy, 1963; Fitz-Gerald, 1964; Hutt & Hutt, 1965). Independent confirmation that arousal or tension is in fact reduced by repetitive movements does exist. Stone (1964) has found that rocking or eye-pressing in blind retardates often preceeds a sleep-like EEG and Oswald (1960) found that very intense rhythmic visual, auditory, and tactual stimulation was capable of inducing behavioral and EEG indications of sleep in normal human subjects.

There is also evidence that impoverished environments increase the incidence of stereotypy. The institutional environment itself in many cases is a rather unstimulating environment, (Provence & Lipton, 1962) and Kaufman (1967) found that institutionalized mental defectives emitted more stereotyped behavior than did a matched group of defectives chosen from the institution's waiting list. The incidence of stereotyped behaviors has also been found to be negatively related to the quality and quantity of staff-patient interaction on different wards or in different institutions (Klaber & Butterfield, 1968). Periods during which organized ward activities are minimal have been found to coincide with periods when a high percentage of patients engage in stereotyped behavior (Kaufman & Levitt, 1965). Both Levy (1944) and Lovaas (1967) report that stereotyped behavior can be induced in normal children by placing them in unstimulating environments. Restricted sensory input has also been implicated in the cage stereotypies of zoo animals (Levy, 1944; Hediger, 1950; Nissen, 1956).

There have been several suggestions (Levy, 1944; Kulka, et al., 1960; Kaufman, 1963; Lovaas, 1967) that the increased incidence of stereotypies in unstimulating environments represents an attempt to increase arousal level via self-stimulation. This suggestion is consistent with the prevalent view that behavioral organization is most efficient at intermediate levels of arousal (Hebb, 1955; Duffy, 1957; Malmo, 1959). Berlyne (1960) has offered the alternative suggestion that behavior typical of subjects who are awake and active in boring circumstances indicates a state of high, rather than low, arousal. Another alternative explanation of these findings appears below.

Conditions influencing the arousal level of the organism are not the only factors affecting the incidence of stereotyped behavior. The presence in the environment of certain types of stimuli appears to be able to reduce the intensity of stereotypies by virtue of the ability of these stimuli to elicit non-stereotyped responses. A number of studies have attempted to discover some of these stimuli.

The presentation of objects or other stimuli to Ss engaging in stereotyped behavior can often reduce these behaviors. Davenport and Mason (1963), Berkson and Mason (1964a), and Hutt and Hutt (1965) have all reported that talking to or handing toys to a mentally defective or disturbed person will cause him to decrease the intensity of his stereotyped behaviors. Guess and Rutherford (1967) found that the presence of attractive toys decreased stereotypy. Working with restriction-reared chimpanzees, Berkson, Mason, and Saxon (1963) found that the presence of objects decreased both repetitive and nonrepetitive stereotypies. Distracting these Ss by tickling them also diminished stereotyped behavior (Berkson & Mason, 1964b).

Correlational analyses have demonstrated that those Ss who emit the most stereotypies on the ward are the Ss who tend to be the least responsive to objects presented in an experimental situation (Davenport & Berkson, 1963; Berkson & Mason, 1964a). These Ss also appear to be the least capable of performing simple experimental tasks, such as retrieving and eating candy (Berkson, 1964).

Lovaas and his co-workers (1971) attempted to produce changes in responsiveness to stimuli by manipulating the incidence of stereotyped behavior. They discovered that a hand held six inches in front of the eyes of a psychotic child and moved rapidly back and forth with the fingers spread elicited stereotypy in two of their subjects. When they used this technique as an independent variable in a study of the responsiveness of these two children to an auditory discriminative stimulus, they found that the Ss took longer to respond on trials preceeded by this stereotypy-inducing technique than they did on trials where the experimenter merely held his hand motionless in front of the subject's face.

These studies indicate that there exists a general reciprocal relationship between stereotyped behavior and other behavior. Manipulations which increase stereotypies decrease responsiveness to stimuli and the presence of stimuli to which the subject responds decreases stereotypy.

A number of workers have attempted to discover techniques which will reduce or eliminate stereotypy in those Ss whose repertoire it dominates.

Several attempts involving various behavior modification techniques have met with some success. Baumeister and Forehand (1972) found both electric shock and verbal command ("Stop rocking!" shouted from behind a one-way mirror) to be effective in reducing the stereotyped rocking of retarded Ss to zero in the experimental situation. Unfortunately, no change was observed outside this situation. Flavell (1973) reinforced retarded Ss for toy play and observed a concomitant decrease of stereotyped behavior. Hollis (1968) found that stereotyped rocking behavior was not emitted while a retarded S was pulling a ball on a FR100 schedule for a candy reward. Overcorrection, a technique which involves simultaneous punishment of undesired behaviors and training of desired ones using differential reinforcement and fading techniques, has been claimed to result in a long-lasting generalized decrease of stereotyped behaviors in disturbed children (Foxx & Azrin, 1973). Risley (1968) was able to replace rocking with imitative clapping and pounding in an autistic child by shouting at and shaking him and by reinforcing generalized imitation. This treatment appeared to have a long-lasting effect. Lovaas (1967) has reported that, among his severely disturbed patients, stereotypy often decreases as desirable behavior repertoires are established using a combination of behavior modification techniques.

It should be noted that the techniques which appeared to have the longest lasting and most general success replaced stereotypy with some type of desired response. In the absence of such alternative responses, stereotypy does not seem to respond to treatment well. The child appears unable to emit alternative responses spontaneously.

Whether these techniques will prove to be generally effective remains to be determined. They do not bring us too much closer to an understanding of the origin of stereotypy, however. The rather complicated interactions between therapist and patient which characterize the most successful of these therapies do not permit an easy analysis of the importance of such factors as reinforcement contingencies, motor training, learning to attend to the proper stimuli, identification with the therapist, arousal changes, and so forth. Even if this analysis were possible, the elucidation of mechanisms underlying a change of behavior in an older organism does not necessarily reveal the mechanism by which that behavior developed earlier.

Berkson (1967) pointed out that this abundance of data about factors which influence stereotypy has not taken us as far as we would like towards an understanding of its causes. Arousal and the elicitation of alternative responses, while effective in manipulating stereotypy over a short time or to a slight degree, tend to be "ephemeral" in the sense that they effect no lasting changes in the incidence or form of the behavior. He speculates about the possible effects of maternal deprivation and institutionalization, but is forced to conclude that we really have no knowledge of the origin of stereotyped behaviors or of their relationship to the problems of psychopathology in general.

Amphetamine-produced Stereotyped Behavior

The production in an experimental animal of an abnormal state which resembles a pathological condition in man has often proved valuable. For example, much attention has recently been paid to psychopharmacological (Schildkraut & Kety, 1967) and behavioral (Suomi & Harlow, 1971) models of psychiatric conditions. The fact that moderate to high doses of amphetamine have been found to produce stereotypies in many animal species and man may offer a new approach to the theoretical and practical problems presented by pathological stereotyped behavior.

Amphetamine in moderate to high doses (usually 1.5 mg/kg and greater) produces stereotyped behavior in many animals and in man (Randrup & Munkvad, 1967). Much of this behavior has the rhythmic, repetitive character which characterizes abnormal stereotyped behavior in humans. In addition, many examples of nonrepetitive stereotypies, such as complex hand movements, self-picking and biting, and the assuming of bizarre postures have been reported following amphetamine injection (Ellinwood, Sudilovsky, & Nelson, 1972).

Perhaps the only benefit of the current epidemic of amphetamine abuse (Kramer, 1972) has been the opportunity to study the effects of high doses of AMP in humans. In the abuser, chronic amphetamine abuse produces a psychotic state whose psychological symptoms fairly closely resemble those of paranoid schizophrenia (Ellinwood, 1972; Griffith, Fann, & Oates, 1972). Many writers have commented upon the bizarre, stereotyped behavior which some of these persons manifest. Scher (1966) has described the process of being "hung up", where the amphetamine abuser will "get stuck" in a repititious thought or act for hours at a time. He might bathe all day long, clean up the house or polish a particular object, hold a note or phrase of music, or engage in nonejaculatory intercourse for long periods. Other reported examples of such behaviors include meaningless, perseverative work on cars, radios, and so forth (Kramer, Fischman, & Littlefield, 1967), and polishing nails or dismantling and reassembling clocks or motors (Rylander, 1966).

A further interesting symptom of amphetamine abuse is the stereotyped picking or rubbing of the skin, seen in about 50% of abusers. These persons report a creeping, itching, or tingling of the skin, and develop a stereotyped sequence of grooming responses accompanied by delusions of parasitosis which may include visual and auditory hallucinations of insects (Ellinwood, 1971).

Ellinwood and Duarte-Escalante (1972) have described the responses of eight Rhesus monkeys to chronic methamphetamine intoxication. In these Ss they observed a variety of patterns of bizarre, stereotyped behavior which began several hours after an injection and continued for 24-36 hours. Certain components of behavior, such as biting, visual examination of the hands, picking or probing manual examination of the body or cage, and side-to-side head and eye movements became incorporated into many different sequences of stereotyped behavior. For example, one S combined a stereotyped foreward thrust of the head with a biting examination of various parts of its body or of the cage. Another S developed several patterns of eye-hand examination involving picking, and probing at its body, at objects, or at the cage, under close visual regard. It often attempted to poke or pick up a minute object, and then to examine its hand closely while opening and closing the fingers or rolling the thumb against the first three fingers. This S used these patterns in a repetitious grooming sequence in which it would clasp its nose and then examine its hand for the result.

During the early part of the experiment these movements were carried out slowly with the appearance of being deliberate or purposeful. As the experiment continued, however, they became increasingly automatic and unrelated to their original purpose.

Ellinwood, Sudilovsky, and Nelson (1972) studied the effects of chronic methamphetamine intoxication in cats. They observed stereotyped side-to-side looking movements, and "obstinate progression," wherein a cat placed facing a wall would tread against it rather than turn aside. Many Ss emitted compulsive sniffing sequences, in which they repeatedly sniffed at a small area of their cages for three or four hours. The animals' hind paws often held unusual postures or performed repetitive movements unrelated to the rest of the cat's behavior. As with the monkeys described above, these behaviors underwent a change in character, at first appearing deliberate or purposeful but becoming appearing compulsive and automatic, as the experiment progressed. Bizarre postures also occurred frequently. In both cat and monkey, the period of stereotyped behavior was preceeded by a period of hypermotility.

In the rat, reaction to amphetamine (AMP) usually takes the form of stereotyped sniffing patterns, licking, or cage biting (Randrup & Munkvad, 1965). Ellinwood and Duarte-Escalante (1972) described two patterns of compulsive sniffing or scanning in the rat. The first consisted of rhythmic side-to-side swings of the neck. The second consisted of a continuously repeated sequence of small nose movements confined to a small area of the cage. These authors also noted the presence of abnormal postures and intraspecific aggressive behavior. Individual Ss developed patterns of stereotyped behavior which were unique in both the acts performed and the location in the cage favored for their performance.

The Ss in Ellinwood's and Duarte-Escalante's (1972) experiment were injected with between four and 16mg/kg methamphetamine, five days per week, for three weeks. Single injections of amphetamines have been found to produce similar effects. For example, Randrup and Munkvad (1965, 1967, 1970), Ernst (1967), Herman (1967), Fog (1969), and Kirkby, Bell, and Preston (1972) all have reported stereotyped sniffing, biting, or licking following a single injection of between 1.5mg/kg and 10mg/kg AMP. The stereotyped behavior typically began 20-30 minutes following the injection and persisted for two to four hours, during which period most other behaviors occurred infrequently or were absent altogether. The period of stereotypy was preceded and followed by a period of heightened motor activity (Schiorring, 1971).

Fog (1969) has shown that a large number of drugs with CNS stimulating properties are capable of producing stereotyped behavior closely resembling that produced by AMP. Phenylethylamines (e.g. amphetamine, methamphetamine, phenmetrazine, pipradrol, methylphenidate, L-DOPA, dopamine, apomorphine, and morphine), indole-ethylamines (e.g. tryptamine, 5-hydroxytryptophan, LSD-25), and other drugs (e.g. cocaine, nialamide) are capable of inducing stereotyped behavior under appropriate circumstances. However, not all central stimulants are capable of producing stereotypies (e.g. caffeine, morphine in a single dose, and nikethamide). The biochemical means by which these drugs produce their effects is not yet completely understood (Mandell & Spooner, 1968). However, much of the evidence which does exist indicates that the primary biochemical effect of AMP is to facilitate synaptic transmission in nerve tracts containing a high proportion of catecholamine-rich neurons. One major tract originates in the midbrain reticular activating system, courses through the medial forebrain bundle, and terminates in various limbic forebrain structures (especially the amygdala, septum, and cingulate gyrus), the preoptic area, the hypothalamus, and the neocortex (Fuxe, Hokfeld, & Ungerstedt, 1970; Stein & Wise, 1970). The second major tract originates in the substantia nigra and innervates the neostriatum, the accumbens nucleus, and the olfactory tuberculum (Fuxe, et al., 1970). Between them, these two tracts contain the vast majority of catecholamine-rich neurons in the CNS. Minor tracts have also been studied, which originate in the arcuate and anterior periventricular nuclei and in the interpeduncular nucleus, and which innervate, respectively, the median eminance and various telencephalic and diencephalic areas (Fuxe, et. al., 1970).

Four modes have been suggested by which AMP facilitates the activity of these pathways. Three of these act to increase the abundance of the putative catecholaminergic transmitter substances norepinephrine (NE) and dopamine (DA) at the postsynaptic receptor sites. In order of their suspected importance, they are: 1. The release of presynaptic NE and DA (Moore, 1963; Glowinsky & Axelrod, 1965; Boaks & Bradley, 1972); 2. The prevention of the inactivation of NE and DA by blocking their reuptake into presynaptic neurons (Glowinsky, Iversen, & Axelrod, 1966; Stein & Wise, 1970); and 3. The inhibition of monoamineoxydase (Glowinsky, Axelrod, & Iversen, 1966). The fourth mode of amphetamine action consists of a direct stimulating effect of AMP at the postsynaptic receptor sites (Van Rossom, Van Der Schoot, & Hurkmans, 1962; Smith, 1963).

Recent efforts to separate the contributions of the NE- and DA- neurons to the pharmacology of AMP are of special interest to the work to be reported here. NE-rich neurons are found primarily in the tracts arising in the midbrain reticular activating system and terminating in limbic forebrain and neocortical areas (Fuxe, et. al., 1970; Stein & Wise, 1970; Snyder, Taylor, Coyle, & Meyerhoff, 1972). Stein and Wise (1970) have argued that this system is primarily responsible for the well-known behavior activating (e.g. Cole, 1967, 1970) and performance stimulating (e.g. Weiss & Laties, 1962; Cole, 1967) effects of AMP. The involvement of these systems in pathological fluctuations of mood has also received considerable attention (Schildkraut & Kety, 1967).

By contrast, the DA-rich neurons are found primarily in the tracts originating in the substantia nigra and terminating in the neostriatum (Fuxe, et al., 1970; Snyder, et al., 1972). Amphetamine-produced stereotyped behavior has been closely linked with these nigrostriatal tracts (Mandell & Segall, 1973). Microinjections of DA or its precursor, DOPA, into the striatum produce stereotyped behavior, and lesions of this area abolish stereotyped behavior in rats given AMP systematically (Randrup & Munkvad, 1970, 1972). Studies of disorders of motor functioning, such as Parkinson's disease and Gilles de la Tourette's disease, have also implicated the striatal DA system (Snyder, et al., 1972; Meyerhoff & Snyder, 1973).

The biochemical and psychopharmacological data cited above offer several additional reasons for believing that pathological and AMP-produced stereotyped behavior may be related. Phenothiazine derivatives (e.g. chlorpromazine), the drugs which have been found most useful in controlling pathological stereotyped behaviors (Berkson, 1965; Hollis, 1968; Davis, et al., 1969), are among those which have specific antagonistic action against amphetamine, and reduce or prevent the stereotyped behavior it induces (Randrup & Munkvad, 1972).

Also, as discussed above, some of the CNS systems upon which amphetamine acts are known to be associated with pathological motor conditions involving repetitive acts, tics, or tremors. And finally, the action of AMP on the brainstem reticular formation parallels the function of arousal in producing pathological stereotypy.

THE PRESENT INVESTIGATION

The work cited above has shown that pathological and amphetamine-produced stereotyped behaviors (AMP-SB) appear to have much in common. Both are characterized by a repetitive, often rhythmic emission of an unusually restricted range of behaviors in an automatic, purposeless-appearing way. Unusual complex hand and limb movements, self-manipulation, and sometimes self-mutilation are common to both. Both classes of stereotyped behavior appear to be related to arousal and to respond in similar ways to tranquilizing drugs.

While the differences in the behaviors should not be minimized, the similarities encourage the view that similar processes are involved in the production of both pathological and amphetamine-produced stereotypies and that the study of one may benefit our understanding of the other. To the extent that these phenomena do share similar causes, the factors which have been found to influence one would be expected to influence the other in a similar way. It was thought that evidence on this point would prove to be of value in determining whether or to what extent AMP-SB will prove to be a useful animal model of pathological stereotyped behavior.

Although the physiological and biochemical mechanisms underlying AMP-SB have received extensive study, researchers have been relatively unconcerned with the study of the stereotyped behaviors themselves. They have not undertaken to determine the various constitutional or experiential factors which influence the incidence or form of AMP-SB. The second purpose of the present investigation was to determine the influence of some of these variables on

AMP-SB.

The first series of three experiments (Dose-Response Studies) was concerned with determining the effect of AMP dosage upon the incidence and form of stereotyped behavior, and upon locomotor activity. Increasing the dosage was conceived of as increasing the arousal level of the Ss, and it was expected that stereotypy would increase with increasing arousal while locomotor activity would bear a curvilinear relationship to arousal. Notice was also taken of the form of the stereotyped behaviors. The three experiments used male and female Ss of different strains of rats in an attempt to determine the generality of the findings and to make an assessment of the importance of constitutional effects.

The second set of two studies (Novelty-Familiarity Studies) was intended to examine the effect of situational factors upon AMP-SB. Experiment IV compared the incidence of stereotypy in rats receiving a single AMP injection on their first or fifth open field trial, and was conceived of as a manipulation of environmentally produced arousal. Experiment V compared the levels of stereotypy of rats replaced in their own home cages or placed into an unfamiliar home cage following an AMP injection. In these experiments it was anticipated that the higher arousal levels of Ss in the relatively unfamiliar situations would result in a greater incidence of stereotyped behavior for these groups.

The final experiment (Stimulus Exploration Study) also exposed AMP-treated Ss to environmental novelty, but in a situation which permitted the observation of exploratory behavior and general activity as well as of stereotyped behavior. The Ss in this experiment were exposed to a novel stimulus while in a testing box with which they were already familiar. Based upon unexpected results obtained in the second set of experiments, it was predicted that the presence of the novel stimulus would decrease stereotypy and evoke exploratory behavior.

DOSE-RESPONSE STUDIES

The effects of amphetamine (AMP) upon complex behavior have received widespread attention (e.g. Cole, 1967, 1970). However, with the exception of Schiorring's (1971) study of AMP dose and stereotyped behavior and activity in the open field, there appears to be little reported work studying the effects of AMP dose on naturally occurring behavior of rats in simple situations. One purpose of the first three experiments was to collect basic information about the influence of a wide range of doses of AMP on several classes of behavior in the absence of other experimental manipulations.

The combined results of the experiments from several laboratories give the general impression that AMP-SB increases with increasing dose (Randrup & Munkvad, 1967), and that general activity bears a curvilinear relationship to dose (Searle & Brown, 1938; Yagi, 1963; Pihl & Greenberg, 1969). However, since the studies which focus on activity are usually uninterested in stereotyped behavior, and vice versa, a unified picture of the influence of AMP on these behaviors is still lacking. The present study observed both stereotyped behavior and locomotor activity over a dosage range wide enough to fully assess the effects of AMP.

In addition, Ellinwood and his colleagues (1970, 1972) have noted that different forms of stereotypy appear to be associated with different AMP doses in the chronically-treated cat and monkey. Comparable data are lacking for the rat given a single dose of AMP. Thus, the present experiment observed the varying forms of stereotyped behavior.

In view of the well-known effects of constitution upon drug response (e.g. Meier, Hatfield, & Foshee, 1963, Gupta & Holland, 1969; Sâtinder, 1972), male and female Ss of four different strains of rats were used in an effort to assess the magnitude of constitutional effects.

General Method

This method section described aspects of Experiments I, II and III common to all. Details of the method unique to a single experiment are dealt with in the report of that experiment.

Subjects

Male and female subjects were used. All subjects were 100-115 days of age at the beginning of testing.

Apparatus and Procedures

Ss were maintained and tested in the McGill University Psychology Department animal colony. Each S was assigned a home cage when delivered to the laboratory. One week prior to the beginning of testing, each S, in its home cage, was placed in its assigned position in the colony. Ss subsequently remained undisturbed, except that food and water were replenished, and litter changed twice weekly. Care was taken to ensure that the litter was never changed fewer than 2 days prior to testing.

The home cage of each S was constructed of moulded plastic and measured 9" X 14" X 6" high. A wire top contained the food hopper and water bottle retainer. These cages were located adjacent to one another in one section of the animal colony. The colony itself was maintained on a 6 a.m. - 9 p.m. light - dim light schedule. The temperature stood at $72 \pm 3°$ F, and the humidity at 40-70% throughout the experiment.

The solutions for injections were prepared from crystaline d-amphetamine sulfate, which was disolved in 0.9% saline solution. These solutions were injected intraperitoneally using a 25 guage 1/2-inch needle. All Ss received their injections between 11 a.m. and 1 p.m. To avoid injecting an excessively large or small volume of fluid, two concentrations of AMP solution were used. Injections of 1.0 mg/kg or less always employed a solution of 0.5 mg/ml. Injections of 3.0 mg/kg or more always used a 4 mg/ml solution.

Each S was given a control injection (0.9% saline) and one injection of each of five doses of AMP. A different dose order was assigned randomly to each S. Ss were injected every third day.

Beginning 15 minutes after each injection, a S was observed for a one minute period every 15 minutes for two hours, making a total of 8 observations. During each observation, the experimenter noted the presence and type of stereotyped behavior and recorded the locomotor activity of the subject. The former was recorded by writing down the predominant type of stereotyped behavior, if any. Four exclusive categories of stereotyped behavior were used: Scanning was recorded when a stationary S emitted repetitive, rhythmic horizontal and/or vertical head or head and body movements, accompanied by sniffing. The category of Licking referred to continuous licking of the walls or floor of the cage. Perambulating was recorded when a S walked either in a repetitive stereotyped manner or following a repetitive path. Perambulating included foreward and backward walking, and usually implied a Scanning S. A Grooming score indicated continuous repetitive grooming of one area of the body.

Locomotor Activity was assessed by counting the number of quarters of the cage into which the S entered with all four paws during each one minute observation period.

Analysis of Results

The basic scores used in the data analysis were the sums of the eight scores for each S at each dose level. In addition to the individual categories of stereotyped behavior, their sum was also analyzed (Total SB). The category of stereotyped behavior labeled Grooming was not analyzed separately due to its extremely low frequency of occurance at all drug levels. However, Grooming scores were retained in the Total SB score.

These scores were analyzed using an analysis of variance. In the case of the analyses of stereotyped behaviors, many zero scores resulted from the injection of the control solution or low doses of amphetamine. It was therefore decided to require a significance level of 1% or less for these initial analyses.

Following a significant dose effect in the basic analyses, trend analyses were performed in order to determine the shape of the dose-response curves. The methods employed are described by Myers (1966). The statistical significance of each resulting F test was evaluated using the criterion proposed by Scheffé (1959). Scheffé has suggested (1959, p. 71) that the power of this criterion be increased by setting the acceptable significance level at 0.10, and this suggestion has been followed.

EXPERIMENT I

Method

Subjects. 16 male and 16 female Wistar rats obtained from the Canadian Breeding Farm and Laboratories served as Ss. At the beginning of the experiment, the males ranged in weight from 335-400g, the females from 230-260g.

Procedure. Ss were injected every third day with one of the following dose levels of the AMP solution: 0.0 (control), 0.25, 0.5, 1.0, 3.0, or 6.0 mg/kg.

Results

Stereotyped behavior and activity scores were analyzed using an analysis of variance in which sex of subject (G) and drug dose (D) were the main variance sources. The analysis of variance tables resulting from the analyses of Total SB, Scanning, Licking, and Perambulating appear in Tables 1-4, respectively. In each analysis, Dose was a significant determinant of incidence of stereotyped behavior ($p < .001$). In the case of Perambulating, Sex and the interaction of Dose and Sex also contributed significantly ($p < .01$). None of the remaining effects reached an acceptable level of significance ($p > .01$). Figure 1 depicts the influence of Dose upon each category of stereotyped behavior. Trend analyses of these dose-response curves revealed significant linear and quadratic trends for Total SB and for Scanning, a significant linear trend for Licking, and a significant quadratic trend for Perambulating.

Table 5 presents the results of the analysis of variance of Locomotor

Table I

Summary of the Analysis of Variance of Total SB in Experiment I

Source	df	MS	F
Between Ss			
Sex (G)	1	21.43	6.04*
Error (I)	26	3.55	
Within Ss			
Dose (D)	5	272.72	105.00***
G x D	5	8.14	3.13**
D x I	130	2.60	

*$p < 0.05$
**$p < 0.01$
***$p < 0.001$

Table 2

Summary of the Analysis of Variance of

Scanning in Experiment I

Source	df	MS	F
Between Ss			
Sex (G)	1	5.72	0.89
Error (I)	26	6.45	
Within Ss			
Dose (D)	5	163.71	50.26***
GXD	5	3.71	1.14
DXI	130	3.26	

***$p < 0.001$

Table 3

Summary of the Analysis of Variance

of Licking in Experiment I

Source	df	MS	F
Between Ss			
Sex (G)	1	4.67	2.65
Error (I)	26	1.76	
Within Ss			
Dose (D)	5	17.77	15.16***
G x D	5	1.77	1.50
D x I	130	1.17	

***$p < 0.001$

Table 4

Summary of the Analysis of Variance of

Perambulating in Experiment I

Source	df	MS	F
Between Ss			
Sex (G)	1	17.36	8.42**
Error (1)	26	2.06	
Within Ss			
Dose (D)	5	11.43	8.20***
G x D	5	6.26	4.49***
D x I	130	1.39	

**$p < 0.01$
***$p < 0.001$

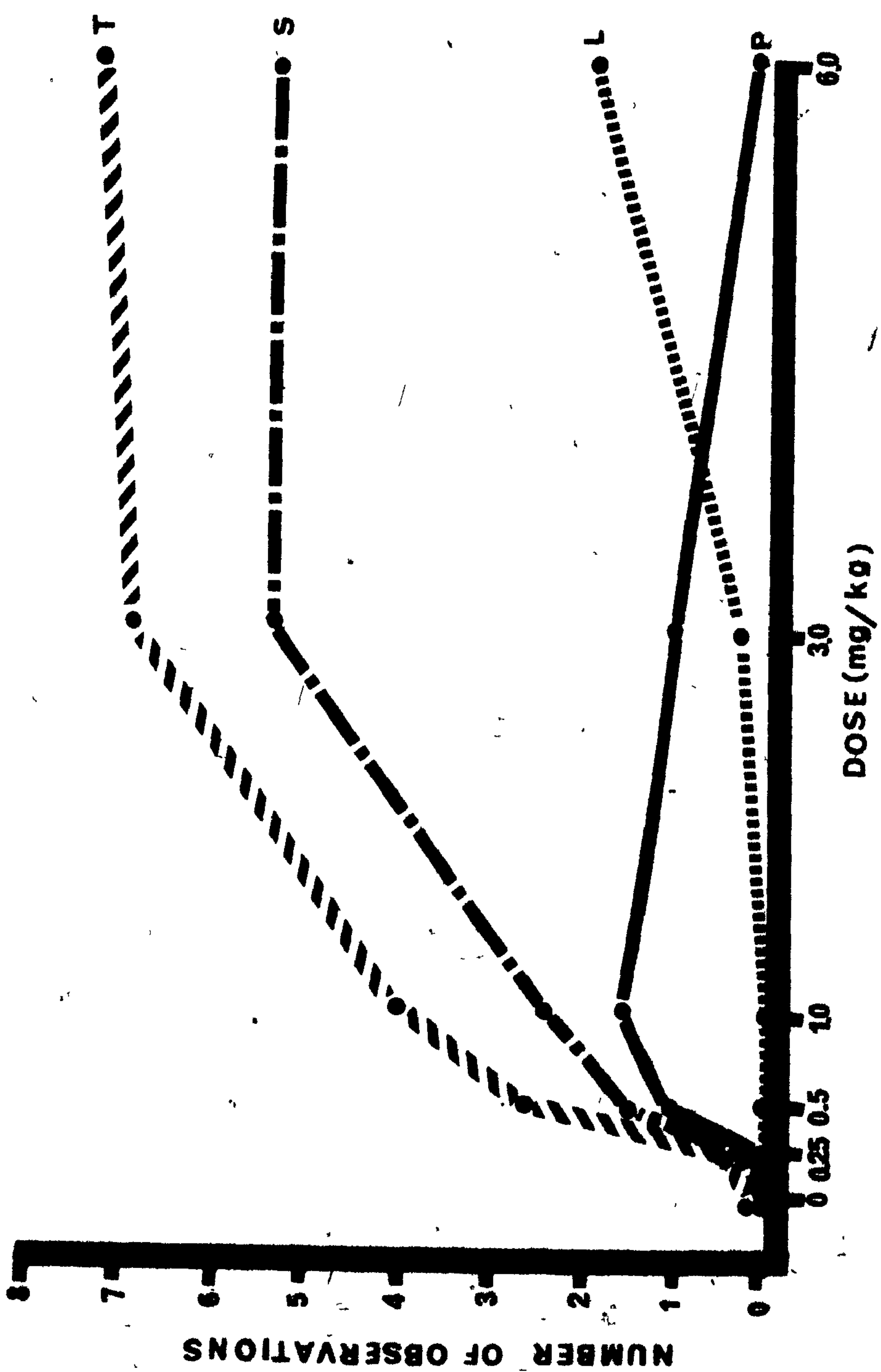

Figure 1. Mean number of observations of four categories of stereotyped behavior in Wistar rats following injections of amphetamine at 6 dose levels. (T = Total Stereotyped Behavior, S = Scanning, L = Licking, P = Perambulating) (n = 32)

Table 5

Summary of the Analysis of Variance

of Locomotor Activity in Experiment I

Source	df	MS	F
Between Ss			
Sex (G)	1	3295.44	10.46**
Error (I)	26	314.96	
Within Ss			
Dose (D)	5	3527.84	24.75***
G x D	5	1206.78	8.47***
D x I	130	142.54	

** $p < 0.01$
*** $p < 0.001$

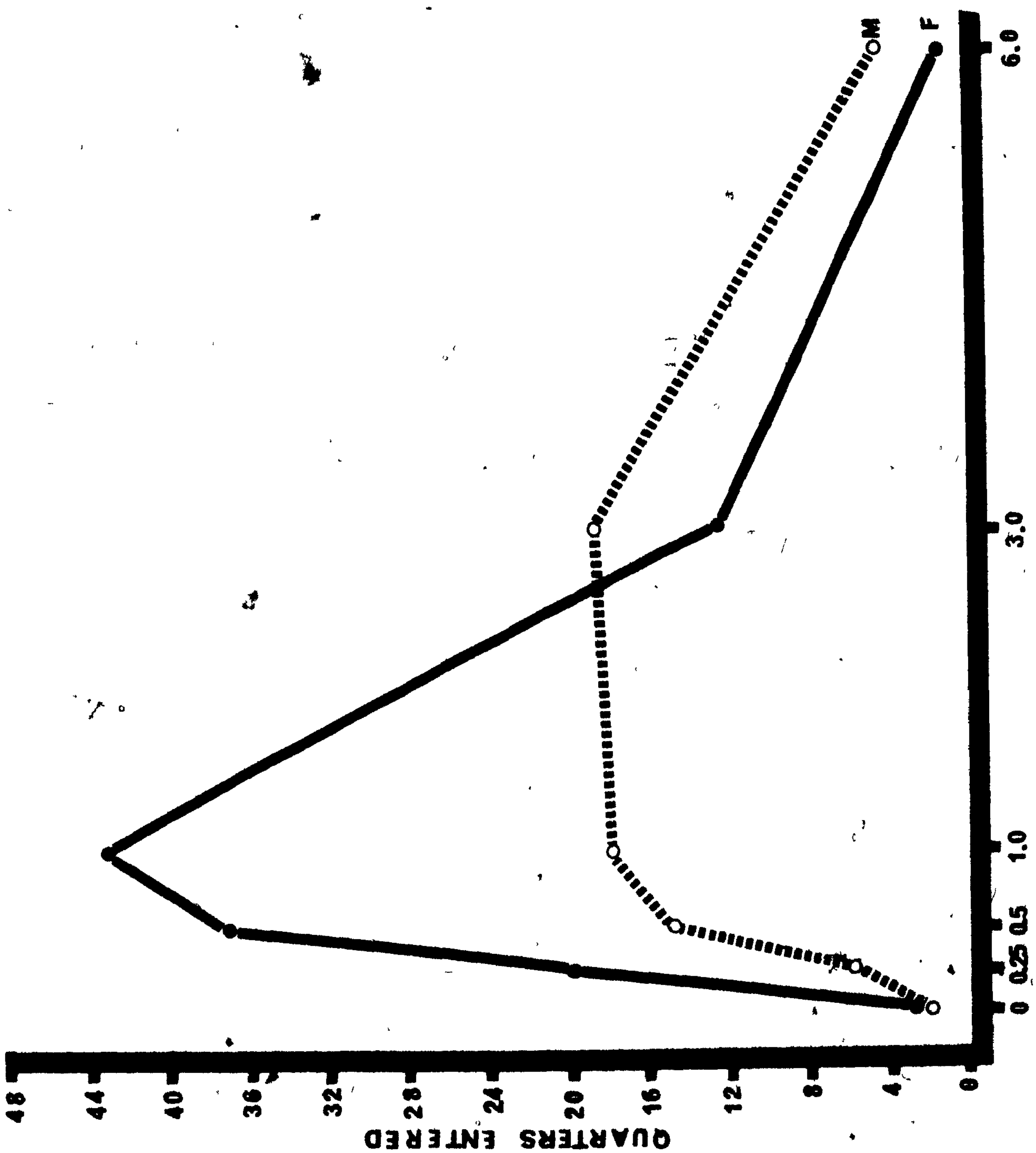

Figure 2. Locomotor activity of male and female Wistar rats following injections of amphetamine at 6 dose levels. (n = 16)

Activity. Sex ($p < .005$), Dose ($p < .001$) and their interaction ($p < .001$) all contributed significantly to the variability of the activity scores. Figure 2 depicts the Sex X Dose interaction. A trend analysis of the dose effect revealed a significant concave downward quadratic trend.

EXPERIMENT II

Method

Subjects. The Ss were 9 male and 10 female Hooded rats of the Royal Victoria Hospital Strain, purchased from Canadian Breeding Farm and Laboratories. The males weighed 275-300 g, the females 150-175 g, at the beginning of the experiment.

Procedure. Ss were injected with 0.0, 0.5, 1.0, 3.0, 6.0 or 10.0 mg/kg of d-amphetamine sulfate in physiological saline.

Results

The results were analyzed in a manner similar to that of Experiment I. Tables 6-10 present the results of the analyses of variance. Dose was a significant determinant of the variance of all of the indices of stereotyped behavior ($p < .01$). Sex and the interaction of Sex with Dose did not reach significance ($p > .01$). Figure 3 depicts the influence of amphetamine dose on the various indices of stereotyped behavior. Trend analyses revealed significant linear and quadratic components in the effect of Dose on Total SB, a significant linear component in its effect on Licking, and significant quadratic trends in its effects on Scanning and Perambulating.

Table 6

Summary of the Analysis of Variance of Total SB

in Experiment II

Source	df	MS	F
Between Ss			
Sex (G)	1	6.69	2.72
Error (I)	17	2.46	
Within Ss			
Dose (D)	5	187.22	69.61***
G x D	5	2.99	1.11
D x I	85	2.69	

***$p < 0.001$

Table 7

Summary of the Analysis of Variance of

Scanning in Experiment II

Source	df	MS	F
Between Ss			
Sex (G)	1	0.82	0.28
Error (I)	17	2.92	
Within Ss			
Dose (D)	5	37.63	12.13***
G x D	5	3.41	1.10
D x I	85	3.10	

***$p < 0.001$

Table 8

Summary of the Analysis of Variance of Licking in Experiment II

Source	df	MS	F
Between Ss			
Sex (G)	1	7.00	3.66
Error (1)	17	1.91	
Within Ss			
Dose (D)	5	110.66	58.39***
G x D	5	3.29	1.73
D x I	85	1.90	

*** $p < 0.001$

Table 9

Summary of the Analysis of Variance of

Perambulating in Experiment II

Source	df	MS	F
Between Ss			
Sex (G)	1	0.74	0.58
Error (I)	17	1.28	
Within Ss			
Dose (D)	5	3.37	3.91**
G x D	5	1.19	1.39
D x I	85	0.86	

$^{**}p < 0.01$

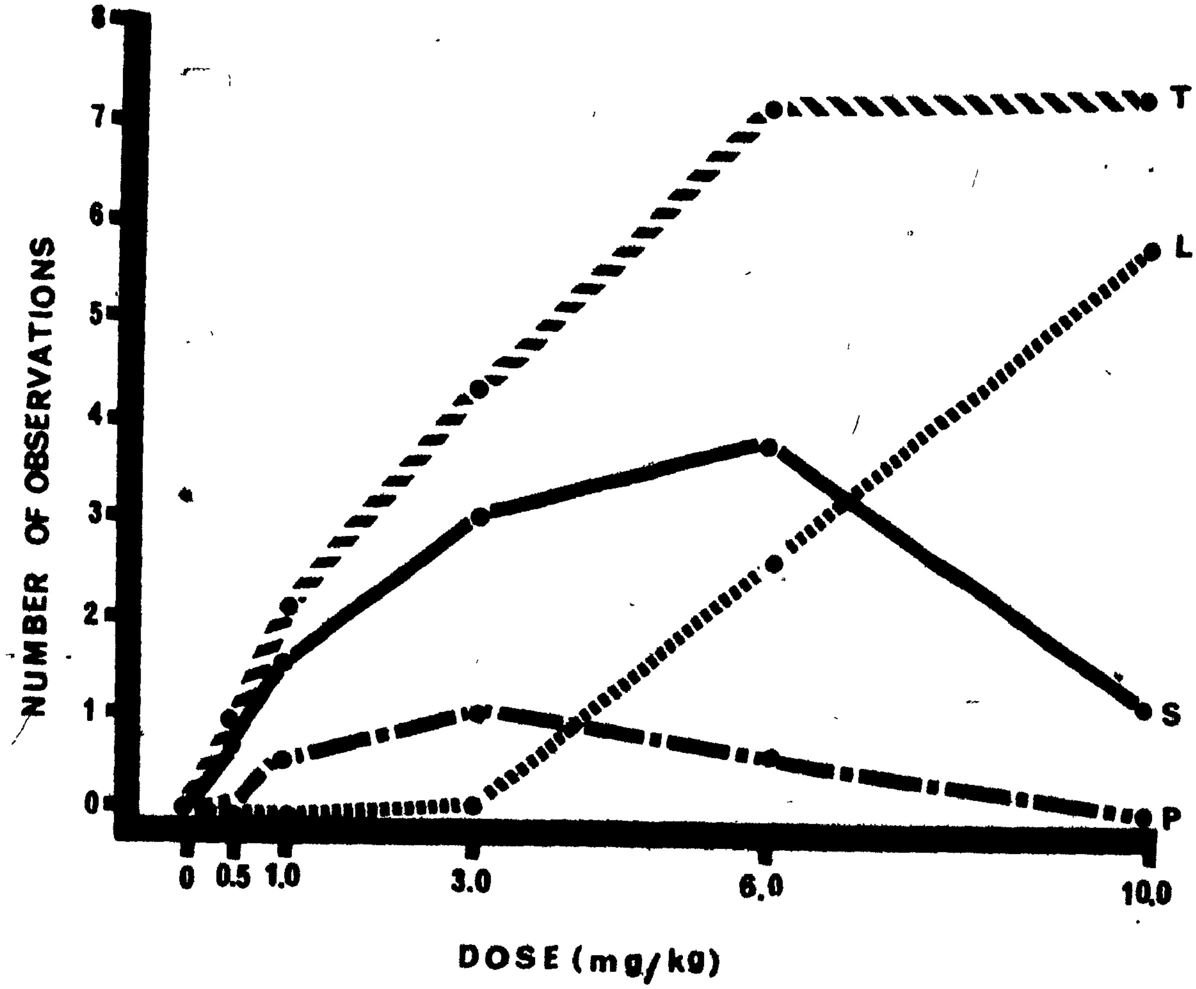

Figure 3. Mean number of observations of four categories of stereotyped behavior in Hooded rats following injections of amphetamine at 6 dose levels. (T = Total Stereotyped Behavior, S = Scanning, L = Licking, P = Perambulating) (n = 19)

Table 10

Summary of the Analysis of Variance

of Locomotor Activity in Experiment II

Source	df	MS	F
Between Ss			
Sex (G)	1	67.79	0.32
Error (1)	17	210.02	
Within Ss			
Dose (D)	5	672.75	8.76***
G x D	5	85.16	1.11
D x 1	85	76.77	

***$p < 0.001$

Locomotor.

The Activity scores also were influenced only by dose ($p < .001$). The trend analysis of this effect disclosed a concave downward quadratic component.

EXPERIMENT III

Method

Subjects. Four male and 4 female rats descended from the Tryon Maze Bright (S_1) and Maze Dull (S_3) strains served as Ss for this experiment. These Ss were bred and raised in the McGill Psychology Department animal colony. The nucleus of animals used to start this colony was obtained from the colony located at the Stanford Research Institute, Palo Alto, California. Ss were weaned at 22 days, segregated by sex at 40 days, and raised in groups of 4 until the beginning of the experiment at 100 days of age. At this time the males weighed 285-315g, and the females weighed 170-210g.

Procedure. These Ss received injections of 0.0, 0.5, 1.0, 3.0, 6.0 and 10.0 mg/kg of d-amphetamine sulphate.

Results

The analyses of variance of the stereotyped behavior and activity scores used Strain of S, as well as Sex of S and Dose, as a main variance source. The results of the analyses of variance of the indices of stereotyped behavior appear in Tables 11-14. Dose and Sex, both as main effects and in interaction, appeared as the dominant variables in these analyses. Dose significantly ($p < .01$) affected all indices of stereotyped behavior, with the exception

Table II

Summary of the Analysis of Variance of

Total SB in Experiment III

Source	df	MS	F
Between Ss			
Strain (S)	1	4.59	3.75
Sex (G)	1	12.76	10.41**
S x G	1	3.76	3.07
Error (I)	12	1.23	
Within Ss			
Dose (D)	5	196.62	253.47***
S x D	5	1.52	1.96*
G x D	5	0.89	1.14
S x G X D	5	1.24	1.59
D x I	60	0.78	

*$p < 0.05$
**$p < 0.01$
***$p < 0.001$

Table 12

Summary of the Analysis of Variance of Scanning in Experiment III

Source	df	MS	F
Between Ss			
Strain (S)	1	0.67	0.18
Sex (G)	1	6.00	1.66
S x G	1	16.67	4.62
Error (I)	12	3.61	
Within Ss			
Dose (D)	5	42.80	21.92***
S x D	5	5.82	2.98*
G x D	5	5.10	2.61*
S x G x D	5	8.32	4.26**
D x I	60	1.95	

*$p < 0.05$
**$p < 0.01$
***$p < 0.001$

Table 13

Summary of the Analysis of Variance of

Licking in Experiment III

Source	df	MS	F
Between Ss			
Strain (S)	1	1.26	0.34
Sex (G)	1	0.09	0.03
S x G	1	0.26	0.07
Error (I)	5	3.68	
Within Ss			
Dose (D)	5	80.14	51.91***
S x D	5	1.69	1.09
G x D	5	7.92	5.13***
S x G x D	5	2.64	1.71
D x I	60	1.54	

***$p < 0.001$

Table 14

Summary of the Analysis of Variance of

Perambulating in Experiment III

Source	df	MS	F
Between Ss			
Strain (S)	1	0.04	0.06
Sex (G)	1	0.04	0.06
S x G	1	2.67	4.04
Error (I)	12	0.66	
Within Ss			
Dose (D)	5	0.30	0.51
S x D	5	1.19	2.04
G x D	5	1.19	2.04
S x G x D	5	0.57	0.97
D x I	60	0.58	

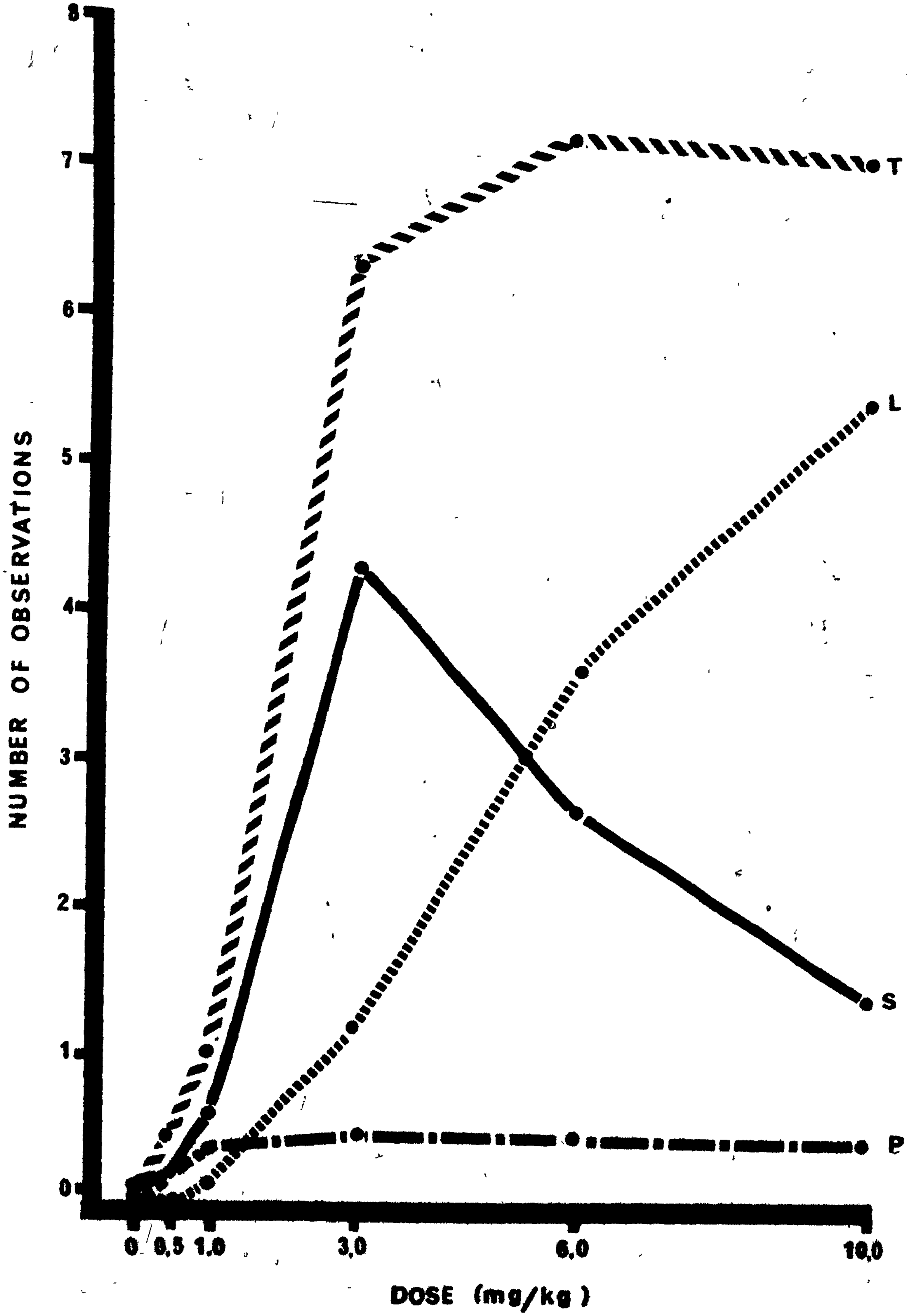

Figure 4. Mean number of observations of four categories of stereotyped behavior in Tryon rats following injections of amphetamine at 6 dose levels. (T = Total Stereotyped Behavior, S = Scanning, L = Licking, P = Perambulating) (n = 16)

of Perambulating, which was unaffected by any of the variables. Total SB was influenced by the main effects of both Dose and Sex ($p < .01$). Figure 4 depicts the effects of Dose upon the components of stereotyped behavior. Trend analyses of these curves disclosed linear and quadratic trends for both Scanning and Total SB, and a linear trend for Licking. In addition, Scanning (Figure 5) was influenced by the three-way interaction of Strain, Sex, and Dose ($p < .01$), and Licking (Figure 6) was influenced by the interaction of Sex and Dose ($p < .001$).

As indicated in Table 15, Dose ($p < .025$) and the Sex X Dose interaction ($p < .005$) made significant contributions to the variance of the locomotor activity scores. Figure 7 depicts the Sex X Dose interaction. The trend analysis of the Dose main effect revealed no linear, quadratic, cubic, or quartic trends.

Discussion

Under the conditions of these experiments, stereotyped behavior is very largely a function of arousal. Drug dosage, conceived of as a manipulation of arousal level, emerged as the overriding determinant of stereotyped behavior in these experiments. Stereotyped behavior, taken as a whole, appears to be a monotonic increasing function of AMP dose. An examination of the dose-response curves of stereotyped behavior for the three experiments (Figures 1, 3, and 4) reveals their marked similarity. Furthermore, the incidence of each of the components of stereotyped behavior appears to have a fairly consistent relationship to dose in all three experiments, although the nature of the relationship differs for each component. Thus, Licking

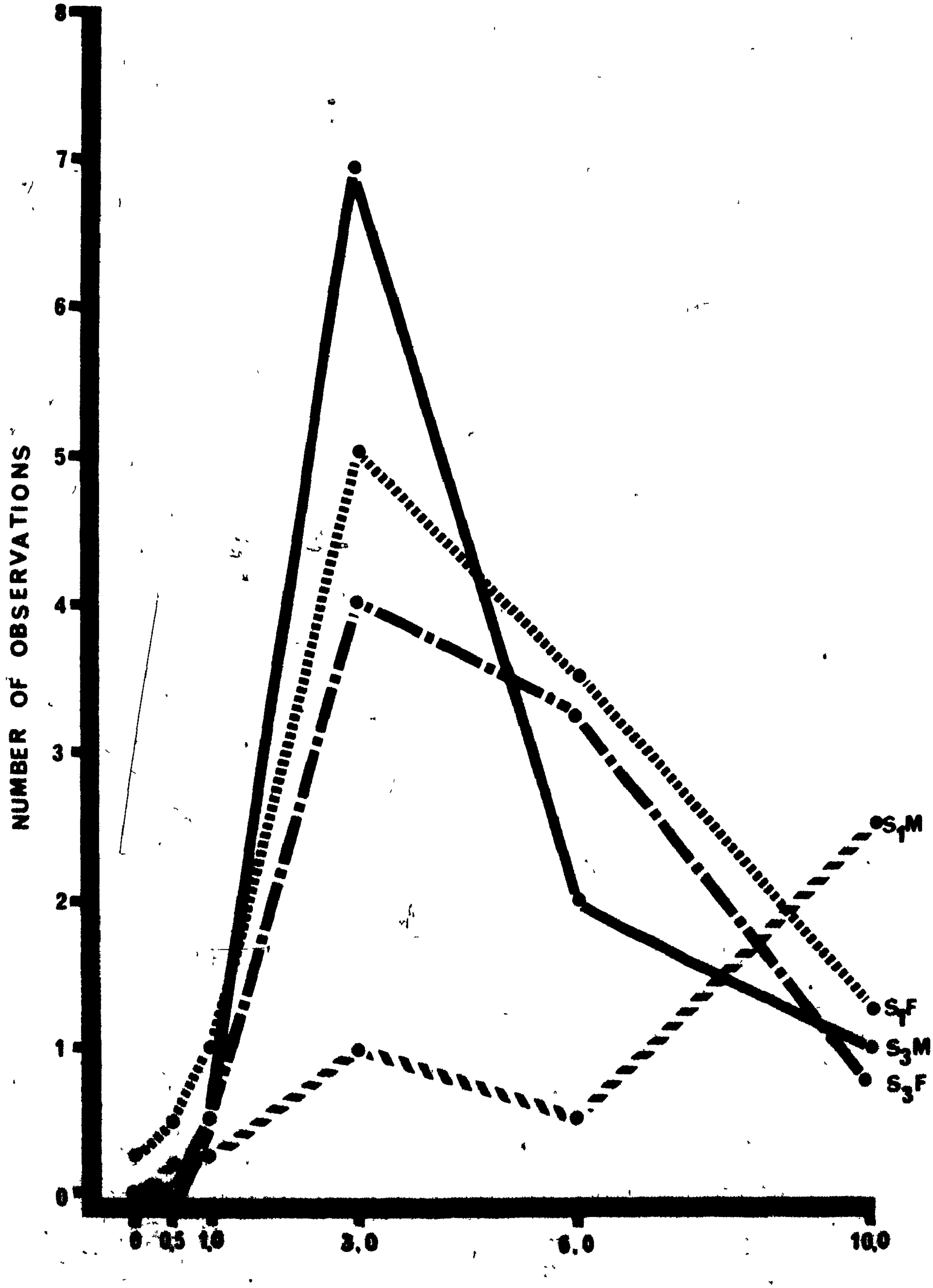

Figure 5. Mean number of observations of stereotyped scanning in males and females of Tryon Maze Bright (S_1) and Maze Dull (S_3) rats at 6 doses of amphetamine. (n = 4)

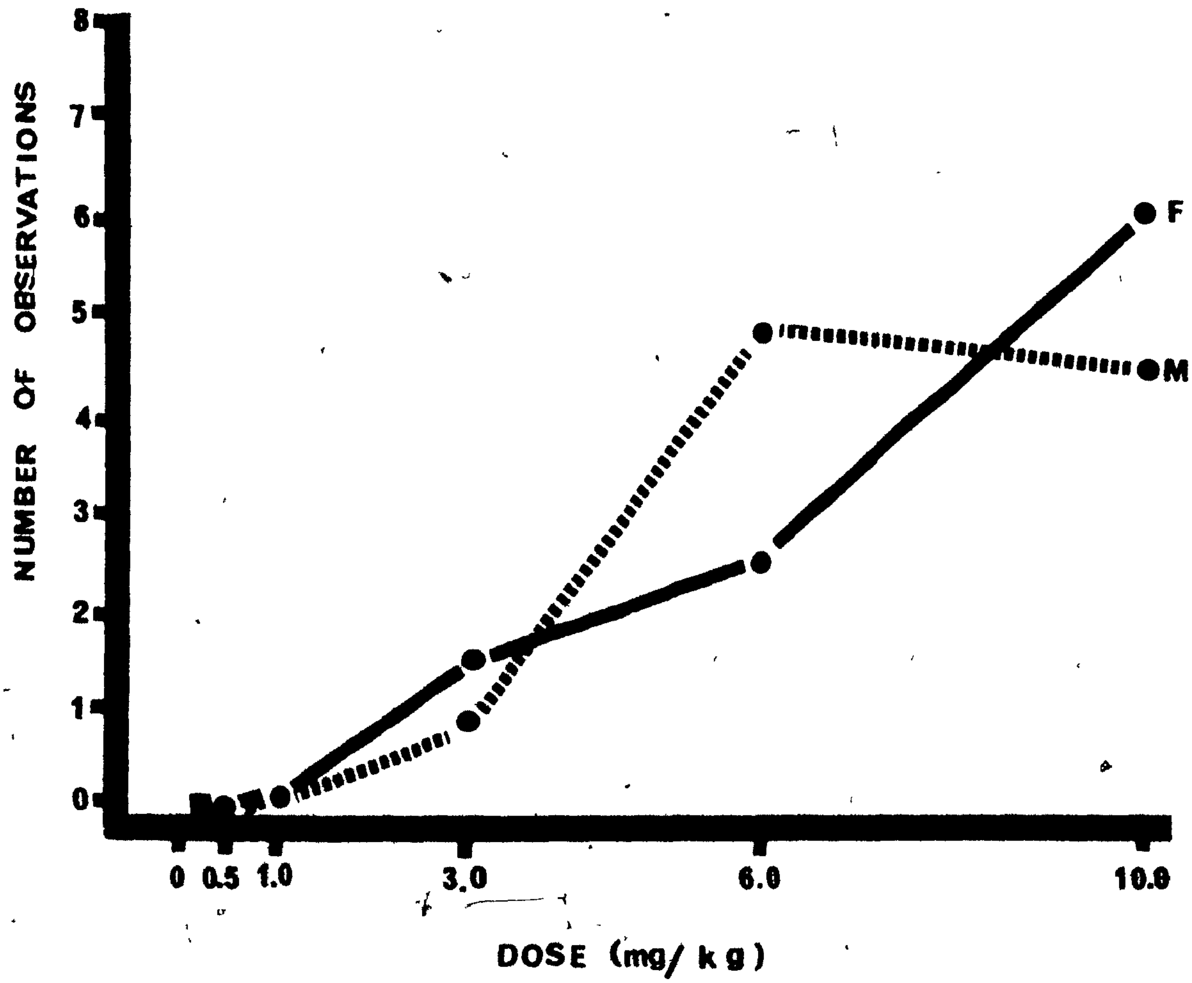

Figure 6. Mean number of observations of stereotyped licking in male and female Tryon rats at 6 doses of amphetamine. (n = 8)

Table 15

Summary of the Analysis of Variance of

Locomotor Activity in Experiment III

Source	df	MS	F
Between Ss			
Strain (S)	1	33.85	0.06
Sex (G)	1	326.34	0.59
S x G	1	1989.26	3.60
Error (I)	12	553.02	
Within Ss			
Dose (D)	5	891.94	3.14*
S x D	5	492.27	1.74
G x D	5	1333.77	4.70**
S x G x D	5	126.19	0.44
D x I	60	283.68	

*$p < 0.05$
**$p < 0.01$

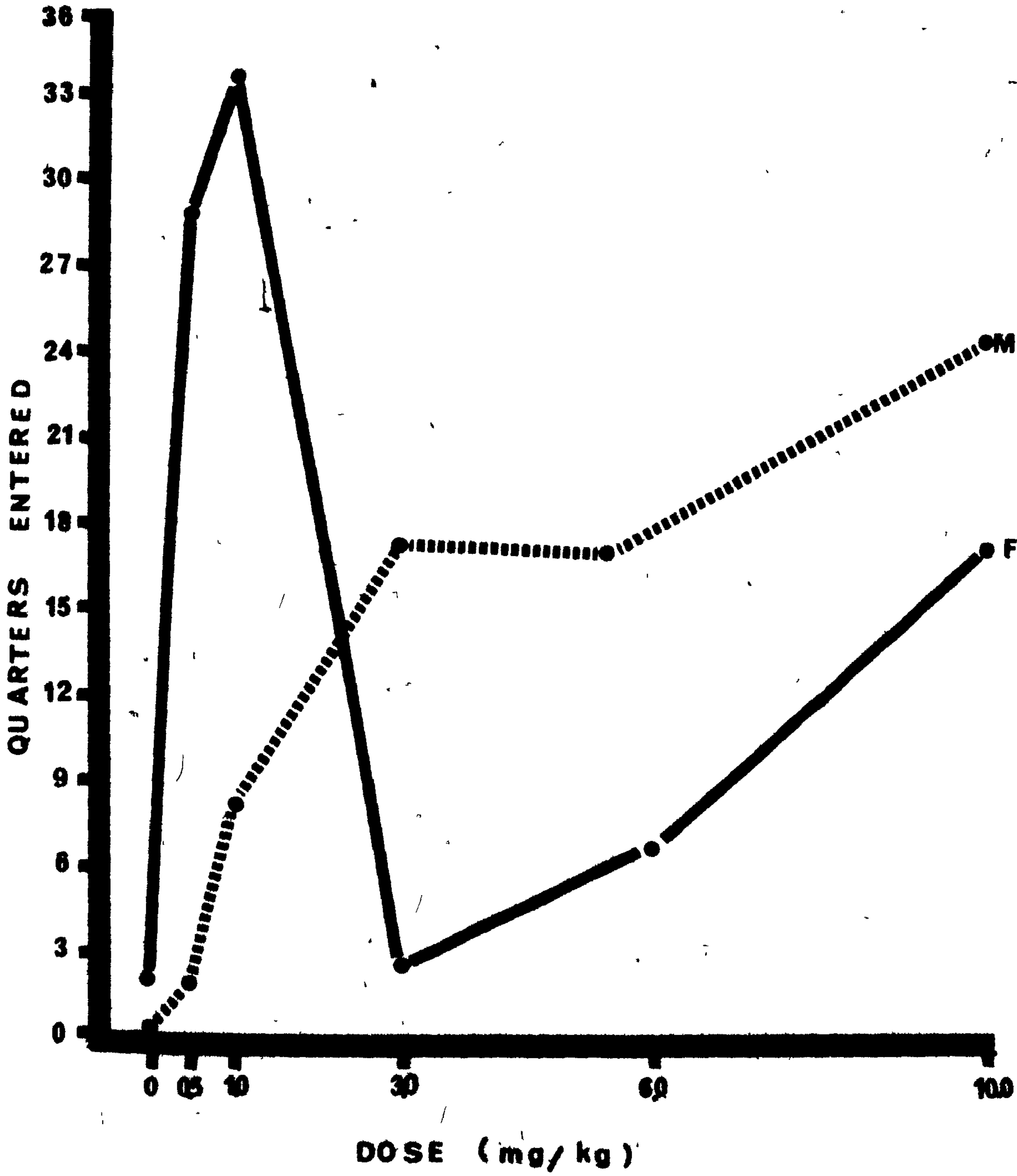

Figure 7. Locomotor activity of male and female Wistar rats following injections of amphetamine at 6 dose levels. (n = 8)

appears to increase linearly with increasing dose, while the dose-response curves of Scanning and Perambulating exhibited a strong quadratic component as well. The significance of the different relationships of the components of stereotyped behavior to dose is not clear.

AMP dose also exerted a powerful influence on locomotor activity. The inverted-U relationship found in Experiments I and II is similar in shape to curves typically found in experiments relating AMP dose to various indices of locomotor activity (Searle & Brown, 1938; Yagi, 1963; Pihl & Greenberg, 1969). It is of interest to note that the dose-response curves for Locomotor Activity consistently differ from those for most types of stereotyped behavior. This difference constitutes evidence that the locomotor activating and stereotypy-producing properties of AMP may work via different mechanisms (Mandell & Segal, 1973).

All of the experiments provide evidence for the existence of constitutional effects, although these effects are generally of smaller magnitude than are those of dose. AMP consistently produced a higher rate of locomotor activity in female Ss than it did in males. The indices of stereotyped behavior did not appear to be as sensitive to sex differences as was locomotor activity. However, Experiment III revealed that strain and sex are capable of influencing the incidence of two components of stereotyped behavior. The significance of these findings is not clear at this time.

NOVELTY-FAMILIARITY STUDIES

Experiments I, II, and III lend themselves to the interpretation that the incidence of stereotyped behavior in the home cage is largely a function of arousal level, where arousal is produced by AMP injection. The two experiments in this group were designed to study the incidence of AMP-SB as a function of environmentally-induced arousal. This arousal was provided in Experiment IV by an open field and in Experiment V by an unfamiliar home cage.

Each experiment used a single dose of AMP of moderate strength. Pilot studies revealed that the stereotyped behavior emitted under the conditions of these experiments was predominantly Scanning. Therefore, no attempt was made to discriminate between the varieties of stereotyped behavior. An observer used an event recorder to record the duration of stereotyped behavior sequences.

EXPERIMENT IV

An unfamiliar, open area is commonly thought to be a frightening, emotionally arousing situation for the rat (e.g. Hall, 1934; Dennenberg, 1964) and it is commonly agreed that unfamiliar situations lose their arousing properties as they become more familiar (e.g. Berlyne, 1960). If the stereotyped behavior produced by AMP is primarily a function of arousal, it should be possible to manipulate the level of AMP-produced stereotypy by manipulating the novelty of the open field. Given equivalent doses of AMP, Ss exposed to the open field for the first time should emit more stereotyped behavior than should Ss previously given several exposures.

Method

Subjects. The Ss for this experiment were 18 male and 18 female Wistar rats obtained from Canadian Breeding Farm and Laboratories. At the beginning of the experiment, the males ranged in weight from 335-400g, the females from 230-260g.

Apparatus. The open field was a circular enclosure 36" in diameter with walls 25" high. The walls were painted flat white. The floor was brown plastic, and was divided by white radial lines and concentric circles into 24 subdivisions of approximately 40 square inches each. The field was illuminated by the fluorescent room lighting. The observer sat adjacent to the field.

For all Ss, the dosage of amphetamine was 3.0mg/kg in a solution prepared with 3.0 mg/ml d-amphetamine sulfate in 0.9% saline.

Procedure. All Ss were maintained in the McGill Psychology Department animal colony under the conditions described in the previous experiments for one week prior to testing. One half of the Ss of each sex were randomly assigned to each of two groups. The Ss in Group I were injected with AMP and observed in the open field on the first day of the experiment only. The Ss in group II were exposed to the open field on five consecutive days. These Ss were administered AMP, and were observed, on the fifth day only. All injections were given 30-40 minutes before the beginning of the trial, which was of 5 minutes duration. The open field was cleaned with alcohol after every trial.

An observer recorded all occasions of stereotyped behavior by pressing a button which activated the pen of an event recorder. The button was pressed when the S had emitted a behavior three times in a rhythmic, substantially unchanged form, and was held down continuously until the S initiated some other form of behavior. The observer also recorded the number of squares into which each S entered with all four feet on the day it received its AMP injection.

Results

The data obtained during the observations were used to compile two indices of stereotyped behavior: The total time which a S spent emitting stereotyped behavior (SB Time), and the total number of occasions upon which the S emitted stereotyped behavior (Bouts). Scores on these two indices and the locomotor activity data were subjected to analyses of variance in which Group and Sex were the main variance sources. The relevant summaries appear in Tables 16, 17, and 18. Contrary to expectation, the Ss given AMP on their first exposure to the open field did not emit more stereotyped behavior than did those given it on their fifth exposure. Both indices of stereotyped behavior demonstrate that they emitted less. Ss in Group I emitted an average of 20.3 seconds and 8.1 bouts, while those in Group II emitted an average of 73.3 seconds and 16.5 bouts. The significance level of these results is less than .05%. Male Ss emitted less stereotyped behavior (30.2 seconds to 63.9) and fewer bouts (8.8 to 15.7) than did female Ss. The significant ($p < .05$) Group x Sex interaction influencing SB Time appears in Figure 8. This interaction did not approach significance for Bouts ($p > .20$).

Table 16

Summary of the Analysis of Variance of

SB Time in Experiment IV

Source	df	MS	F
Sex (G)	1	10234.7	13.90***
Group (T)	1	24806.2	33.68***
G x T	1	3990.03	5.42*
Error	32	736.44	

*p < 0.05
***p < 0.001

Table 17

Summary of the Analysis of Variance of

Bouts in Experiment IV

Source	df	MS	F
Sex (G)	1	427.11	9.98**
Group (T)	1	641.78	15.00***
G x T	1	18.78	0.44
Error	32	42.80	

**$p < 0.01$
***$p < 0.001$

Table 18

Summary of the Analysis of Variance of *Locomotor Activity* in Experiment IV

Source	df	MS	F
Sex (G)	1	4181.78	3.92
Group (T)	1	9344.44	8.75**
G x T	1	1547.11	1.45
Error	32	1067.80	

**$p < 0.01$

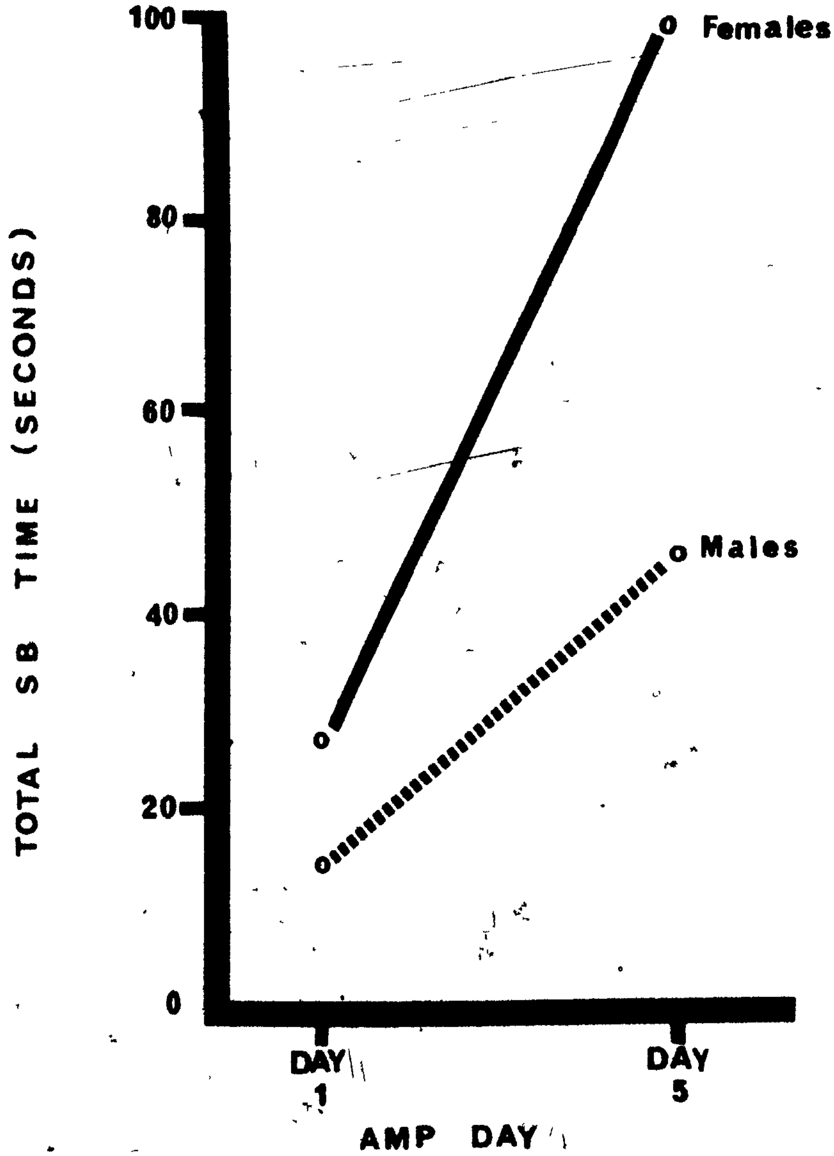

Figure 8. Mean number of seconds of stereotyped behavior emitted by male and female rats tested on the first and the fifth days of exposure to an open field. (n = 9)

An analysis of the locomotor activity measure (total sections entered) also revealed differences between the groups. Ss given AMP on trial 1 were significantly less active than were those given it on trial 5 (63.3 sections entered to 95.6, $p < .01$). Neither the main effect of sex ($p > .05$) nor the Group x Sex interaction ($p > .20$) was significant.

EXPERIMENT V

Because the main result of Experiment IV ran contrary to expectation, it was decided to attempt to replicate it in a different context: The home cage. In the present experiment an attempt was again made to manipulate the arousal value of the testing environment by manipulating its familiarity, this time by testing AMP-treated Ss either in their own home cage or in an unfamiliar cage of identical design.

Method

Subjects. Ss used in this experiment were 12 male Wistar rats obtained from Canadian Breeding Farm and Laboratories. They ranged in weight from 250-300g at the beginning of the experiment.

Apparatus. All Ss were housed and tested in plastic cages with wire tops, identical to those described in Experiments I, II, and III. The AMP solution used for injection was prepared in a concentration of 2mg/ml d-amphetamine sulfate in 0.9% saline.

Procedure. All Ss were housed individually in the animal colony for one week prior to testing. During this period, their cages were not touched, other than to replenish food and water.

On the day of testing, each S was taken to the testing room in its home cage, weighed, injected with 2.0mg/kg AMP, and returned to its home cage, which remained in the testing room. One half hour later, the S was removed from its home cage,held by hand for five seconds, and placed into one of two types of cages. One half of the Ss were returned to their original home cages. The other half were placed into an unfamiliar cage of identical construction and dimensions, but which had been freshly washed and which contained fresh sawdust. The original cage top was returned in both cases. The assignment of Ss to the familiar cage group or to the unfamiliar cage group was random.

Each S was observed continuously for the next one half hour. This period of observation was divided into 6 five-minute time blocks. The first four minutes of each block were spent recording stereotyped behavior, using the method and criteria described in Experiment IV. During the fifth minute of each block, the observer recorded locomotor activity, defined as the number of quarters of the cage which the S entered with all four feet.

Results

The two indices of stereotyped behavior defined in Experiment IV, SB Time and Bouts, and the locomotor activity measure were analyzed by analysis of variance in which type of cage (Familiar or Unfamiliar) and observation period (1-6) were the main variance sources. Both cage type and period significantly affected SB Time (Table 19): Ss returned to familiar home cages emitted significantly more stereotypies than did Ss placed in unfamiliar

Table 19

Summary of the Analysis of Variance

of *SB Time* in Experiment V

Source	df	MS	F
Between Ss			
Group (G)	1	140450.	27.90***
Error (1)	10	5033.26	
Within Ss			
Period (P)	5	19638.7	15.48***
G x P	5	1981.37	1.56
P x 1	50	1268.55	

***$p < 0.001$

cages ($p < .01$); all Ss emitted more stereotyped behaviors during the last observation periods than they did during the first ($p < .001$). The two variables did not interact ($p > .10$). Neither of the main effects made a significant contribution to the variance of Bouts (Table 20). However, their interaction was significant ($p < .01$). This interaction is diagrammed in Figure 9. During all observations except the first, Ss placed into familiar cages emitted fewer bouts than did Ss placed into unfamiliar cages. This relationship is reversed in the first period. These two indices taken together indicate a difference in mean bout length. Ss returned to their original cages emitted a few very long bouts. Neither the two variables individually nor their interaction influenced the activity scores (Table 21).

Discussion

In both Experiments IV and V, AMP-treated Ss placed into a relatively novel environment emitted less stereotyped behavior than did those placed into a familiar environment. This effect holds when both environments are relatively familiar (Experiment V) and unfamiliar (Experiment IV).

Experiments I, II, and III have shown that the role of AMP-produced arousal in generating stereotypies is considerable. However, to conceive of the amount of stereotyped behavior as directly reflecting the degree of arousal does not appear to be warranted, since the additional arousal produced by unfamiliar surroundings did not produce an increase in stereotyped behavior. It may be that the "arousal" produced by the drug and the "arousal" produced by novelty are different, and are not "additive." In fact, they would have to be "subtractive" to fit the pattern of results in

Table 20

Summary of the Analysis of Variance

of Bouts in Experiment V

Source	df	MS	F
Between Ss			
Group (G)	1	105.13	2.82
Error (I)	10	37.29	
Within Ss			
Period (P)	5	2.33	0.20
G x P	5	39.73	3.38**
P x I	50	11.75	

**$p < 0.01$

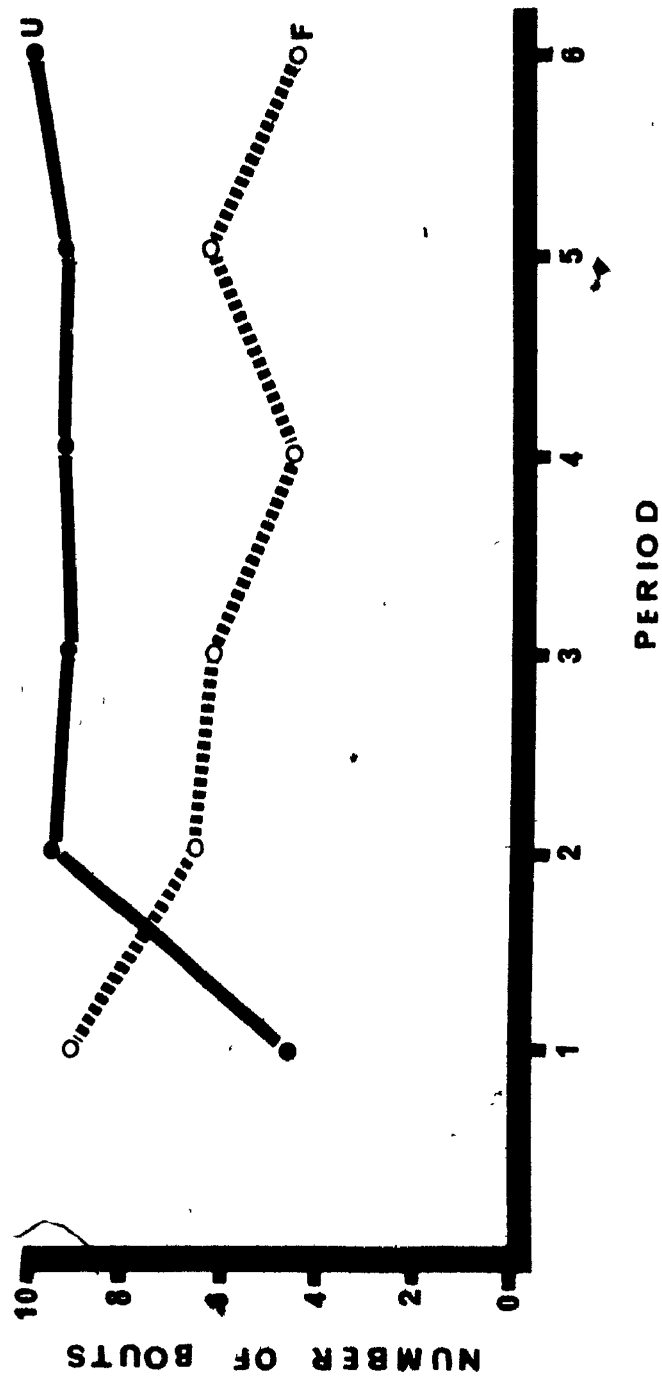

Figure 9. Mean number of bouts of stereotyped behavior emitted by rats in Familiar (F) and Unfamiliar (U) cages following amphetamine injection. (n = 6)

Table 21

Summary of the Analysis of Variance

of Locomotor Activity in Experiment V

Source	df	MS	F
Between Ss			
Group (G)	1	0.22	0.02
Error (I)	10	13.19	
Within Ss			
Period (P)	5	1.26	0.47
G x P	5	2.19	0.83
P x I	50	2.65	

the present experiments. While there is no a priori reason that arousal from internal and external sources should be additive, several experiments have obtained results which do support an additive conception of internal and external arousing factors (Berlyne, 1967, 1969), and which consequently cast doubt on a "subtractive" interpretation of the results of the experiments reported here.

Another possible explanation of these results makes use of the inverted-U function which has been hypothesized to relate arousal to behavioral efficiency (Hebb, 1955; Duffy, 1957; Malmo, 1959). It could be argued that, for the highly aroused Ss of experiments IV and V, the additional increase in arousal produced by a novel environment decreased stereotyped behavior because the subjects became overaroused to the point of being hardly able to emit any behavior at all. The fact that the Ss in Experiment IV who were tested during their first exposure to the open field emitted less locomotor activity than did those who were tested on their fifth day of exposure supports this interpretation. However, the results of Experiments I-III argue against such an interpretation. AMP in doses two to three times higher than those used in the present experiment further increased stereotypy, rather than decreasing it. Furthermore, the doses used in Experiments I-III approached the maximum usable dose in Wistar Ss. Pilot studies using 10.0 mg/kg produced appreciable subject mortality.

It appears that an interpretation of the effects of novelty on stereotyped behavior solely in terms of the arousal-producing aspects of novelty faces difficulties. Neither of the two interpretations offered above are entirely convincing.

Under natural conditions, situations which produce arousal also provide cues to the appropriate response to the situation (e.g. Bindra, 1968): A hungry animal should search for and eat food, an angry animal should fight, a frightened animal should freeze or flee from danger. Novelty, too, has behavior-guiding or response-selecting properties in addition to its arousing properties: A curious animal explores (Berlyne, 1960).

The results of Experiments IV and V can perhaps be clarified by focusing attention on this behavior-guiding aspect of novelty. The greater degree of novelty encountered by drug-injected Ss placed into an open field for the first time or into an unfamiliar cage would be expected to elicit or select a higher frequency of exploratory responses in these Ss, compared to Ss placed into familiar situations.

In several of the studies of pathological stereotypies described above, investigators found that stereotypies were reduced in a variety of circumstances which promoted the appearance of alternative, non-stereotyped responses (Davenport & Berkson, 1963; Berkson & Mason, 1964b; Hollis, 1968; Flavell, 1973). It is likely that novelty-induced exploratory behavior functioned in the same manner in Experiments IV and V. Rats placed into the relatively familiar environments were aroused by the AMP, but the familiar environments provided few behavior-guiding cues. In broad terms, then, stereotyped behavior may be characteristic of situations in which the arousal component of a strong motivational state is present but the response-guiding component is not.

In the rat, locomotion has typically been associated with exploration (Berlyne, 1960), and thus the finding that AMP-injected rats were less active on their first than on their fifth exposure to the open field (Experiment IV) appears incompatable with the hypothesis that they emitted less stereotyped behavior because they were exploring more. However, there are several reasons for questioning whether locomotion accurately reflects exploration in Experiment IV. The ability of AMP to stimulate high levels of locomotor activity in the Ss' home cages in Experiment I-III should serve as a warning that locomotion may be an unreliable index of exploration in AMP-treated animals. A similar conclusion was reached by Kumar (1969) as a result of an experiment which independently assessed novelty-directed and locomotor activity in AMP-treated Ss. He found that AMP increased Y-maze arm entry but decreased food trough investigation. In addition, Whimbey and Dennenberg (1967), working with undrugged rats, have pointed out that trying to infer the strength of exploratory motivation from open field activity is very difficult. Their factor-analytic study revealed that open field activity is related to both exploration and emotionality, and that the nature of this relationship changes between the first and subsequent open field trials.

STIMULUS EXPLORATION STUDY: EXPERIMENT VI

Experiments IV and V found that AMP-injected Ss emitted less stereotyped behavior in a novel environment than they did in a familiar one. This result was explained by assuming that the stimuli in this novel environment had evoked exploratory responses which were incompatible with stereotyped behavior. However, since the novel features of the environment could not be specified it was impossible to determine whether any exploratory behavior in fact occurred.

In the experiment to be reported below, an attempt was made to discover whether a decrease in AMP-SB in the presence of a novel stimulus was actually accompanied by exploration of that stimulus. Baseline rates of stereotyped behavior and activity were established in a situation with which the Ss were already familiar. A novel stimulus was then placed into the situation, and the Ss' orientation toward, approach to, and contact with it were measured, as were stereotypies and general activity. Saline-injected Ss were also tested in order to establish normal values of stimulus exploration in this situation.

Method

Subjects. The Ss for this experiment were 33 male Wistar rats obtained from Canadian Breeding Farm and Laboratories. These Ss ranged in weight from 170-230g at the beginning of the experiment.

Apparatus. Each S was tested in one of three identical observation boxes. These boxes were constructed of 1/2" unpainted plywood, measured

10 X 12 X 10" high inside, and had a plexiglass top and a wood shaving floor. Each box was located 18" beneath a mirror angled so that an observer could record the S's behavior from a sitting position beside the box. The boxes were located in the experimental room described in the previous experiment.

The novel stimulus was a card which measured 10" X 12" and which consisted of alternating black and white vertical stripes 3/4" wide. It was constructed by applying black electrical tape to white poster board. The stimulus could be placed flush against one end wall of the observation box. Vertical red lines painted on the side walls 1 1/2" from the stimulus demarcated the area of proximity to the stimulus card, when it was in place.

The concentration of the amphetamine solution used for injections was 2.0 mg/ml d-amphetamine sulfate in 0.9% saline solution.

Procedure. The Ss were brought into the animal colony approximately two weeks prior to testing. They were housed in groups of three in the home cages described in the previous experiments. Beginning five days prior to testing, each rat was given a 15-minute habituation session on four consecutive days. The S was always placed in the same box. During these sessions the stimulus card was not in place.

Each S was tested on the day following its fourth habituation session. It was brought to the laboratory and given an i.p. injection of either 2.25 mg/kg AMP (n=23) or saline (n=10). Assignment of Ss to the amphetamine (AMP) and saline (SAL) groups was random.

Forty minutes following the injection a 25-minute test was initiated. The test was divided into five five-minute time periods. The first period served as a baseline period, during which the stimulus card was not present.

The observer inserted the stimulus card into the box at the beginning of the second period, and removed it at the end of the third period. During the fourth and fifth periods the stimulus was again absent. Thus, behavior in the presence of the stimulus (Periods 2 and 3) could be compared to behavior when the stimulus was absent (Periods 1, 4 and 5).

Using a six-channel event recorder, the observer continuously recorded the occurrence of 5 categories of the Ss' behavior. Perambulation was recorded when the S changed its location in the apparatus using all four legs. Scan Other was recorded when the S sniffed at or emitted head movements directed at anything other than the stimulus. The Scan Stimulus category included behavior identical in form to Scan Other, but which was emitted while the S's nose was pointed toward the stimulus card, when present. Stimulus Proximity was recorded when the S's head was within 1 1/2" of the stimulus. Stimulus Contact was recorded when the S's nose was touching the stimulus card. Stimulus Proximity and Stimulus Contact were never scored simultaneously. The last three categories could only be scored during Periods 2 and 3 while the stimulus card was present.

The sixth channel on the event recorder was used to record the occurrance and duration of any stereotyped behavior which occurred. The specific form of the stereotypies was not considered. The criterion of stereotypy described in Experiment IV was used in this experiment.

Results

The average duration of each of the five behaviors observed was summed in each period to determine how much of the behavior was accounted for by the observation categories. Together, the five categories accounted for an average of 88% of the total duration of the test for the AMP Ss (range across the five periods: 85% - 90%). During most of the remaining time the Ss were alert but motionless. The five categories accounted for only 30% of the total duration of the test for the SAL Ss (range: 11% - 60%). These Ss too were motionless during most of the remaining time. Immediately after presentation or removal of the stimulus they appeared alert. At other times they appeared asleep. Grooming was also seen occasionally in both groups.

Because no SAL S was ever observed to emit stereotyped behavior, an analysis of variance was performed on the Stereotyped Behavior scores of the AMP Ss only. The results of this analysis, summarized in Table 22, revealed a significant Period effect. The effects of Period on stereotyped behavior are pictured in Figure 10. Multiple comparisons of the period means, by the method of Scheffé (1959), indicated that the means in period 2 and 3 were significantly lower than those in periods 1, 4 and 5. It was also found that the level of stereotyped behavior in period 2 was not different from that in period 3, and that there were no significant differences in stereotyped behavior in the three periods in which the stimulus was absent. That is, the AMP Ss emitted significantly less stereotyped behavior in the presence of the novel stimulus.

The stimulus-directed behaviors displayed by all Ss during Periods 2 and 3 were analyzed by analysis of variance. Tables 23, 24, and 25 contain summaries of each analysis, and the results are presented graphically in Figure 11. The AMP and SAL Ss were not found to differ on any of these measures. However, the Ss in both groups habituated to the stimulus to some

Table 22

Summary of the Analysis of Variance of

Stereotyped Behavior in Experiment VI

Source	df	MS	F
Period	4	52563.8	34.37***
Error	88	1529.41	

***$p < 0.001$

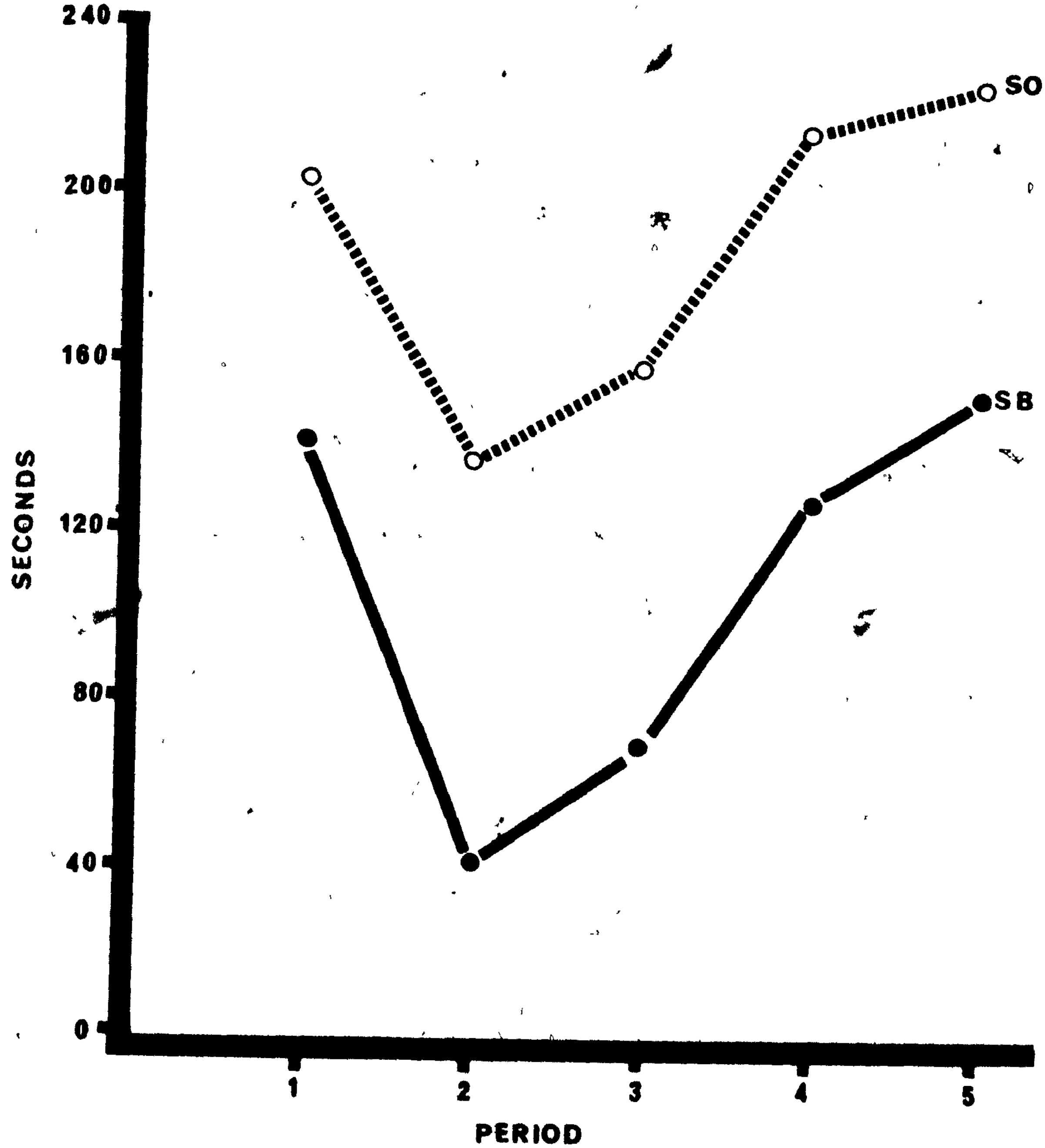

Figure 10. Mean number of seconds of Scan Other (SO) and Stereotyped Behavior (SB) emitted by subjects injected with amphetamine. (n = 23)

Table 23

Summary of the Analysis of Variance of Scan Stimulus in Experiment VI

Source	df	MS	F
Between Ss			
Group (G)	1	36.56	0.18
Error (I)	31	199.14	
Within Ss			
Period (P)	1	2388.02	24.42***
G x P	1	45.93	0.47
P x I	31	97.79	

***$p < 0.001$

Table 24

Summary of the Analysis of Variance

of Stimulus Proximity in Experiment VI

Source	df	MS	F
Between Ss			
Group (G)	1	386.12	0.93
Error (I)	31	415.54	
Within Ss			
Period (P)	1	541.23	3.26
G x P	1	6.79	0.04
P x I	31	165.95	

Table 25

Summary of the Analysis of Variance

of Stimulus Contact in Experiment VI

Source	df	MS	F
Between Ss			
Group (G)	1	54.91	0.04
Error (1)	31	1138.67	
Within Ss			
Period (P)	1	2596.91	8.22**
G x P	1	0.17	0.00
P x I	31	316.00	

**p < 0.01

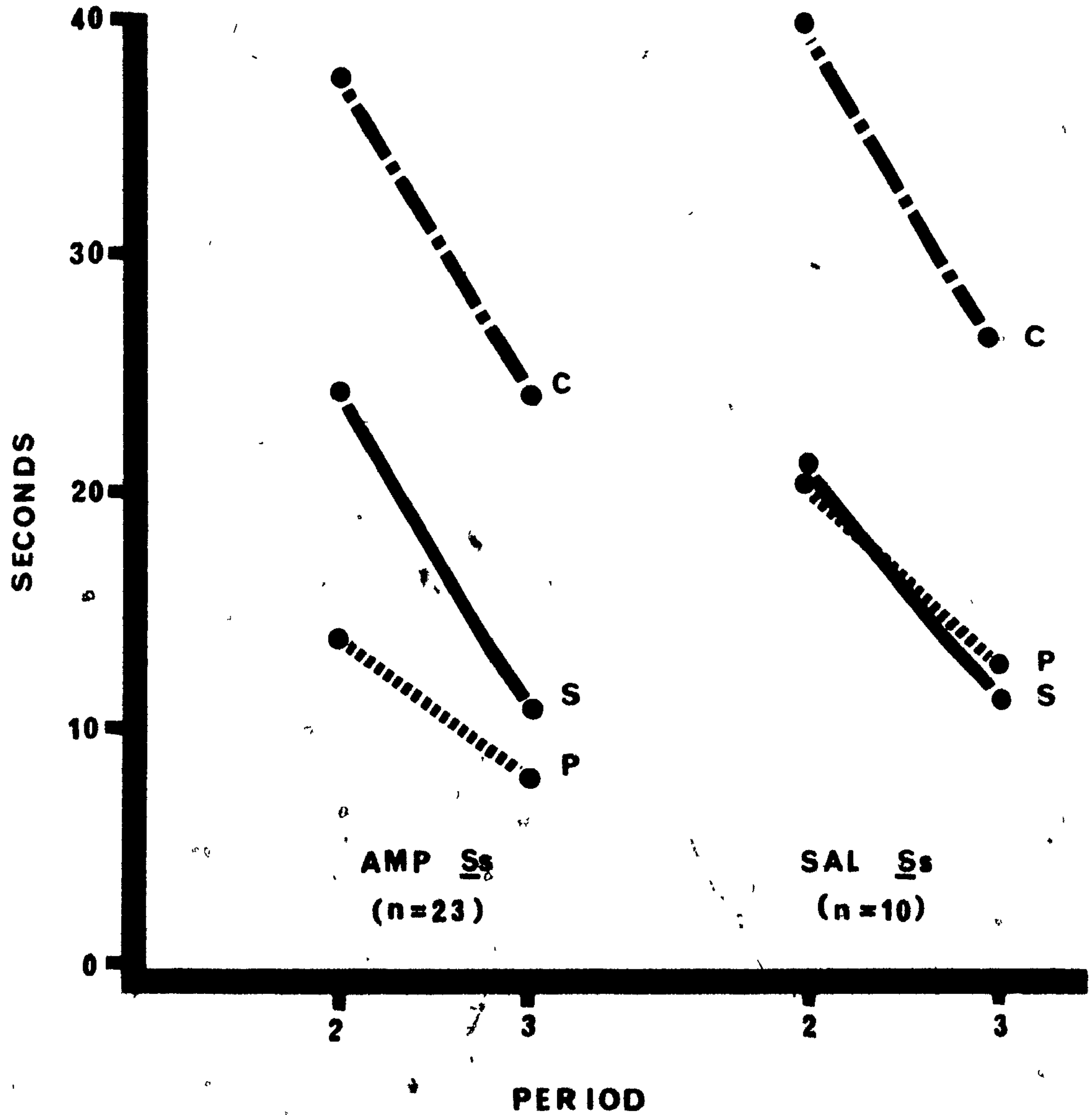

Figure 11. Mean number of seconds of stimulus-directed behavior emitted by amphetamine - and saline-injected rats. (C = Stimulus Contact, P = Stimulus Proximity, S = Scan Stimulus)

extent. The Scan Stimulus ($p < .001$) and Stimulus Contact ($p < .01$) scores were significantly higher in Period 2 than in Period 3. The analysis of Stimulus Proximity scores did not reveal this difference, however ($p > .05$). Drug condition and Period did not interact for any of the three categories of behavior ($p > .20$).

Summaries of the results of the analysis of variance performed on the Perambulation and the Scan Other scores appear in Tables 26 and 27. Group, Period, and their interaction contributed to the variance of both of these behaviors. Comparisons of individual means were made using the method of Scheffé. The AMP Ss emitted more Perambulation than did the SAL Ss, as shown graphically in Figure 12. The high level of activity of the AMP Ss dropped only after removal of the stimulus in Period 4. Among the SAL Ss, the presentation of the stimulus significantly increased Perambulation. The decrease in Perambulation following the removal of the stimulus was not significant.

Scan Other for the AMP group is shown graphically in Figure 10. This behavior decreased significantly in the presence of the novel stimulus. The level of this behavior in Period 1 did not differ from that in Periods 4 and 5.

The method of observation used in this experiment permitted stereotyped behavior to be recorded independently of any specific component of behavior. The Ss emitted bursts of rhythmic head movements of several seconds duration, often ending with a sideways head turn. As a consequence, the Stereotyped Behavior and Scan Other measures were confounded. In order to separate non-stereotyped from stereotyped scanning, a second measure of scanning (non-SB

Table 26

Summary of the Analysis of Variance

of Perambulation in Experiment VI

Source	df	MS	F
Between Ss			
Group (G)	1	57290.4	13.52***
Error (I)	31	4236.01	
Within Ss			
Period (P)	4	3262.57	10.11***
G x P	4	1113.14	3.45**
P x I	124	322.56	

**p < 0.01
***p < 0.001

Table 27

Summary of the Analysis of Variance

of Scan Other in Experiment VI

Source	df	MS	F
Between Ss			
Group (G)	1	622114.	96.76***
Error (1)	31	6429.42	
Within Ss			
Period (P)	4	15015.8	11.60***
G x P	4	23286.1	17.99***
P x I	124	1294.69	

***$p < 0.001$

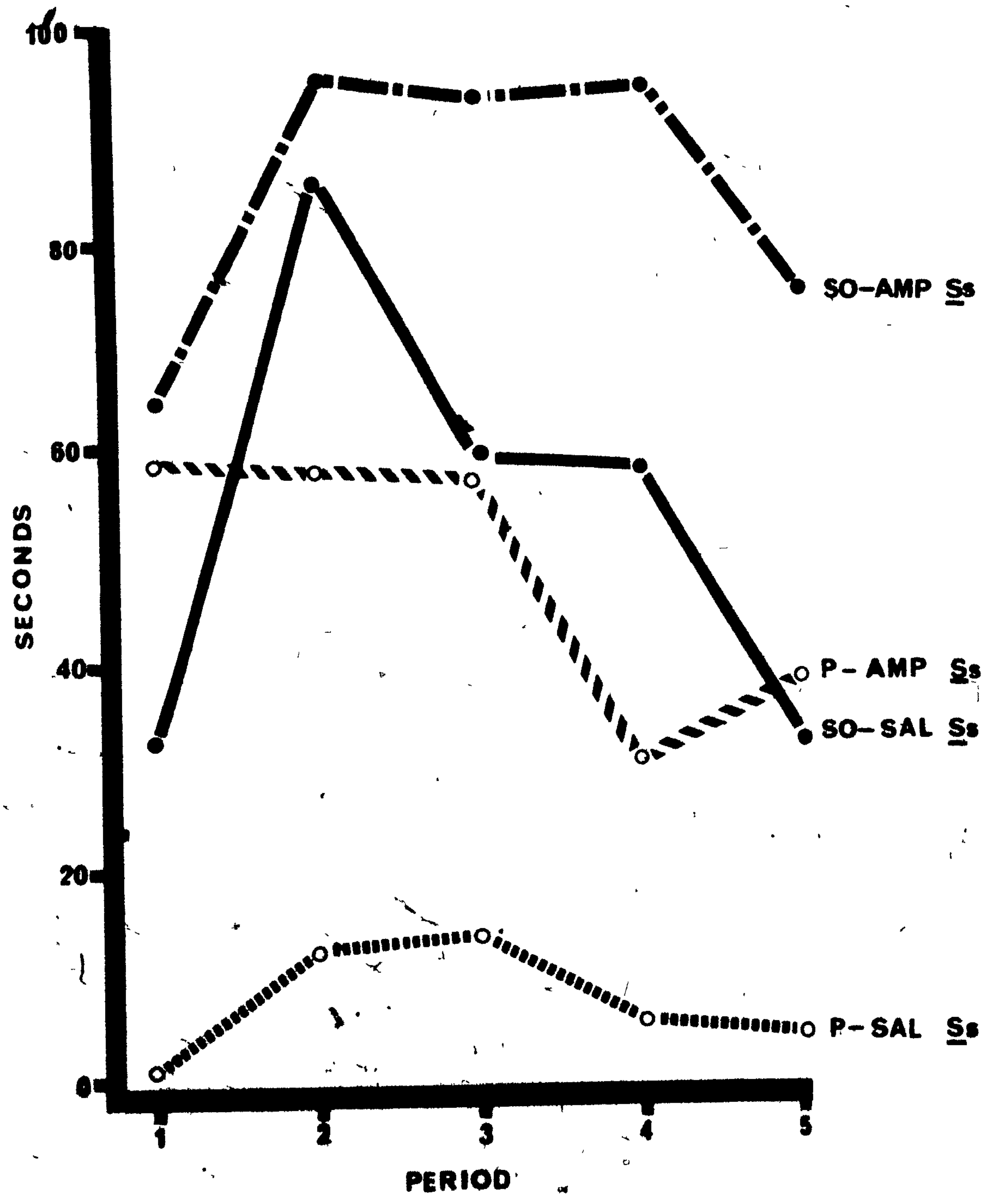

Figure 12. Mean number of seconds of Perambulating (P) emitted by AMP and SAL Ss, of Scan Other (SO) by the SAL Ss, and of non-stereotyped Scan Other (SO) by the AMP Ss. (AMP n = 23, SAL n = 10)

Scan O) was derived, in which all occasions of stereotyped Scan Other were eliminated from the total Scan Other score.

An analysis of variance was performed on the Scan Other scores of the SAL Ss and the non-SB Scan Other scores of the AMP Ss. The summary of this analysis appears in Table 28. Both Group ($p < .01$) and Period ($p < .001$) significantly affected the scores. However, the two variables did not interact. These data are shown graphically in Figure 12. The overall level of this behavior was higher for the AMP Ss, and in both the AMP and SAL groups, the presentation of the novel stimulus in Period 2 caused an increase. In neither group is the drop between Periods 3 and 4 significant, but the drop between Periods 2 and 5 is significant in the SAL group, and Period 5 is significantly lower than the average of Periods 2, 3, and 4 in the AMP group.

To further analyse the relationships among the behaviors, several correlation coefficients were calculated. Among the AMP Ss, stereotyped behavior in periods 2 and 3 combined correlated negatively with Total Object Exploration (obtained by summing Scan Stimulus, Proximity and Contact) ($r = -.61$, $p < .01$), and with Perambulation ($r = -.52$, $p < .01$). Total Object Exploration and Perambulation were unrelated ($r = -.03$, $p > .20$). During periods 1, 4, and 5, stereotyped behavior and Perambulation were not significantly correlated ($r = -.23$, $p > .10$). In the saline-treated subjects, however, Total Object Exploration and Perambulation were positively related ($r = .70$, $p < .02$).

Discussion

Subjects injected with amphetamine emitted less stereotyped behavior in

Table 28

Summary of the Analysis of Variance

of Non-Stereotyped Scan Other in Experiment VI

Source	df	MS	F
Between Ss			
Group (G)	1	39998.9	8.92**
Error (I)	31	4484.23	
Within Ss			
Period (P)	4	8008.22	7.11***
G x P	4	1452.55	1.29
P x I	124	1126.98	

**$p < 0.01$
***$p < 0.001$

the presence of a novel stimulus than in its absence. This decrease was accompanied by stimulus-directed behavior which did not differ in duration from that of the saline-injected control Ss. Together, these findings may be interpreted as meaning that the ability of a novel stimulus to reduce stereotyped behavior is related to its tendency to elicit exploratory behavior. The significant negative correlations found between stereotyped behavior and exploration, and between stereotyped behavior and perambulation are consistent with this interpretation. In general, then, this experiment supports the hypothesis suggested earlier that, in the AMP-aroused subject, stereotypy occurs in the absence of stimuli capable of eliciting any alternative motivated responses.

Exploratory behavior and stereotypy appear to be competitive responses in this situation. No S was ever observed to explore and emit stereotyped behavior at the same time, even though these responses are not physically incompatible. The inference that the decrease in stereotypy was caused by the elicitation of alternative exploratory responses is not completely justified, however. An alternative interpretation assumes that stereotyped behavior is itself capable inhibiting exploratory behavior, and that presentation of the novel stimulus caused a decrease in stereotypy, which in turn enabled exploratory behavior to emerge. On the basis of the present experiment, there is no way of determining whether either of these possibilities is correct.

In the present study, the experimenter lacks control over the form and time emission of both the stereotyped and the alternative (exploratory) behaviors. As a result, it is impossible to determine the exact nature of the reciprocal relationship between stereotypy and exploratory behavior. A preferable experimental procedure would involve using as an alternative behavior a response such as a discriminated approach or avoidance, the form and emission of which would be more directly under experimental control.

GENERAL DISCUSSION

The present investigation reports six experiments which explored the effects of amphetamine dose, environmental novelty, and the presence of a novel stimulus on stereotyped behavior and locomotor activity in rats. Their general purpose was to discover the extent to which the major variables known to affect the incidence of pathological stereotyped behavior in mentally deficient or psychotic persons would similarly influence the incidence of stereotypies produced in rats by amphetamine injection.

The aim of the three Dose-Response Studies was to explore the effect of AMP dose upon four components of stereotyped behavior and upon locomotor activity. Male and female Ss of four strains of rats were tested. The major finding of these experiments was that the incidence of stereotyped behavior tended to be an increasing function of AMP dose, while locomotion was related to AMP dose in an inverted-U fashion. Individual components of stereotyped behavior (scanning, perambulation, and cage licking) bore different relationships to dose, but the forms of these relationships varied little among Ss of varying constitution. The basic findings were interpreted as meaning that the Ss' arousal levels mediated the incidence of stereotypy.

The two Novelty-Familiarity Studies examined the relationship between environmental novelty and stereotyped behavior in Ss treated with AMP. One study compared the incidence of stereotyped behavior in an open field among Ss who either had no previous experience or had had four previous trials in it. The other study examined the result of placing an AMP-treated S into an unfamiliar home cage rather than into the cage it had occupied for the previous week. Contrary to a prediction based upon the arousing properties of environmental novelty, both experiments found that the incidence of stereotyped behavior was lower among Ss placed into a novel environment than among Ss placed into a relatively familiar one. An explanation of this result was attempted, based upon the ability of a novel environment to evoke exploratory behaviors incompatable with stereotypies.

A final experiment, designed to test this hypothesis, exposed rats to a novel stimulus in an otherwise familiar environment. An observer recorded all occurrences of stereotyped behavior, of stimulus-directed (exploratory) behavior, and of locomotor activity. The prediction that any decrease in stereotyped behavior caused by the novel stimulus would be accompanied by an increase in stimulus-directed behavior was confirmed.

Taken together, these experiments appear to indicate that arousal level and the elicitation of alternative responses are both important factors in determining the incidence of stereotyped behaviors. Amphetamine dose was an extremely potent determinant of both the incidence and form of stereotypy. The ability of novelty to reduce AMP-SB was also demonstrated to be an important effect, and the established ability of novelty to evoke exploratory behavior makes it reasonable to conclude that it is the elicitation of this alternative activity which results in the decrease of stereotyped behaviors.

The conclusions drawn from these experiments should be accepted with caution for several reasons. One of these reasons concerns the generality of the interpretation that stereotypies are reduced by stimuli which evoke alternative responses. Novel stimuli were employed to evoke exploratory responses in all of the experiments reported here. It is possible that stimuli which evoke alternative responses other than exploration would not be effective in reducing stereotyped behaviors. Since familiar stimuli are known to evoke alternative responses and reduce pathological stereotypies (Berkson & Mason, 1964a,b; Hollis, 1968), the findings of the present investigation have only partly demonstrated a similarity with pathological stereotyped behaviors.

A second basis for questioning the interpretations is the possible existence of experimenter bias effects (Rosenthal, 1966). The experiments reported here are vulnerable to two sources of bias. First, they were not run "blind." The observer was potentially aware of the drug condition of the Ss he was observing. Second, because each study used only one observer, no formal assessment of reliability was conducted.

Attempting to conceal the drug treatment given a S is a common source of difficulties in many drug experiments. The basic problem lies in the fact that any acute experienced observer can usually tell easily whether a S has been injected with a drug and can also guess the approximate dose. Under these conditions, the use of technically correct blind procedures is no guarantee against biased observing.

Instead, safety from bias is usually sought in the observation procedure itself, and the generally accepted procedure is for two or more observers to empirically establish their ability to observe reliability either before or preferably during the experiment.

Various difficulties made the gathering of reliability data impossible during these experiments. However, there are several reasons for believing that the data reported fairly accurately reflect the behavior emitted by the

Ss. First, it has been well established that stereotyped behavior can be observed reliably. A number of experiments have reported reliability coefficients, and these are above .90 for most behaviors under most conditions (Berkson & Davenport, 1962; Guess, 1966; Kaufman, 1967; Klaber & Butterfield, 1968; Baumeister & Forehand, 1972). Second, the observer who made the observations in these studies had had approximately six years of experience in the observation of rat behavior in a wide variety of experimental settings prior to participating in these experiments. Third, the observer was well aware of the dangers of bias in a situation lacking the usual reliability assessment, and took appropriate precautions. Evidence that these precautions were successful is seen in the fact that the results of Experiment IV contradicted the observer's expectations. Also, the effects of major interest turned out to be very powerful, making the results less sensitive to distortion by experimenter bias than they would otherwise be.

Assuming that the results of these experiments may reasonably be interpreted as confirming the important roles of arousal and the elicitation of alternative responses in determining the incidence of amphetamine-produced stereotypy, this work stands in clear support of a unified concept of pathological and amphetamine-produced stereotyped behavior. These behaviors appear to have more in common than mere similarity of form, and may share underlying physiological and biochemical causes.

The similarities in pathological and amphetamine-produced stereotyped behavior are seen most clearly in the case of their modification by changes of arousal level. A wide variety of conditions which may reasonably be interpreted as manipulating arousal increase pathological stereotyped behavior, and these conditions have their parallel in the effects of AMP dose in the present experiment. The total amount of stereotyped behavior emitted by Ss in Experiments I-III varied directly with AMP dose, and the large amount of evidence linking AMP action, reticular formation activation, and behavioral arousal (e.g. Schildkraut & Kety, 1967; Stein & Wise, 1970) suggests very strongly that this effect is mediated by increased arousal level.

The fact that stereotypies are associated with high arousal levels in the present experiments lends support to suggestions (Hutt & Hutt, 1965; Berkson, 1967; Davis, et al., 1969) that individuals whose behavior is dominated by pathological stereotyped behavior are chronically in a highly aroused state. This finding also suggests that individuals who engage in stereotyped behavior in unstimulating environments are not engaging in self-stimulation in order to raise their arousal to an intermediate level (Levy, 1944; Lovaas, 1967). Rather, these subjects may be in a highly aroused state in spite of their unstimulating surroundings. Normal subjects who have been observed to emit stereotyped behavior in unstimulating environments (Levy, 1944; Lovaas, 1967) may likewise be in a state of high arousal. Berlyne's (1960) suggestion that the state of boredom involves a high, rather than a low, arousal level is consistent with this speculation. The question of whether the subject emitting stereotyped behavior is attempting to reduce tension or arousal, as has been suggested by several authors (Lourie, 1949; Hutt & Hutt, 1965), cannot be determined from the results of the present experiments.

If a chronically high state of arousal does underlie pathological stereotyped behavior, the results of the present experiments suggest a disorder of catecholamine function or metabolism as a possible cause. There seems little doubt that AMP's effects on catecholamine metabolism are the primary determinant of amphetamine-produced stereotypy (Randrup & Munkvad, 1972; Mandell & Segal, 1973) and a disorder of catecholamine metabolism may underlie pathological stereotypy in mental deficiency and psychosis as well.

One result of such a conceptualization might be the development of more effective chemotherapeutic agents for use in the reduction of pathological stereotyped behaviors. Lovaas, et al. (1971) have claimed that the active suppression of stereotypy is a necessary first step in the treatment process. The currently effective behavior modification techniques (Risley, 1968; Foxx & Azrin, 1973) typically require individually-supervised daily training sessions of several hours duration. Drug therapy is clearly an attractive alternative. As information about the metabolism and function of catecholamines increase, an inevitable by-product will be the development of chemical agents with very selective effects on various aspects of catecholomine function. Some of these agents may be effective suppressants of stereotyped behavior.

The present investigation has also found that stimuli which tend to elicit exploratory responses are effective in reducing stereotypy. Again, this finding parallels a common result of studies of pathological stereotyped behavior. In experiments where subjects were handed or exposed to easily available novel objects, stereotypy typically decreased (e.g. Berkson & Mason, 1964b; Hutt & Hutt, 1965). The incidence of stereotypy was also decreased in other situations in which some response other than stereotyped behavior was elicited (Hollis, 1968; Flavell, 1973).

The findings of the present investigation are of significance to those attempting to reduce pathological stereotypy using behavior-modification techniques. They suggest that an approach which involves identifying stimuli which have a strong tendency to elicit alternative responses and presenting these stimuli, along with appropriate reinforcers, to begin to build desirable behaviors will be effective. Under the conditions of the present investigation, novel stimuli appear to be a particularly effective means of eliciting alternative responses.

This approach is the opposite of that recommended by Lovaas and his colleagues (1971), who feel that stereotypy must be eliminated by punishment before any socially desirable behavior can be established. This difference of approach appears to be based upon the fact that Lovaas's subjects were unresponsive to environmental stimulation while they were emitting stereotypies (Lovaas, et al., 1971). Other studies, too, have shown that Ss with high baseline rates of stereotyped behavior are less responsive to objects placed near them than are Ss with low baseline rates (Davenport & Berkson, 1963; Berkson & Mason, 1964a). The AMP-injected Ss of the present experiment appeared by contrast, to be quite responsive to the environment: The durations of stimulus-oriented behaviors in Experiment VI (see Figure 11) were very similar to those of the saline-injected Ss.

Studies emphasizing chronic AMP treatment may clarify this difference. Working with cats and Rhesus monkeys, Ellinwood and Duarte-Escalante (1972) have obtained evidence that during chronic, but not acute, treatment with AMP stereotyped behavior becomes very automatic and compulsive in appearance, and is accompanied by a marked reduction in responsiveness to stimuli. They have also observed peculiar aberrations of attention. For example, some of their cats ignored stimuli placed close by but were extremely sensitive to stimuli at a distance. Lovaas's (1967) study of autistic children reports similar observations. These considerations suggest that chronic, rather than acute, AMP treatment may be the more appropriate model for the experimental study of stereotyped behaviors.

The results of this investigation suggest that an optimistic attitude be taken towards the future of therapeutic reduction or elimination of pathological stereotypies. Recent advances in our understanding of mechanisms underlying the stereotyped behaviors produced by amphetamine suggest that more effective therapeutic techniques and a more accurate appreciation of the causes of stereotyped behavior lie in the not-too-distant future.

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