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AN EXAMINATION OF OPERANT-RESPONDENT
INTERACTION IN THE DEVELOPMENT OF
TOLERANCE TO ETHANOL

by

Brady Justin Phelps

A dissertation submitted in partial fulfillment
of the requirements for the degree

of

DOCTOR OF PHILOSOPHY

in

Psychology

UTAH STATE UNIVERSITY
Logan, Utah

1992

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I dedicate this paper to my parents, who fostered in me a love of reading and a love of animals.

Brady J. Phelps

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ABSTRACT

An Examination of Operant-Respondent Interaction
in the Development of Tolerance to Ethanol

by

Brady J. Phelps, Doctor of Philosophy

Utah State University, 1992

Major Professor: Carl D. Cheney, Ph.D.
Department: Psychology

In four experiments, pigeons performed on schedules of food reinforcement across two different contexts. One context consisted of having the operant chamber fully illuminated, with increased noise levels, and reflective aluminum foil draped over the chamber sidewalls. This context was paired with oral injections of water. Another context consisting of having the chamber dark except for response keylight and at ambient noise levels was paired with oral injections of ethanol. Ethanol dosages were determined by using a dose that doubled the average variable-ratio postreinforcement pause. These procedures established the dark context as a conditioned stimulus capable of producing Pavlovian conditioned tolerance to ethanol. This tolerance was expected to be context specific to the dark context.

At the same time the reinforcement schedule produced a learned compensation or tolerance for the ethanol that would not be limited to

one context. Tolerance was defined here in behavioral terms: a variable-ratio (VR) schedule of reinforcement with high rates of responding and little or no pausing after food delivery, similar to behavior following water delivery but in this case, after ethanol delivery.

To test the efficacy of the context specific tolerance relative to the reinforcement-schedule-acquired-tolerance, probes were conducted. These consisted of delivering ethanol while the context predicted water.

The results indicated that most subjects displayed tolerance that was not context specific. However, for a minority of subjects, the acquired respondent tolerance was highly context specific, being present only in ethanol paired context. In explanation, those subjects who displayed context specific tolerance also tended to have more behavioral disruption from smaller doses of ethanol than other subjects. This subset of subjects showed more sensitivity to ethanol. At the higher doses, Pavlovian tolerance may have been hindered by the prolonged systemic effects of the ethanol. These same dosages allowed for more intoxicated practice and enhanced the learned tolerance from the reinforcement schedule.

The implications of this research point to additional studies of how and why tolerance to the behavioral effects of a drug is acquired.

(176 pages)

STATEMENT OF THE PROBLEM

The process by which an organism develops tolerance, or a state of progressively diminished sensitivity or responsiveness to a drug, is typically described as due to decreased responsivity by receptor cells as a result of repeated exposure to the drug. In other words, decreased responsiveness to a drug is considered to be the physiologically inevitable outcome of repeatedly experiencing the drug.

However, there are two major bodies of research which indicate that tolerance will not inevitably result merely from repeated drug experience but rather that tolerance can be categorized as a learned response. This research treats tolerance as a learned response either in terms of classical or respondent conditioning (Siegel, 1975b), or operant conditioning (Schuster, Dockens, & Woods, 1966). Studies investigating possible interactions between these two types of conditioning and the development of tolerance are practically nonexistent. This dissertation examined operant-respondent conditioning interaction as these processes relate to the development of tolerance to ethanol. Here, and in the literature, the generic term drug is used to describe a wide range of psychoactive or behaviorally active substances. Wherever possible, the precise chemical is named.

It has been known that the specific effects of many narcotic substances can be modified by factors in the environment (Barrett, 1985). These factors include the setting events as well as the

consequences which maintain certain behavior; much of this sort of occurrence is operant conditioning (Skinner, 1938).

Barrett (1985) lists six environmental variables which can modify the effects of drugs on behavior; these variables are listed in Table 1.

Table 1

Environmental Variables Influencing the Behavioral Effects of Drugs

1. Rate of responding
 2. Consequences of responding
 3. Behavioral history
 4. Pharmacological history
 5. Drug-behavior interaction
 6. Environmental context
-

Of these variables, the influence of environmental context on the behavioral effects of a drug is usually discussed in terms of events or consequences in a different, temporally removed environmental setting. For instance, McKearney and Barrett (1975) showed that the standard rate-decreasing effects of d-amphetamine on punished behavior of squirrel monkeys were reversed when the conditions occurring in a separate component of the schedule were changed from extinction to avoidance. With the avoidance schedule in effect in the alternate component, d-amphetamine increased punished behavior to more than 600% of control levels; furthermore, this change in responding was not seen in the absence of the drug.

Barrett and Stanley (1980) studied the effects of ethanol on pigeons responding on a multiple fixed-interval fixed-ratio schedule of reinforcement. The fixed-interval (FI) schedule was correlated with a red light and was held constant at three minutes. The fixed-ratio (FR) schedule, correlated with a green light, varied from FR30 to FR150, in steps of 30, during different phases of the study. The rates of responding during the FI schedule did not change with increments in the FR size when drug free, but the effects of ethanol on responding under the FI schedule were related to the size of the FR. At the smallest ratio of 30, ethanol either did not affect or it decreased responding under the FI schedule. However, when the ratio was largest at 150, ethanol increased FI responding. Thus, both these studies demonstrate that the behavioral effects of a drug can be changed by altering the response requirements in a different, somewhat temporally remote, schedule component.

However, one way of viewing the efficacy of environmental context on the behavioral effects of drugs would be in terms of a higher order stimulus setting, or what Sidman (1986) has termed the five-term contingency. Sidman argues that this extension of the three-term contingency of operant conditioning (Skinner, 1938) can provide the explanatory basis for sources of behavioral variability due to context. To apply the five-term contingency in an analysis of the differential behavioral effects of drugs as a function of five-term control, the effects could be explained in terms of higher order differential reinforcement and resultant stimulus control contingencies and not a global context.

Returning to the behavioral effects of drugs, a study by Lubinski and Thompson (1987) clarifies the relationship of context and drug effects. These researchers taught pigeons to "report" drug effects or, in other words, to behave in a specific way dependent upon what type of drug the animal had been given. In a simulation of a conversation between a questioner and an answerer, the pigeons learned to peck a specific color key while under the influence of cocaine, another color key after receiving morphine, and yet another color key when water was injected. The subjects learned to do this with high accuracy. This behavior can be seen as a relation between internal and external stimuli. The three-term contingency between a specific color key, pecking that color key, and the subsequent reinforcement only exists in the presence of specific antecedent stimuli, in this case, internal drug stimuli. These internal stimuli are not drug produced, they are the drug. Catania (1971) states that drugs do not produce stimuli, but rather are stimuli in and of themselves. A physical stimulus is any environmental change that can be quantified through empirical means and a functional stimulus is a physical stimulus that can demonstrably affect behavior (Poling, 1986). Drugs can be seen as functional stimuli. This concept was first promoted in the text Stimulus Properties of Drugs (Thompson & Pickens, 1971). Drugs can act as unconditional or conditional stimuli, reinforcers or punishers, or as in the Lubinski and Thompson (1987) study, as discriminative stimuli. A discriminative stimulus affects the probability of a behavior by virtue of the stimulus having a history in which that behavior was successful in producing an environmental change. The stimulus can

change behavior as long as the environmental change can affect behavior--either reinforcing or punishing. A drug can be established as a discriminative stimulus by reinforcing a response following drug administration and not reinforcing that response when the drug is not delivered. If the drug is an effective discriminative stimulus, the response that was reinforced in the drug state will now reliably occur when the drug is administered but not when the drug is withheld. Any drug that serves as a discriminative stimulus is able to function as such because the presence of the drug results in detectable effects, or sensory consequences (Poling, 1986). Despite the fact that Catania (1971) and Poling (1986) share a common theoretical orientation, the contradiction between how each defines stimuli is difficult to reconcile, and as such will be left to others.

Now, if the subjects of Lubinski and Thompson (1987) had been trained in a specific environmental context, a particular chamber for example, and then placed in a significantly different context for a test condition, a noisier or brighter chamber perhaps, any behavioral variability from the earlier performances could be attributed to the effects of the differential context. Henceforth, a model of the differential behavioral effects of drugs as a function of context could be shown. This model could emerge from a history of compound stimulus (drug and context) training. That is, given training while in a specific internal drug state and in a specific external environmental context, if changing the environmental context for testing while maintaining the same internal state produces a behavior change, then it

is shown that the external environment can control behavior independent of the internal drug state.

Significance

Humans often display different behavior while in similar drug states dependent upon environmental context. For example, we act one way after four mixed drinks in the presence of friends and a much different way in the presence of a police officer. Dornbush, Freedman, and Fink (1976) found that the "subjective" effects of marijuana commonly reported by middle class Americans are rarely reported by Jamaican field workers and vice versa. Krikstone and Levitt (1975) emphasized the importance of environmental setting in determining the effects of marijuana. They describe marijuana smoking in three stages. The first stage involves inhaling the smoke deeply and holding it in the lungs for 20-40 seconds. The second stage is "learning to" recognize the subjective effects of the drug and finally, to identify and report these effects as being pleasant. This learning process must be necessary as it is reported that few people get "high" when smoking marijuana for the first time. Obviously, a different environmental context would influence what subjective effects were recognized, deemed pleasant, and reported. The differences in behavior and reported effects in these studies and everyday observations might not be due to contextual effects; additionally, it might be difficult to identify the specific context and contingencies that are responsible for the different behaviors seen while in the same drug state among humans. Also, the rules and expectations that people have learned about drugs can no doubt modify a drug experience. But, by employing contextual

control, an animal model for the phenomenon of differential behavioral drug effects dependent upon the immediate environmental context can be developed. The changes in the effects of a drug that can result from modifying the environment are not solely quantitative but also qualitative, and for this and other reasons deserve study (Barrett, 1985).

Epstein (1984) states that at least four classes of behavior have defied experimental analysis--covert behaviors ("feelings," "thoughts," etc.); complex, typically human behaviors that are not readily available to analysis due to biological or environmental variables (the use of language, problem solving, "self concepts" and related topics); behavior that is under the control of temporally remote stimuli (remembering, memory); and novel behavior ("creativity"). Based in part on Epstein's argument to experimentally analyze these areas, I studied different behaviorally "expressed" drug effects dependent upon immediate environmental context. I intended to develop an animal model for covert behavior--behaving differently due to internal drug stimuli, similar to the study by Lubinski and Thompson (1987); and further, to develop an animal model for complex, unique human behavior of different behavioral drug effects as a function of the environmental setting.

Justification

Although this study was a basic analysis of environmental influence on the behavioral effects of drugs, several studies point to the potential social implications of such research. Barrett (1985) reported that the lethality of both d-amphetamine and morphine can be considerably modified by such factors as number of animals housed

together, room temperature, lighting, and noise levels. In addition, Poling, Kesselring, Sewell, and Clary (1983) demonstrated that combinations of pentazocine (Talwin), a synthetic narcotic, and tripeleennamine (Pyribenzamine), an antihistamine agent, could have much different lethality rates, dependent upon number of animals housed together. These two drugs are often combined to use as a substitute for heroin. At some dosages, as many as twice the number of mice died following injection if they were housed communally rather than individually. Poling (1986) suggests these results indicate that individuals who have received a potential overdose of what users call "T's and blues" may die if exposed to highly stimulating or stressful environments. Even more important and controversial is the research (Pattison, Sobell & Sobell, 1977; Sobell & Sobell, 1973) that proposes that individuals, often called alcoholics, can recover from their dependence on alcohol and learn to resume and control a stable pattern of moderate alcohol drinking and not lose control of their lives. These studies tend to indicate that many, if not all, of the effects of drugs can be modified by nonpharmacological factors, some of which arise as a function of the different stimulus properties of drugs.

As previously stated, drugs can serve as discriminative stimuli, which can affect behavior through a conditioning history with either a reinforcer or a punisher. Drugs can serve as reinforcers to either maintain or increase the probability of a response or as punishers to decrease the probability of a response. Drugs can also function as unconditioned stimuli (US), defined as a change in the environment that reliably elicits an unconditioned response (UR), without any special

conditioning history. If a drug has US properties, a conditioned stimulus (CS) that reliably predicts the US may come to elicit a conditioned response (CR). In many instances, but not all, the CR closely resembles the form or topography of the UR elicited by the drug US. For instance, a cancer patient receiving chemotherapy that itself induces nausea may eventually come to have this same reaction (nausea) upon merely entering the office where the treatments are given.

Respondent conditioning can also account for what has been termed the "needle freak" phenomenon. Drug users who inject their drugs report that the act of preparing and injecting their drug is very pleasant. A heroin user was quoted as saying, "Sometimes I think that if I just shot water, I'd enjoy it as much" (unnamed, in Powell, 1973, p. 591).

Although CRs and URs are often similar in topography, this may not have to be the case. Siegel (1983a) states that pharmacological CRs are often opposite in direction to the actual pharmacological UR. Research by Siegel (1975b; 1976; 1977a; 1977b; 1978a; 1978b; 1978c; 1979a, 1979b; 1983a; 1983b; 1984) suggests a model of drug tolerance based on respondent conditioning. In 1927, Pavlov suggested that the administration of a drug agent could be a conditioning process between the drug US and the immediately available environmental cues serving as the CS. Siegel argues that the environmental stimuli reliably correlated with administration of a drug become established as CSs which elicit CRs that are antagonistic to the URs elicited by the drug US. These CRs compensate (antagonize) to some extent, for the URs elicited by the drug, and with repeated CS-US pairings, reduce the magnitude of the response to the drug (i.e., tolerance). The CRs are

thought to compensate for the URs by consisting of autonomic responses opposite in direction to the UR. An example would be a bradycardia response which would counteract a tachycardia response to a drug.

Siegel's original formulation, while the most widely cited version of Pavlovian acquired tolerance, has been revised by other researchers (Eikelboom & Stewart, 1982; Poulos, Wilkinson & Cappell, 1981). In the new formulation, the UR and the CR mirror each other, as in other Pavlovian procedures. The basic difference arises in the definition of what event constitutes the US. In the original formulation, the US was defined as the effects of a given drug; in the revised theory, the US is a physiological response to the drug's effects.

In the former case, the US is a change in the afferent input to the homeostatic mechanisms while in the latter, the US is an altered efferent output of homeostatic mechanisms. These two changes dictate differing adjustments on the part of the organism to maintain homeostasis and are simply a matter of specifying where a drug acts and the subsequent feedback changes. Tolerance conditioned through Pavlovian procedures arises, but the stipulated stimuli and responses are very different. Most literature still refers to the original formulation, but the theoretical machinery is not fully explained to all researchers' satisfaction.

From this model, it can be argued that what is learned in this procedure is a response (the CR) which prepares the organism for the US, but only in the presence of specific environmental cues (the CS) that were present when the drug had been administered previously. In the absence of these cues, the former tolerance response may not be

present. Siegel's research underscores the importance of context and conditioning factors in modifying drug effects; these factors may even control the outcome of drug overdoses. Siegel states that

a considerable amount of research has demonstrated environmental specificity in the display of tolerance: maximal tolerance is observed when the drug is administered in the context of the usual predrug cues, but not in the context of cues not previously associated with the drug. A user would be at risk for "overdose," according to this analysis, when the drug is administered in an environment which had not been previously paired with the drug. (Siegel, 1979a, p. 132)

An animal study by Siegel, Hinson, Krank, and McCully (1982) indicates the importance of environmental context to enable survival after large drug doses. They gave three groups of opiate inexperienced rats differential histories of exposure to heroin. One group received injections of dextrose in the housing colony or in a noisy experimental chamber and later were given an injection of a large dose of heroin in the same context as the earlier injection. Another group was given a history of small doses of heroin in the colony and then given the large dose in the noisy chamber. The third group was given a history of small heroin doses as well as the large dose in the colony. Mortality rates across the groups of rats differed significantly. Of the control group with no previous heroin exposure, 96.4% died. And while 32% of the rats who received the large heroin dose in the same context as previous exposure died, twice as many rats died who received the large heroin dose in a different context than with previous injections of heroin.

Siegel (1984) states that about 1% of heroin addicts die yearly due to an overdose. Many of these individuals died as a result of a

dose that would not be predicted to be fatal for an experienced user and, in fact, some victims expire following administration of a dose that was well tolerated on the day before. It appears that death from overdose may come about as a result of tolerance breakdown; the user who has tolerated high doses fails to do so on the occasion of the overdose. This failure of tolerance is possibly due to the drug administration taking place in a different environmental context than during previous drug administration. From interviews with the survivors of heroin overdoses, Siegel has found an outcome similar to the animal study mentioned earlier. Among ten heroin overdose survivors, seven individuals reported that the overdose occurred in untypical circumstances. Two individuals reported they had self administered in locations where they had never done so before. Another victim overdosed after injecting in the midst of a large group of people. This individual, who had been using heroin for approximately 10 years, had never before taken heroin with so many other people or done so in his living room. From the findings of these interviews and other studies, Siegel argues that drug anticipatory CRs can modulate tolerance to the potentially lethal effects of opiates and other substances, both among infrahuman and human subjects.

While the premise of Siegel's model of tolerance is that of respondent conditioning processes, other researchers have proposed that the development of tolerance can represent an operant conditioning process. Originally put forth by Schuster et al. (1966), this model states that tolerance comes about as a function of the action of the drug on the organism's behavior in meeting reinforcement

contingencies. That is, the initial effect of a drug is behaviorally disruptive and as a result, reinforcement opportunities are missed. Any behavior that the subjects can emit that will compensate for the behavioral disturbance will increase reinforcement. These operant behaviors will therefore increase in probability, increasing reinforcement further to eventually equal or approximate baseline reinforcement frequency. Schuster et al. (1966) demonstrated that the administration of d-amphetamine disrupted the interresponse time (IRT) behavior of rats being reinforced on a differential reinforcement of low (DRL) response rate schedule; consequently, subjects missed many reinforcement opportunities, in some cases almost half. General activity levels were higher over the course of drug administration but with continued daily administration, the animal's performance on the schedule of reinforcement progressively changed towards behavior observed under water control conditions. These results suggest a specificity among behaviors that will show tolerance to chronic drug administration, those behaviors upon which reinforcement is contingent. These researchers concluded that operant reinforcement contingencies represent one class of variables that can influence the development of tolerance to amphetamines.

The difference between operant and respondent acquired tolerance is in the nature of the specific learning. In the respondent formulation, an overall tolerant effect can be seen but which is context specific. In the operant formulation, the tolerance will be limited to specific response classes but generalizing across contexts.

Other studies have confirmed Schuster et al. (1966) and extended the operant model of tolerance to include barbiturates (Tang & Falk,

1978), ethanol (Chen 1968; 1972; 1979; Wenger, Berlin, & Woods, 1980; Wenger, Tiffany, Bombardier, Nicholls, & Woods, 1981), LSD (Commissaris, Lyness, Cardon, Moore, & Rech, 1980) and phencyclidine (Woolverton & Balster, 1979), with human and nonhuman subjects. Still other researchers have studied the development of tolerance as an operant-respondent interaction process (Beirness & Vogel-Sprott, 1984; Smith, 1991a, 1991b) based on Rescorla and Solomon's (1967) conclusion that a strict distinction between the two learning paradigms is not pragmatic and is used largely for convenience. In these studies, the typical procedure has been to vary the amount of reinforcement given to subjects while under the influence of a drug, holding context constant, or to employ different groups of subjects in conditions of differing context and differential reinforcement contingencies to measure the emergence of tolerance. Other research has held operant reinforcement constant and varied the context.

No study to my knowledge has examined the effects of holding operant reinforcement conditions fixed and examined the effects of modifying the environmental context. This study investigated parameters of tolerance established by operant and respondent processes by means of altering the respondent conditioning context while holding the operant contingencies constant. This methodology is intended to be analogous to a typical human situation of drug use--to hold ongoing behavior and reinforcement stable and only modify the setting. Despite the fact that this study was a basic experimental analysis, the importance of such studies extends beyond the laboratory and findings can often be generalized to many aspects of society.

SURVEY OF LITERATURE

This section is a review of the literature of drug tolerance that has been interpreted in either respondent or operant conditioning parameters, among human or nonhuman subjects.

The Respondent Conditioning Tolerance Model

Pavlov (1927) suggested that the typical drug administration procedure corresponded to his conditioning paradigm; the CS consists of those procedures, rituals, or other contextual cues that reliably precede the systemic effects of the drug agent, with the actual central effects of the drug composing the US. Siegel (1983b) states that the context elicited conditioned response (CR) occurring prior to the actual pharmacological act should interact and summate with the unconditioned response (UR) and, consequently, pharmacological conditioning may very well result in the alteration of the overall response to the drug. Whereas most respondent conditioning results in a CR that is similar to the UR, in drug studies the CR that is elicited as a function of the context predictive of the US-UR relation, is commonly opposite in direction and effect to the UR. This response may have survival value for the organism in the face of repeated challenges of the chemical agent (Barrett, 1985). This effect was first reported by Subkov and Zilov (1937) who found that dogs who had been given a history of epinephrine administration, which elicited a tachycardiac response, subsequently displayed an antagonistic, bradycardiac response

when given a placebo in the usual administration environment. Similar compensatory CRs opposed to pharmacological URs have been reported by Goldberg and Schuster (1967; 1970), Guha, Dutta, and Pradham (1974), Siegel (1972; 1975a; 1975b; 1978c), and other studies.

These drug-compensatory CRs attenuate the UR; that is, as the drug is repeatedly administered in the presence of the same predrug cues, drug-compensatory CRs would be expected to increasingly negate the effects of the drug and thus show tolerance. On the basis of this conditioning account, tolerance will not always result from repeated drug exposure. Rather it should result following repeated drug administration in the presence of specific environmental cues that have signalled the drug in the past. Experiments by Adams, Yeh, Woods, and Mitchell (1969) and Kayan, Woods, and Mitchell (1969) demonstrated that rats displayed this analgesic-tolerant response to the final morphine injection in a series, only if this last injection was administered in the context of the same environmental cues as the prior injections. More recent research has confirmed this outcome and extended the earlier observations regarding the situational specificity of morphine analgesic tolerance, employing a wide range of dosages and a variety of analgesic measures (Advokat, 1980; LaHoste, Olson, Olson, & Kastin, 1980; Siegel, 1975b, 1976; Siegel, Hinson, & Krank, 1978; Tiffany & Baker, 1981).

Siegel et al. (1978) exposed two groups of rats to an equivalent history with both an audiovisual cue and morphine injections during the initial tolerance development phase of the study. The cue and drug were always correlated for the paired group, and never associated for

the unpaired group. In a subsequent test phase, rats in both groups were administered the drug in the presence of the cue, and the analgesic effect of the drug was measured. Despite the fact that the groups did not differ in pharmacological histories, the paired group who had a history of drug-cue relations displayed significantly less analgesia than the unpaired group who had never received the drug in the context of the audiovisual cue.

The group of subjects who had never experienced the drug in the context of the cue displayed a high degree of analgesia that would be expected to be seen in completely nontolerant rats--subjects with no previous experience with morphine. In other words, analgesic tolerance does not inevitably result from repeated morphine administrations.

According to this conditioning model, paired group subjects but not unpaired group subjects displayed tolerance because only for the former group were the analgesic effects of morphine attenuated by a drug antagonistic CR. Also, if following either specific context paired or unpaired morphine administrations during the tolerance development phase of the study, all subjects are administered a placebo in the presence of the paired signal, paired group rats were shown to be hyperalgesic (Krank, Hinson, & Siegel, 1984). That is to say, paired group rats displayed an enhanced sensitivity to painful stimulation when the usual predrug cues are followed by administration of an inert substance in contrast to the unpaired subjects who showed no such response.

In another demonstration of respondent attenuation of the unconditioned effects of morphine, Mucha, Volkovskis, and Kalant (1981)

showed that the locomotor activity diminishing effects of morphine will progressively decrease if morphine is administered to rats in an open field test setting. The same increases in activity were not seen among rats given morphine in a different setting (the home colony) and with rats given water in the open field setting. As a result, the authors concluded their findings were due to respondent conditioning processes. Figure 1 summarizes this and other studies of the respondent conditioning model of tolerance.

Attenuating Morphine Tolerance With Environmental Manipulation

Based on the respondent conditioning model of tolerance, it should be expected that nonpharmacological manipulations of the predictive CS that are well known to attenuate respondent conditioning, should likewise attenuate compensatory CR acquisition and consequent tolerance. Several such CS manipulations have been studied regarding morphine tolerance: respondent extinction, CS pre-exposure, and partial respondent reinforcement.

Extinction, in respondent terms, is a procedure of diminishing the strength of established CRs by presenting the CS in the absence of the US. If tolerance develops as a function of predrug CSs eliciting drug compensatory CRs, tolerance should be subject to extinction by repeated placebo administrations in the previously drug predictive context. Several studies have examined this possibility and although numerous procedural differences existed among the different experiments, all of them employed two groups of subjects, both of which were given a series of morphine injections to develop tolerance. Some days later, all

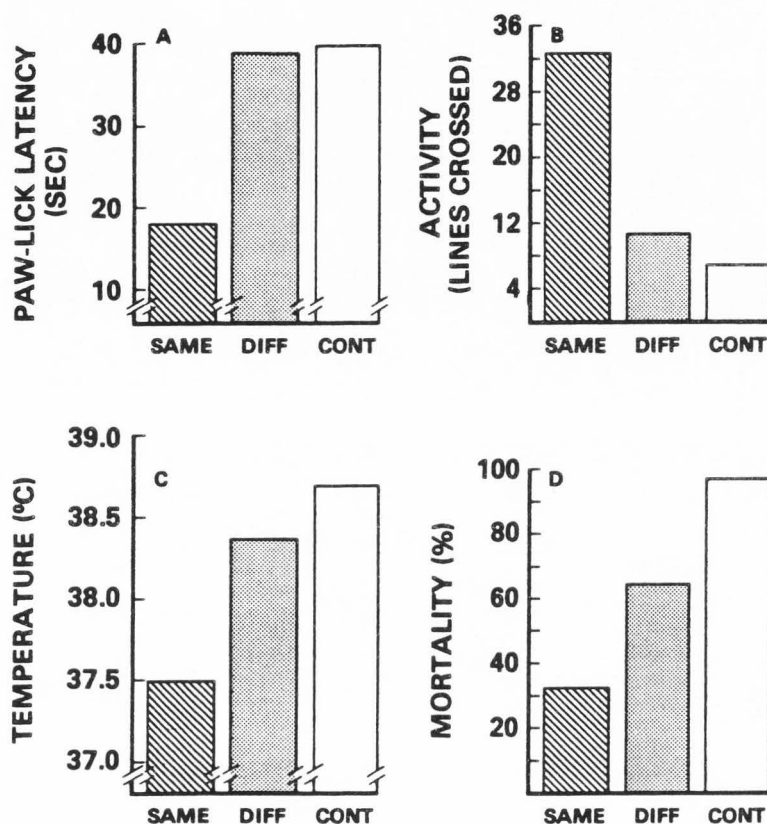


Figure 1. This reproduction from Siegel (1983a), summarizes the results of studies showing the context specificity of tolerance. Panel A shows the analgesic effect of morphine (Siegel et al., 1978), B - the locomotor activity decreasing effect of morphine (Mucha et al., 1981), C - the hyperthermic effect of morphine (Siegel, 1978c), and D - the lethal effects of morphine (Siegel et al., 1982). All four studies shown employed a basic similar design, to give two different groups of subjects a drug history in one of two different environments and then a final injection in either the same environment as previous injections (same) or in a different environment than in which injections had been given previously. The results from the final drug administration are presented here.

subjects were again given at least one further morphine injection. The two groups of subjects differed only with respect to their histories during the interval between the initial series of morphine administrations and the final administration. Subjects (rats) in the experimental groups received daily placebo (vehicle) administrations in the formerly drug-correlated context. Rats in the control group were simply left in their home colony undisturbed during the period that the experimentals received the placebo. The responses of the experimental animals to the final drug administration were demonstrative of the effects of extinction--these rats responded more to the final morphine dose; that is, they were less tolerant than control group rats. However, both groups were exposed to the effects of morphine equally as often and at identical intervals and according to physiological theories of tolerance, both groups should have developed equivalent levels of tolerance at final administration.

Siegel (1978c) exposed two different groups of rats to histories of morphine in one of two different environments and measured the temperature increasing effects of the drug. Both groups were subsequently given a final injection of morphine in either the same environment as prior injection or in a different environment. Only those subjects who received the final injection in the previously drug-correlated environment displayed a tolerant response to the morphine's hyperthermic effects. Later this tolerant group was given a series of placebo injections in the previous drug-associated context and the tolerant response did not emerge in another morphine challenge.

This extinction effect which supports the respondent conditioning model of tolerance has been demonstrated with respect to the analgesic

(Siegel, 1975b; 1977b; Siegel, Sherman, & Mitchell, 1980), hyperthermic (Siegel, 1978c), and lethal (Siegel, Hinson, & Krank, 1979) effects of morphine.

Prior exposure to a potential CS tends to decrease the effectiveness of that CS when it is later paired with a US during conditioning. If tolerance develops as an association between predrug contextual CSs and the drug US, the course of tolerance development should be affected by the novelty (or nonnovelty) of contextual cues present at drug administration. More specifically, experimental subjects that receive placebo administrations in the experimental setting prior to receiving morphine should be slower to develop, or not develop, tolerance compared with a control group that receive no such predrug exposure to the administration context, despite the fact that both groups receive equivalent drug experience. This hypothesis has been supported. The development of tolerance to the analgesic effects of morphine is retarded by a CS pre-exposure procedure (Siegel, 1977b; Tiffany & Baker, 1981).

Partial reinforcement in respondent conditioning describes a procedure in which the US is paired with the CS less than 100% of trials. This procedure has been reported to hinder CR acquisition and thus should also retard tolerance. Partial reinforcement has been studied by interspersing CS-alone trials (placebos) between CS-US trials (drug administrations) for one group of subjects. A control group is continuously reinforced; that is, these subjects are never exposed to environmental cues correlated with drug administration without actually receiving the drug. The control animals were left

undisturbed in the colony during the intervals that experimental subjects receive placebos. Both groups again are identical with respect to pharmacological histories. Nonetheless, the partially reinforced experimental subjects are much slower to acquire tolerance to the analgesic (Krank, Hinson, and Siegel, 1984; Siegel, 1977b) and thermic (Siegel, 1978c) effects of morphine relative to the continuously reinforced control subjects.

Other studies (Siegel et al., 1982; Siegel, 1984; and Siegel & Ellsworth, 1986) have applied the respondent conditioning model of tolerance to explain human and animal death following apparent drug overdoses. Siegel et al. (1982) reported that rats injected with high doses of heroin in the same environment as previously correlated with smaller heroin doses were more likely to survive than animals with identical drug histories given the final large dose in a different context.

Siegel and Ellsworth (1986) reported the case of a terminal cancer patient who had regularly been given morphine every six hours for four weeks in his bedroom. Morphine was never given in any other setting. The bedroom was dark and contained hospital-like apparatus. On the day the overdose took place, the patient was found in the brightly lit living room by a family member who had administered the morphine to the patient on previous days. The patient appeared to be in pain and it was time for an injection; consequently, the patient's son delivered the typical morphine dose. However, the patient's reaction was very atypical—breathing became shallow and the patient's pupils constricted. A few hours later the patient died, apparently due to

the effects of the morphine. Although the patient's son was confident that he had prepared and delivered the morphine in the usual manner, he was very distraught until he learned of the conditioning theory of tolerance in an undergraduate psychology class, at which point the young man was substantially relieved. No postmortem examination was conducted to determine the role of morphine in the death, but the fact that a dose that was well tolerated six hours earlier in the usual context, produced a distinct overdose-like response can be described in terms of responsively conditioned tolerance.

The role of conditioned tolerance to ethanol has also been investigated in several studies involving human subjects (Annear & Vogel-Sprott, 1985; Beirness & Vogel-Sprott, 1984; Dafters & Anderson, 1982; Jones, 1974; Lightfoot, 1980; Shapiro & Nathan, 1986). Jones (1974) suggested that social drinkers are more tolerant to ethanol when it is ingested at the same approximate time as in the past--than when the ethanol is "unexpected" and consumed at an untypical time. Performance on a "cognitive" task (Raven's Progressive Matrices Test) was compared following ethanol consumption in the afternoon (1:00-5:00 p.m.) or evening (5:00-10:00 p.m.). The results showed that performance on the test was impaired more following afternoon drinking than following evening drinking. This differential effect of ethanol could not be attributed to generally better "cognitive" functioning in the evening since control subjects, who drank no ethanol, showed better performance in the afternoon than later. Jones concluded that ethanol had less of an effect on cognitive performance (i.e., the subjects were more tolerant to its effects) in the evening relative to the afternoon

because most subjects had a history of drinking in the evening and had "learned" to compensate for the disruptive effects of ethanol. Jones stated that drinking alcohol in the afternoon may be a very different experience from drinking it in the evening and attributed this to differences in human circadian rhythms. Another explanation is that the time of day that drinking usually occurs can be seen as a context in which tolerance develops and a significant variation from this context would produce a lack of tolerance and more impaired functioning.

Lightfoot (1980) further demonstrated that, among humans, ethanol tolerance can be modulated by environmental cues. In this experiment, male college students drank a significant amount of beer--almost 16 ml/kg for a 70 kg subject over a 30 min period, a procedure intended to raise their blood alcohol level to about 0.07%. The subjects drank the beer in a distinctive setting for each of four daily sessions. However, on the fifth session, their abilities on a number of perceptual-motor and intellectual performance tasks were measured. Each subject drank and was assessed in either the previous drinking context or a distinctly different environment. On the majority of the tasks, tolerance to the ethanol was more pronounced if the drinking had taken place in the familiar context than in the alternative context. Furthermore, these subjects also evidenced alcohol-compensatory CRs on several assessments when they were given nonalcoholic beer in the context where they had previously consumed real beer. Consequently, Lightfoot concluded that respondently conditioned drug compensatory responses explained her results.

Whereas Siegel (1983b) stated that Lightfoot (1980) provided comprehensive evidence that the respondent conditioning model is applicable to ethanol tolerance among humans, Annear and Vogel-Sprott (1985) criticized Lightfoot for not considering the possibility that the college students had "mentally rehearsed" to compensate for the effects of ethanol. In their study, Annear and Vogel-Sprott had four groups of social drinkers learn a visual-motor pursuit task and then drink the same dose of ethanol (0.62 g/kg) during each of five drinking sessions. Sessions 1 and 5 provided pre- and posttreatment measures of ethanol effects on task performance. During Sessions 2 to 4, two groups mentally rehearsed the task after drinking either in the same test environment or in a significantly different context. The other two groups were not allowed to rehearse following drinking and just performed an audio signal detection task in the test context or in the alternative environment. The subjects who mentally rehearsed the task in the same environment showed the least impairment on the task (i.e., were the most tolerant to the alcohol). The group who did not mentally rehearse and were tested in the different environment showed the least tolerance. The groups who mentally rehearsed in a different environment and the groups who did not rehearse but were tested in the familiar context did not show as much impairment as the nonrehearsing, different environment groups. However, there was no statistically significant difference between the impairment of the rehearsing, different environment group and the nonrehearsing, same environment group, and between these two groups and the nonrehearsing, different environment group. Annear and Vogel-Sprott concluded that the evidence

from their study was consistent with the hypothesis that respondent conditioning is involved in the development of behavioral tolerance to ethanol among humans, but they also included the possibility that mental rehearsal, a unique human ability, may also contribute to tolerance. However, this conclusion must consider the fact that the subjects of Lightfoot's study consumed considerably more alcohol than the subjects of this later study, and this might disrupt any ongoing mental rehearsal. With this consideration in mind, the more plausible explanation still lies in terms of respondently conditioned tolerance specific to the drug correlated context.

Baker and Tiffany (1985) reported research that adds a degree of complexity to the respondent conditioning tolerance paradigm. Using rats as subjects in a standard pain threshold procedure to assess context specific morphine tolerance, these researchers found that with increasing drug dosage, the impact of drug cues becomes smaller, relative to the tolerance that could be seen when drug delivery occurs in the absence of drug cues. Baker and Tiffany (1985) found that rats given .50 mg/kg doses of morphine displayed persistent context dependent tolerance across repeated test trials. However, rats given a 3.00 mg/kg dose showed that the tolerance specific to drug cues diminished across test trials and was not present by the third such trial. In summary, as drug dose increased, the proportion of a tolerance response that could be attributed to a history with drug predictive cues decreased.

Le, Khanna, and Kalant (1987) replicated Baker and Tiffany (1985) and extended those findings to include ethanol. In this study, rats

were used in a Pavlovian conditioning paradigm of tolerance to ethanol's hypothermic effect. It was found that context specific tolerance occurred for a dose of 2.00 g/kg of ethanol, but with a higher dose, 4.00 g/kg, tolerance was found in the presence and the absence of drug related cues. These findings again suggested that Pavlovian conditioning plays a major role in tolerance produced by low but not by high treatment dosage. While none of these studies examined any indices of operant behavior and a dosage effect, a subsequent study, Le, Kalant, and Khanna (1989), did.

Bennett and Samson (1991) conducted a study of Pavlovian acquired tolerance in a simulation of "real world" settings and contingencies. Two groups of adult male social drinkers, one group of low drinkers--three or fewer drinks per week, and moderate drinkers--8-15 drinks per week, played a video game in the natural environment of drinking--a bar setting or in a lab setting. Each subject played the video game three times before and after having consumed two mixed drinks (2.00 ml 40% ethanol/kg body weight) in each of the settings. There were no contingencies placed on game performance. This was simply a matter of play the game and see how well one did. Briefly, the results showed significantly more of the detrimental effects of ethanol in the lab setting, or in other words, much more tolerance was found in the bar setting than in the lab setting. But, no difference was found between groups despite their different histories of drinking and time spent in bar settings. This outcome does not fit with earlier findings that different exposure to ethanol results in different levels of tolerant response to ethanol predictive cues. The authors speculated that they

may have emerged due to the low level of intoxication produced; at higher levels of intoxication, a difference between the groups might be seen. The authors also argued that expectancies or rules the subjects followed about behaviors in the different settings may have influenced their responding. With either explanation in mind, the robustness of conditioned tolerance can be seen to vary considerably across various studies.

This review has attempted to emphasize the recently recognized importance of respondent conditioning processes involved in the development of behavioral tolerance to drug effects. Much of this literature has interpreted tolerance to be the result of drug compensatory responses that arise from classical conditioning. However, drug compensatory responses may also arise as a function of operant reinforcement and the responses that are emitted to compensate for a drug's effects and recover disrupted reinforcement contingencies. The following section surveys some literature regarding operant conditioning interpretations of tolerance.

The Tolerance Model Based Upon Operant Conditioning

It is known that organisms with identical pharmacological histories may display radically different levels of tolerance to drugs. Studies examining tolerance to a wide variety of drug agents-- amphetamines (Campbell & Seiden, 1973; Schuster et al., 1966), barbiturates (Tang & Falk, 1978), ethanol (Chen, 1968, 1972, 1979; LeBlanc, Kalent, & Gibbons, 1976; Mann & Vogel-Sprott, 1981; Wenger et al., 1980; Wenger et al., 1981; and others), morphine (Smith, 1979);

LSD (Commissaris et al., 1980), and phencyclidine (Woolverton & Balster, 1979) have consistently reported that regular administrations of a drug just prior to behavioral training will facilitate the development of tolerance more so than the same drug dose given after identical training sessions. In many studies of tolerance to ethanol, rats were given the drug just prior to, or shortly after, daily trials on a moving belt, shock avoidance task. In these experiments, the course of tolerance development was followed at four-day intervals by testing all animals following ethanol administration. A finding typical among these studies was that the subjects who were given the drug before the experiment developed tolerance at a moderately rapid rate. Groups of subjects who were given an identical dose after the session developed tolerance at a much slower rate or to a lesser degree and water controls who received ethanol only on test days did not develop tolerance at all. As a result, it has been argued that the before treatment groups quickly developed tolerance as a function of an increased opportunity for reinforcement of learned responses that compose tolerance. This proposition has been supported by studies reporting that tolerance emerges by the organism learning specific responses that are reinforced and which overcome a drug's effects. This finding was initially reported by Schuster et al. (1966). In this study, the behavioral effects of d-amphetamine in rats at a dosage of 1.00 mg/kg were assessed on baseline performances involving food or shock avoidance reinforcement. In the first experiment, food was delivered according to fixed interval (FI) 30 sec, or according to a differential reinforcement of low (DRL) rate reinforcement schedule.

Chronic drug administration resulted in initial increases in overall activity levels which had the effect of decreasing the frequency of food delivery regardless of the schedule of reinforcement. However, with continued daily drug administration, the subject's performance gradually shifted toward behavior observed under water control conditions. That is, tolerance developed in that the drug lost its effect and reinforcement density returned to baseline.

In the second experiment, a Sidman avoidance paradigm was employed in which an avoidance response had to occur at least every 30 sec or a floor grid shock would onset and continue until a response was emitted or the shock remained on for 10 sec. Again, the effect of the d -amphetamine was to increase overall activity levels including a uniform increase in response rate throughout the drug regimen that led to a decreasing rate of shock reinforcement. However, under these contingencies the subject's performance remained stable at the elevated response rate with the decreased shock reinforcement rate. These researchers concluded that tolerance to the behavioral effects of a drug will develop in those aspects of an organism's behavioral repertoire where the drug acts to disrupt the organism's behavior in meeting reinforcement contingencies. Conversely, Schuster et al. (1966) concluded that behavioral tolerance would not develop where the actions of the drug facilitate, or do not affect the organism's behavior in meeting reinforcement (in this case, avoidance) contingencies.

Administration of the stimulant increased the response rate in the FI component but this change did not alter reinforcement frequency;

subsequently, tolerance did not develop to the rate-increasing effects of the d-amphetamine under the FI as it had to the changed DRL performance. But for one subject who displayed a reduction in response rate and frequency of reinforcement on the FI, tolerance did develop on this schedule also. In other words, tolerance to the behavioral effects of a drug would only develop as a function of decreased reinforcement frequency resulting from the effects of a drug. Whatever behavior the organism can emit to compensate for the disruptive effects of the drug and reduce the reinforcement loss would be reinforced and then increase in frequency and consequently restore reinforcement levels to predrug baseline levels.

As previously mentioned, data from a number of studies have found similar results to that of Schuster et al. (1966). For example, Chen (1968, 1972) reported that rats run in a circular maze for food reinforcement developed behavioral tolerance to ethanol rapidly but animals exposed to the same amount of ethanol without the opportunity to run the maze while intoxicated failed to develop tolerance to the effects of the ethanol.

Further evidence for the importance of reinforcement on the development of tolerance was demonstrated by Smith (1979). In this study, pigeons responded for food on a multiple FI 10 min FR 30 schedule of reinforcement, and 10.00 mg/kg of morphine was administered daily. The effect of the morphine was to decrease responding to approximately 60-90% of baseline levels, but measurable tolerance developed over the course of five daily sessions. However, the rate of tolerance development differed depending on whether or not the presence

of the drug coincided with behavioral training on the schedule of reinforcement. For those animals given daily injections and daily sessions on the schedule, response rates recovered to approximately 80-95% of baseline levels. For animals given daily injections but only placed on the reinforcement schedule on the fifth daily session, responding under the FI schedule recovered to approximately 90% of baseline measures but in the FR schedule, response rates were only approximately 20-25% of baseline. It may be argued that these results can be attributed to a differential context effect through the respondent conditioning interpretation of tolerance, but that view fails to explain the difference in the recovery of responding in the FI as opposed to the relative lack of recovery under the FR schedule. However, when one considers the nature of the response requirements of these two schedules, the differences can be explained in terms of the contingencies. On the FI, all that the subjects had to do was to emit one response after 10 minutes to earn reinforcement--a contingency that favored long pauses and little responding, which happened to coincide with the effects of the drug, long pauses and decreased responding. On the other hand, the FR schedule required 30 responses before reinforcement. A drug that had the effect of reducing response rate and increasing the length of pausing would have more of an effect on a response dependent schedule such as an FR than on a time and response dependent schedule, such as an FI. Therefore, it can be inferred that response rate recovery would progress faster on the FI than on the FR schedule.

A study that further stresses the role of reinforcement in the development of tolerance is that of Mansfield, Benedict, and Woods (1983). A modified drug administration before behavioral training or drug administration after behavioral training procedure was used in this study to measure the influence of reinforcement contingencies on ethanol tolerance. Tolerance to ethanol was assessed among rats on both a behavioral task--staying on a moving belt (4 cm/s) to avoid shock and an autonomic response--body temperature. The subjects were divided into four groups and given injections of ethanol at 2.00 g/kg and daily training on the moving belt under one of four conditions: (a) daily injection of ethanol before training sessions; (b) daily injection of ethanol after training sessions, with no ethanol exposure while in training; (c) rats given daily injections of ethanol after training sessions, but every fourth day ethanol was administered before a training session; and (d) rats given water before training sessions but given ethanol every fourth session. The dependent measure in training and testing was mean time off the moving belt, in seconds, during which the subjects received electric shock. Sessions consisted of three 60 sec trials and training continued for 28 sessions. Over the course of training, subjects who were given ethanol before sessions showed a progressive decrease in mean time spent off the moving belt, ranging from approximately 30 sec cumulative at the start of training to approximately 10 sec off the belt on the last day of training. In contrast, the group of rats who received intermittent exposure to ethanol had mean times off the belt of approximately 40-50 sec throughout training, as did the water animals. Rats that never

experienced the moving belt task while intoxicated had mean off belt times very close to zero throughout training. At 24 hours after the last training session, all animals were tested on the moving belt task following ethanol injection. Among animals equally exposed to ethanol during the 28 day training, only those that had performed daily on the behavioral task while intoxicated showed tolerance to the motor disruptive effects of ethanol. This group of rats had mean times off belt of approximately 15 sec--responding typical of that seen during training. Groups of rats that had received either intermittent ethanol experience or no ethanol experience while on the moving belt had mean times off the belt of approximately 40-50 sec, roughly equivalent to the animals that had only been given water before most sessions, animals that would not have been expected to develop tolerance equally to the other groups. Conversely, all animals developed tolerance to the temperature decreasing effects of ethanol equally throughout training and testing. This result is contradictory to Siegel's (1975) argument that tolerance does not inevitably result from repeated drug administrations. Tolerance will develop merely from repeated exposure to a drug but this process can be facilitated through conditioning. As a result, Mansfield et al. (1983) concluded that the augmented development of tolerance appears to reflect a specific response that was acquired by the organism as a function of reinforcement.

Le et al. (1989) examined the development of tolerance to ethanol's motor impairment with rats on a shock avoidance task. This study involved manipulation of chronic treatment dose, test trial dosage, and opportunity to perform while intoxicated. The results of

the experiment showed that after a chronic treatment regimen involving a large dosage (4.00 g/kg), intoxicated practice did not differentiate whether tolerance developed or not. With a smaller chronic dosage, that of 2.00 g/kg, intoxicated practice was found to be functional in tolerance to motor impairment from ethanol. These outcomes were found under ethanol challenges of 1.60 g/kg, 2.00 g/kg, and 2.40 g/kg. To put it another way, tolerance to ethanol's motor impairing effects developed whether or not rats received intoxicated practice during a chronic treatment regimen, with the qualifications pertaining to treatment dosage in effect noted above. This study represented a complicating factor to the view that tolerance emerges due to some "behavioral compensation" an animal or human may engage in to recover or prevent loss of reinforcement. But, this experiment also raises other questions. What would have been the effect of larger test dosage, in particular, dosage equivalent to the larger treatment dosages, namely 4.00 g/kg? Following a chronic treatment dosage of 4.00 g/kg, why employ a smaller treatment dosage to test for tolerance as a function of intoxicated practice? If a larger test dosage had been used, then intoxicated practice might have been seen to be a functional variable for tolerant behavior after the larger treatment regimen, as it was with the smaller treatment regimen. The outcomes of this logical additional manipulation would probably be more akin to earlier studies (Mansfield et al., 1983; Wenger et al., 1981) that had shown that intoxicated practice was essential for the development of tolerance.

Holloway, King, Michealis, Havland, and Bird (1989), Holloway, Bird, Holloway, and Michealis (1988), and Bird and Holloway (1989) presented a series of investigations in the acquisition of behavioral tolerance to ethanol. All studies used rats as subjects on schedules of reinforcement. The Holloway et al. (1988) study is noteworthy because of its methodology. In the first experiment, dose-effect analyses were used to measure the effects of ethanol on an FR30 schedule of reinforcement, but in addition, the maximally tolerant dosage was given to all subjects. That is to say, the maximum tolerable dose was arrived at as a dose of ethanol that did not completely suppress responding but which reduced responding to 20% of water baseline sessions. The experimental design employed a straightforward pre-session, post-session design to allow or prevent intoxicated practice. The pre-session group of rats developed tolerance, the post-session group did not.

To control for classical conditioning associated with the IP ethanol delivery, another experiment was conducted. Here, a chronic ethanol regimen involving an experimental diet in which 40-50% of the caloric value was present as ethanol. To control for health factors, another group of rats was placed on a control diet in which 40-50% of the calories were available only from a maltodextrin mixture, another source of calories alone. Following a period of three weeks on the altered diets and during which the subjects performed daily on the FR30 schedule, ethanol challenges of 1.50 g/kg, IP were administered prior to schedule performances. The ethanol diet rats displayed considerable tolerance, not seen with the control diet subjects, and the researchers

concluded that these procedures had minimized the role of classical conditioning in the development of tolerance. In addition, the tolerance effect was found to be relatively intact six months after the last ethanol challenge. Since most tolerance to ethanol's effects on physiological measures declines rapidly and is absent after two weeks, Holloway et al. (1988) also concluded that this prolonged tolerance was due to a learned, behavioral compensation, due to a loss of reinforcement. Holloway et al. (1989), and Bird and Holloway (1989) replicated the 1988 findings of prolonged acquired tolerance due to a learned, behavioral compensation; the exact mechanism of the behavioral compensation is, on the other hand, unknown.

Watanabe (1990) investigated the interaction between a context predictive of drug delivery and schedule of reinforcement performance by pigeons from a slightly different approach. Here pigeons were trained to peck on a MULT FR 30-F13' schedule. Prior to each session, each subject was given an injection of d-amphetamine (2.00 mg/kg) or pentobarbital (7.50 mg/kg or 10.00 mg/kg). Sessions preceded by drug delivery were paired with the presentation of a red light on the ceiling of the chamber. Other sessions, preceded with water injections, were paired with a white ceiling light. For test sessions, the subjects were given water and placed in a chamber with the red light illuminated, the context predictive of drug delivery. During these test sessions, the CS red light came to exert an isodirectional (druglike) effect on the operant performance, as a function of which drug the CS had predicted. For another group of subjects, these experimental manipulations were conducted for sessions with the key

light covered, which prevented responding. For those subjects who could not respond in the presence of the CS, identical test trials as described above showed that the CS exerted no isodirectional effects on behavior. Watanabe concluded that responding in the presence of the CS was necessary to establish the conditioned drug effects. No tolerance effect was observed in this study, due somewhat to the spacing of drug delivery, on every third day, and because neither drug caused significant reinforcement loss or delay. Another interesting aspect of the outcome of this study is that the subjects were not experimentally naive, having been used in several schedule studies and that all were habituated to the red light prior to drug conditioning. Latent inhibition would predict retarded conditioning to a CS, and this may also be a factor in the absence of tolerance here.

Smith (1991a, 1991b) reported results from studies that looked at the operant-respondent interaction from a different approach than most. Smith (1991a) investigated acquired tolerance to a cannabinoid, 1-nantradol, among rats on a schedule of food reinforcement. In the second study, rats were again used as subjects with their schedule performance studied under the influence of phencyclidine. Both studies involved the use of contextual manipulations--with the sidewalls of an operant chamber being transparent or covered with black paper. The primary dependent variable was response rate in both studies. Smith (1991b) reported that tolerance acquired to phencyclidine on a simple schedule of reinforcement did not extend to a complex schedule in the altered chamber. Tolerance that did develop was found to extend to a complex schedule including a different manipulandum when tested in the

same chamber. The results of the other study were very similar. Both studies overlooked the effects of the altered chamber on the subject's performance on the same schedule of reinforcement. These outcomes tended to indicate that respondent processes did overwhelm the operant process, at least in these experiments. The results here were also different in that drug delivery occurred before and after experimental sessions in different experimental phases. It would seem that the procedure would have tended to retard any context specific tolerance, but the results did not indicate as such.

Whereas the overwhelming majority of studies observing the effects of reinforcement on tolerance have employed nonhuman subjects, a few experimenters have examined the development of tolerance to ethanol among humans through operant procedures (DeVillaeer, 1979; Vogel-Sprott, 1976, 1979; Mann & Vogel-Sprott, 1981; Beirness & Vogel-Sprott, 1984). In the 1981 study, the development of tolerance to ethanol was assessed in two experiments with male college students. In both experiments, the subjects were given pretraining on a visual motor pursuit task that required the subjects to track a moving light source with a light sensitive stylus. A test on this task consisted of two 50 sec trials separated by a 30 sec intertrial interval. Following initial training, the subjects were randomly assigned to either receive alcohol or a placebo drink and then further tested on the pursuit task for four drinking sessions. On each of the drinking sessions, the ethanol subjects were given alcoholic drinks (0.88 ml 96% alc/kg) mixed 1:2 with a carbonated drink and divided into three equal drinks which were served at 20 min intervals. Placebo subjects received an equivalent

amount of carbonated beverage with a few ml of alcohol added for flavor.

Preceding these test sessions, a pretest on the pursuit task was administered prior to the first drink; this served as the subject's drug-free baseline against which five subsequent tests under ethanol or the placebo in that session would be compared. The differences between a subject's baseline and each of their subsequent scores under ethanol or placebo were calculated to provide measures of change in performance. A negative difference would indicate that post drinking performance was impaired relative to the nondrug performance, a positive difference would indicate improved performance. Following each test, all subjects were given feedback based on their performance and received monetary rewards for nonimpaired performance.

On the first test drinking session, the alcohol subjects were significantly impaired relative to the placebo subjects; the alcohol subjects had mean changes of about three seconds more off target than their baseline performance. But by the third and fourth sessions, the alcohol subjects had surpassed their baseline times by between .5 to 2 seconds on the average. The placebo subjects had performances that varied about their baseline scores. And while it could be concluded that the alcohol subjects developed tolerance as a result of reinforcement for nonimpaired performance, this experiment did not control for practice by having alcohol subjects tested over multiple sessions without reinforcement. The second experiment was conducted to control for such practice effects. In this experiment, a different group of subjects was given identical training and then assigned to one

of two ethanol groups or to a placebo group. Then, over the course of four drinking sessions, the placebo group and one ethanol group were provided with feedback and monetary reward for nonimpaired performance and the remaining ethanol group was not given any feedback or reinforcement concerning their performance on the pursuit task. Only those ethanol subjects provided with reinforcement were seen to develop tolerance to the effects of the ethanol. And in two more subsequent drinking test sessions in which the previously reinforced ethanol subjects were run on the task in extinction, their performance deteriorated to impairment levels seen in the first session. Based on these results, Mann and Vogel-Sprott (1981) concluded that their outcome was directly analogous to the data from animal studies in that tolerance was acquired through reinforcement of nonimpaired behavior.

Beirness and Vogel-Sprott (1984) also studied the effects of operant reinforcement on the development of ethanol tolerance among college students. Their subjects were given equal training on a visual-motor pursuit task in which the subjects had to center a pointer over a lit target that would appear randomly on a tracking screen. A single test consisted of 100 target presentations. The subjects were then randomly divided into four groups to be given different test conditions. One group was given information concerning their performance and contingent monetary reward for nonimpaired functioning, the CR group; another group was provided with information only regarding their performance, the IO group. A third group was given monetary reward noncontingent on their performance, the NCR group, and finally a fourth group that was given neither information

nor reward of any kind, the NR group. All groups performed the task twice before a drinking test session and then with a dose of ethanol at 0.34 ml absolute alcohol/kg served in three equal drinks given at 20 min intervals. The subjects were tested on the task on 12 trials during each of four drinking test sessions and on a fifth session, all subjects were given dealcoholized beer as a placebo. The effects of the ethanol on performance were assessed by the differences between the subjects' drug-free trials and the subsequent trials under the influence of ethanol. These researchers did not supply data relevant to mean degree of performance impairment of the subjects after drug consumption relative to baseline levels, but instead presented their results in terms of reduction in impairment across trials for the different groups. The most rapid decrease in impairment (or the fastest development of tolerance) was displayed by the contingent reinforcement group which had a mean reduction in impairment of 2.38% per session. The information only group averaged an 1.005% reduction in impairment over the sessions; the noncontingent reinforcement group had a still lower rate of reduced impairment, averaging 0.942% reduction across sessions. The nonreinforcement group showed no reduction of impairment across sessions. In the fifth session conducted under placebo conditions, all subjects performed the task under operant extinction; this session was conducted to test for responsively conditioned compensatory responses unattenuated by the ethanol. In the absence of the ethanol to act against the compensatory responses, this compensation should result in facilitated performance. This effect was seen and was greatest in the contingent reinforcement

group that had developed tolerance the most rapidly. All groups, except the nonreward group, showed a significant change toward facilitated performance under the placebo. Although this study interpreted the placebo results in terms of respondent elicited compensatory responding, it would seem that the results are more likely to be due to the operant history given the subjects, which explains why essentially the same differences in performances occurred in extinction or in reinforcement. The testing context was the same for all subjects and all subjects had the same respondent conditioning potential as a result. Consequently, although experimenters concluded that their findings were the function of an operant-respondent interaction, their results can most clearly be interpreted in operant conditioning parameters. The subjects who developed tolerance most rapidly were given the most potent reinforcement. Relative to the other groups these same subjects showed the strongest facilitated performance after being given a placebo and tested in extinction following their enriched reinforcement history.

As this study and others reviewed above have shown, a significant body of research has examined tolerance as the result of a respondent or an operant conditioning procedure interacting with a drug, but studies looking at possible interactions between the conditioning procedures are rare. From the existing research, it would appear that the development of tolerance to the effects of a drug represents both respondent and operant processes. However, rarely has a study adequately measured the efficacy of either of these processes programmed in opposition to the complementary process. This study

represents a unique contribution in that effects of these processes will be manipulated in antagonistic procedures. The maintenance and measurement of operantly conditioned tolerance in a specific context and subsequently in a radically altered context attempted to sort out the efficacy of operant and respondent tolerant processes and focus on an unanswered empirical question.

Finally, in this dissertation, little or no mention has been made of any tolerance arising merely due to repeatedly experiencing a drug. Such tolerance does occur and is usually referred to as dispositional tolerance or nonassociative tolerance. The impact of this tolerance will also arise as a result of behavioral demands upon the physiology of an organism. According to Poulos and Cappell (1991), behavioral demands or challenges to an organism's homeostasis are necessary for the discrimination of disturbances to homeostasis. These disturbances are requisite to drive physiological adaptive processes that restore homeostasis. The detection of drug-induced shifts away from homeostasis serve to activate innate homeostatic responses which can directly lead to nonassociative tolerance. In drug regimes in which environmental cues reliably predict drug delivery, these responses can be conditioned to these cues for conditioned tolerance to develop. Poulos and Cappell (1991) discount the operant formulation of conditioned tolerance as simply not explaining enough other phenomena such as the development of tolerance to the anticonvulsant and hypothermic effects of ethanol, or for morphine-induced analgesia. In their words, "it is difficult to understand how the induction of a convulsion or the application of pain can constitute a reinforcing

state of affairs that the organism would be motivated to reinstate" (Poulos and Cappell, 1991, p. 397).

In response, an operant researcher could point out that the responses mentioned above would seem to be conditioned reflexes which are mediated more so by preceding, eliciting stimuli rather than by stimuli that serve as consequences that follow responses (Hineline, 1986). If the responses to be measured were more sensitive to the selecting consequences, the concept of what is a "reinforcing state of affairs" to be reinstated would be more obvious. Another objection to Poulos and Cappell (1991) could be their very limited view of operant conditioning, which, by the way, is stated more broadly earlier in their paper,

...by itself, the drug's presence does not constitute a functional disturbance for the organism. The organism must interact with relevant features of the environment for a drug effect to be biologically detected as a functional disturbance.... (Poulos and Cappell, 1991, p. 391)

Presumably, when an organism interacts with relevant features of the environment, stimuli that precede and elicit conditioned reflexes as well as stimuli that select operant behavior through reinforcement and punishment would both be experienced. Also, the operant formulation predicts that tolerance will only develop for behaviors necessary to regain reinforcement loss. An analgesic state can be seen as a change to which reinforcement would not necessarily develop. These theorists view the operant theory of tolerance too narrowly. Poulos and Cappell (1991) do not do away with the operant version of conditioned tolerance but do add the environment as having a role in nonassociative tolerance.

In addition, the emphasis that Poulos and Cappell (1991) place on the concept of homeostasis harks back to drive-reduction theory. In this case, homeostasis as a regulator of behavior can be seen as the ultimate intervening variable inside the organism. Drive reduction theory has been criticized as involving an infinite number of drives and as simply not necessary to explain behavior. Both of these criticisms apply here to homeostasis.

METHOD

Introduction

In most studies of the context dependent modification of drug tolerance, the dependent variables have been mortality rates, pain tolerance, thermal reaction, or some other respondent. The development of context dependent tolerance in the presence of stable operant behavior and subsequent manipulation of tolerance by changing the context and measuring the behavioral change that results has not been examined in great detail. This experiment will employ a single-subject research design but with experimental and control groups for macro-comparisons.

Experimental Phase--Experiment One

Subjects. Four experimentally naive common barn pigeons (*Columba livia*) of unknown age and gender served as subjects in the first experiment. Pigeons were selected as subjects due to their acute sensitivities to brightness (Blough, 1958), and because the species is most often the subject of choice for schedule of reinforcement studies (Ferster & Skinner, 1957). In many studies of the behavioral aspects of drug tolerance, rats have been employed as subjects, with the selection of pigeons the research can be extended to another species. Naive subjects were used in the later experiments. Each subject was maintained throughout at approximately 80% of its ad libitum feeding

weight. All supplemental food was provided in home cages no sooner than 30 min following an experimental session. Water was also freely available at all times in home cages.

Apparatus. A single pigeon chamber (Colburn Instruments Modular Small Animal Test Cage, model E10-10) with interior dimensions of 29.5 cm x 29 cm x 24 cm individually housed subjects during experimental sessions. One of the walls contained a houselight (GE #1820 bulb), three response keys (the two side keys being inoperative), and an opening for food delivery. The two sidewalls were clear plexiglass.

The circular 2.5 cm response key was located 19.5 cm from the chamber floor. A force of approximately 5 N through a distance of 1 mm was required to close the microswitches behind the response key. Only the center key was used in training and experimentation. The key (including an Industrial Electronic Engineers In-Line Digital Display units fitted with Kodak Wrattan filters) was transilluminated by a blue light during training and experimental sessions. The response key was darkened and inoperative during food hopper lifts.

Reinforcement consisted of 3s access to pigeon checkers (Purina racing pigeon checkers) available inside the hopper food aperture (5.2 cm x 5.3 cm), centered 3.75 cm above the floor. The food hopper, when raised, was illuminated by a single, 29-volt bulb located inside the food aperture. The chamber was enclosed in a ventilated, light, and sound-attenuated box. Sound attenuation and ventilation were provided by a blower mounted on the chamber as well as an exhaust fan located in the room.

Experimental events were controlled by a Commodore 64 microcomputer, a Commodore interface (Crossman, 1984), and a Commodore 1541 disk drive. All experimental events from all sessions of the experimental phases were stored on floppy disks for analysis. Experimental information was also transcribed from the computer video display monitor onto session data sheets.

Training Phase. Once a subject's weight equalled or was less than 90% of its ad libitum feeding weight, each subject was placed in the experimental chamber with the houselight illuminated and approximately 5-10g of food placed in the food aperture. This procedure was intended to adapt the subjects to the experimental chamber and to learn to eat from the food aperture. Each subject remained in the chamber for a minimum of 15 min, at which point the experimenter checked to see if the pigeon had consumed the available food. Subjects repeated this procedure until all available food was consumed in the specified time or if at the completion of three consecutive sessions in which the bird had not consumed the food, a new subject was selected. Upon successful completion of one session involving the aforescribed procedure, the subjects were exposed to an autoshaping procedure (Brown & Jenkins, 1968).

This procedure had an intertrial interval (ITI) of 54s and a interstimulus interval (ISI) of 6s. More specifically, at the completion of every 54s ITI, the center key was transilluminated with a blue lamp for the 6s ISI. A response to this lit key resulted in a 3s hopper presentation. If the subject did not respond during the 6s ISI, the key was darkened, and a programmed 3s hopper lift took place.

Responses during the ITI had no scheduled consequences. The houselight remained on through all autoshaping sessions.

Autoshaping continued until 20 or more ISI responses of sufficient strength to close the microswitch were recorded within one session and these training sessions lasted until 40 hopper presentations occurred. Any subject which failed to emit 20 or more ISI responses within three consecutive sessions was replaced with another experimental subject.

Following autoshaping, all subjects were trained on a progressive series of fixed-ratio (FR) schedules of reinforcement, one schedule per day, as follows: FR 1, 2, 5, 10, and 20. Whenever the fixed response requirement was met, the key darkened and the hopper operated for 3s. These FR sessions were intended to adapt the subjects to emitting multiple responses before being reinforced, and lasted for 30 min or until 30 hopper lifts had occurred, whichever happened first.

Developing operant-respondent conditioned tolerant behavior and testing for context specificity. After initial shaping, the subjects were exposed to the experimental contingencies. All subjects were placed in the darkened experimental chamber for 10 min. This was done to temporally isolate the events of leaving the home cage, weighing, and being carried to the chamber from the act of being injected with a drug agent. At the end of the 10 min, the subjects were removed from the chamber, given an oral injection of 2.00 g/kg of 25% ethanol (V/V), and placed back in the chamber for a 20 min pre-session interval to allow for adequate drug absorption and distribution.

The dose of 2.00 g/kg was arrived at from the results of Barrett and Stanley (1980) who determined that 2.00 g/kg was a "high dose" in

terms of its effect on pigeons' behavior. This dose is roughly equivalent to a 150 pound person consuming 4.75 ounces of 25% ethanol all at once and on an empty stomach.

When the 20 min interval elapsed, session onset was signalled by center key light illumination and the subjects could obtain reinforcement on a variable-ratio (VR) 20 schedule. A variable-ratio schedule of reinforcement was used during experimentation to generate a high rate of responding with little or no pausing and to produce patterns of responding that were less rigid and more likely to be demonstrative of the effects of the ethanol, more so than FR behavior (Dews, 1955). The houselight was not lit during these sessions. The only light in the chamber was from the key light and the hopper light during reinforcement. These sessions lasted for 30 min or 30 hopper lifts, for a minimum of 10 sessions to the point at which stable schedule behavior was obtained. The criteria were no new high or low values for running response rate, overall response rate, and postreinforcement pause for five consecutive sessions, to a maximum of 15 sessions. As soon as the stability criteria were met, the subjects were tested for conditioned tolerance.

Specifically, the procedure differed in that the chamber conditions were altered. During the 10 min pre-session interval, the chamber houselight was illuminated, reflective aluminum foil was draped over the clear chamber sidewalls, and the ambient noise levels were increased by 15-20 dB. The usual ethanol delivery occurred, and after the absorption interval, the response key became illuminated and the reinforcement schedule was then in effect.

The remaining subjects experienced the same context and contingencies but only received an injection of water before each session. These sessions were continued for an equivalent time as the experimental group. Experimental data regarding any changes in rate of responding and pause length were used to gauge any changes in behavior as a function of the altered context. These sessions lasted for 30 min or 30 hopper lifts and continued, for a minimum of ten sessions, until stable behavior was again obtained for five consecutive sessions.

Experimental Phase--Experiment Two

Subjects. Six experimentally naive homing pigeons (*Columba livia*) of unknown age and gender served as subjects in the second experiment. Each subject was maintained throughout experimentation at approximately 80% of its ad libitum feeding weight. All supplemental food was provided in home cages no sooner than 30 min following an experimental session. Water was freely available at all times in home cages.

Apparatus. The experimental apparatus employed in the first experiment was used in experiment two. Likewise, the experimental subjects were given the same initial training procedures prior to the experimentation proper, as described in experiment one.

Developing operant-responder conditioned tolerant behavior and testing for context specificity. Following shaping and preliminary schedule training, the six subjects were exposed to the experimental manipulations to develop tolerance to the behavioral effects of ethanol. A reversal-replication experimental design with two different types of probes was employed, the details of which are explained in the following text.

The subjects were initially placed in the darkened experimental chamber for 10 min. This was intended to establish the chamber as the conditioning context and to disrupt any possible chaining of stimuli such as the act of weighing, carrying, and placing the animal in the chamber as parts of the conditioning process. At the end of the 10 min, each subject was removed from the chamber and given an oral injection of either water or the ethanol solution. Injection of each agent was dictated according to the phase of the experiment. The very first phase of the experiment involved exposing the subjects to the chamber in the "bright, noisy" condition. That is, the subjects first performed on the VR schedule of reinforcement with the chamber houselight illuminated, the ambient noise levels increased from 15-20 dB by a noise generator, and with reflective aluminum foil draped over the clear sidewalls of the chamber. This experimental condition was paired with oral injections of water. Following an injection of water, each subject was placed back in the chamber for a 20 min pre-session interval to allow for absorption of the injected agent. At the end of the 20 min interval, session onset was signalled by the center keylight illumination, with reinforcement becoming available on the VR 20 schedule of reinforcement. The session terminated following 30 reinforcement deliveries or 30 min, whichever occurred first. Data were collected on all three dependent variables for all sessions.

Upon completion of four consecutive sessions in this experimental condition, the subjects were exposed to the altered context which was paired with injections of ethanol. Four sessions in each condition were arrived at based on the fact that a minimum of three data points

are necessary to detect directional trends in the data (Kazdin, 1982). Sidman (1960) raised a similar point about minimum and optimal number of experimental sessions. To further support this manipulation, McPherson and Osborne (1988) reported fewer numbers of alternations (in their case, five-day alternations as opposed to ten-day alternations) resulted in greater and more reliable across-condition behavioral changes due to different stimulus control.

After the subjects had experienced a minimum of two exposures to each experimental condition, a probe session for context dependent tolerance was conducted. That is, following the fourth session in the second series of ethanol sessions, the subjects were again given an injection of ethanol but were exposed to the experimental conditions predictive of water delivery (that is, houselight illuminated, noise levels increased, reflective foil present); the same schedule of reinforcement was in effect. After this probe session, the subjects again experienced the experimental conditions previously in effect. Four more sessions of water injections in the water predictive context were followed by four sessions with ethanol deliveries in the context predictive of ethanol. Another probe ensued after these eight sessions; this test was of the same type as described earlier to assess context dependent tolerance. Briefly, the procedure involved delivering ethanol while the environment was predictive of water delivery. Subsequent to this probe, the original experimental conditions were reinstated for three more series of the conditioning procedures. The subjects then underwent four sessions of water delivery in the environment predictive of water, followed by four

ethanol sessions in the original context for ethanol delivery and finally four more sessions of water delivery in its context. Afterwards, four consecutive probe sessions, identical to the two earlier tolerance probes, were administered. Multiple probe sessions done in a consecutive fashion allowed for observations of the endurance of contextually conditioned tolerance. Again, the same operant schedule of reinforcement was in effect across all sessions. Directly after these probe sessions, probes for conditioned facilitated behavior took place. These probes consisted of delivering water to the subjects while in the presence of the context predictive of ethanol delivery. Since the respondently conditioned tolerance had been described as consisting of compensatory mechanisms to negate the unconditioned effects of the ethanol and as the operant behavioral compensations also overcame the ethanol's effects, facilitation of behavior as well as tolerant behavior was expected.

Following these experimental manipulations, all subjects were placed on the same schedule of reinforcement across the same conditions of experiment two but in the absence of any injected agent to obtain an operant baseline level of schedule behavior. Baseline consisted of 16 sessions, two alternations across both contexts. This was done following the conditioning procedures to avoid any confounding of results due to a preexposure to the CS--the experimental chamber environment.

Experimental Phase--Experiment Three

Further contextual alternations. Four additional naive subjects were run under the same conditions as in the second experiment but with

the response key illuminated red during those sessions in which tolerance to ethanol was being conditioned. In sessions preceded by water delivery the keylight was blue as in the earlier experiment. Tolerance probe sessions also had the blue keylight present. The color red was selected as being very divergent from the color blue. Data were collected on the same three parameters.

Experimental Phase--Experiment Four

Attenuating respondent conditioned tolerance while establishing operantly conditioned tolerant behavior. Four new animals served as experimental subjects in this experiment. All animals were given the same initial training procedures in the same apparatus as described earlier. Following initial shaping, these subjects were given a conditioning history different than that of the subjects in earlier conditioning. Here the subjects were weighed and placed in the darkened experimental chamber, again for the 10 min interval. Following this, the animals were given an injection of water and returned to the chamber for the 20 min pre-session interval. Upon the expiration of the 20 min, the VR-20 schedule of reinforcement was again in effect and data were collected for the same three dependent variables--mean postreinforcement pause, mean overall response rate, and mean running response rate. The parameters of number of reinforcement, delivery, and duration of session were the same as in earlier experimentation. However, here the subjects were given the same injection history across both environments. The subjects were given injections of water before each session in which house and keylight, increased noise and reflective foil were present and also

were given injections of water before each session in which the chamber was illuminated by only the keylight with ambient noise levels. And as in experiment three, a different color keylight was present for each setting.

This conditioning history was imposed for a total of 16 sessions--two alternations across both contexts. The operant schedule of reinforcement was in effect across all contexts for all sessions. The purpose of this conditioning history was to attenuate the emergence of subsequent respondent conditioned tolerance through pre-exposing the subjects to the potential CS context before any exposure to the ethanol US. A novel CS has more efficacy to be conditioned with a US than a familiar CS (Siegel, 1983b); as a result, the pre-ethanol conditioning history should interfere with the context to be paired with ethanol becoming an effective CS to develop respondent tolerance.

Following the pre-ethanol conditioning history, the subjects were exposed to the same conditioning regimen as in experiment three. However, the predicted effects should not be the same as in this case, stable operantly conditioned tolerance behavior would have been established but respondent conditioned tolerance should have been hindered. The behavioral change in response to the tolerance probes was expected to be minimal.

In summary, these progressively detailed experimental manipulations were intended to help delineate the contributions of operant and respondent processes to the development of behavioral tolerance to ethanol.

RESULTS

In a 1958 review paper, Dews suggested that the effects of drugs on behavior could be attributed to one or a combination of four factors: (a) the type of species and the individual animal; (b) what the animal was doing - responding or not and the rate of that response; (c) what affect the environment has on the animal (the presence or absence of eliciting, reinforcing or punishing, and discriminative stimuli); and (d) the animal's history. These same four factors were seen as being operational factors in this study. The results of this study can be interpreted clearly for the most part as relations among the independent variables which were the schedule of reinforcement and the dosage of ethanol, the environmental manipulations (which might best be described as a contextual variable, owing to the nature in which it was presented or not), and the dependent variables, including the length of the postreinforcement pause (PRP), and rates of responding. The dependent variable that displayed the most significant and consistent change as a result of the experimental manipulations happened to be the length of the PRP, with the response rate data showing similar effects, but to a lesser degree. To aid in remembering the sequence of events, Figure 2 provides a timeline of experimental procedures.

Timeline Experiment One Control Subjects

VR-20 schedule performance measured following water delivery. Data collected for a minimum of 10 sessions to a maximum of 15 sessions in the dark and silent context, the chamber at ambient noise levels and illuminated by the keylight alone.

VR-20 schedule performance measured following water delivery but in the bright and noisy altered context, with elevated noise and houselight illuminated. Data collected to point of stability for a maximum of 15 sessions.

Timeline Experiment One Experimental Subjects

VR-20 schedule performance measured following ethanol delivery. Data collected for a minimum of 10 sessions or until behavioral stability in the dark and silent context.

VR-20 schedule performance measured following ethanol delivery, but in the bright and noisy altered context. Data collected to point of behavioral stability.

Timeline Experiment Two, Exp. Three, and Exp. Four Subjects

VR-20 schedule performance measured for 16 tolerance conditioning sessions. Water or ethanol delivery alternating every four sessions, water being paired with the bright and noisy context and ethanol with the dark and silent context. The keylight was illuminated blue in all conditions in experiment two; in experiments three and four the keylight was blue preceding water delivery and was illuminated red preceding ethanol delivery.

Tolerance probe 1 conducted-usual dose of ethanol administered in context predictive of water delivery.

Eight more tolerance conditioning sessions, contexts and water or ethanol delivery alternating every four sessions.

Tolerance probe 2 conducted-usual dose of ethanol delivered in context predictive of water delivery.

Twelve more tolerance conditioning sessions, contexts and water or ethanol delivery alternating every four sessions.

Four consecutive tolerance probe sessions-usual dose of ethanol administered in context predictive of water delivery.

Four consecutive conditioned facilitation sessions in which the usual dose of water was given in the context predictive of ethanol.

Baseline sessions in which VR-20 performance was measured across both contexts in the absence of water or ethanol delivery. Data collected for 16 sessions-two alternations across both contexts.

Figure 2. Experimental timeline for experiments 1-4. Deviations from this timeline that occurred in experiment one were due to variables extraneous to the experiment.

Experiment One

In experiment one, two subjects (BP-5 and BP-8) were given injections of water before each experimental session as a control condition. These subjects were reinforced on the same schedule of reinforcement across the environmental contexts discussed earlier. However, when these control subjects were exposed abruptly to the altered context, their behavior showed clear and consistent changes apparently due to the environmental changes. This effect is most evident in the mean postreinforcement pause data, as shown in Figure 3. Further, a gradual and minor decrease in mean PRP can be seen across all sessions for both BP-5 and BP-8. Figure 4 displays the average running response rate data. The change in response rate data complementing the decreasing PRP was not seen here. The data pertaining to mean overall response rate were judged to be indistinct from the running response rate data. As a result, the graphed data of average overall response rate are presented in the appendix.

The observed changes in the behavior of animals in which no context specific conditioned tolerance would have developed constituted a challenge to the validity of the experiment. Whatever behavioral change that would result from exposing the subjects with chronic ethanol exposure in a particular context and then placing these subjects in the modified context would be virtually uninterpretable. The actual behavior of the subsequent treatment subjects was either stable across the contexts or showed a transient effect opposite in direction to that of the control subjects; again, the behavioral outcomes are most clearly seen in the mean postreinforcement pause

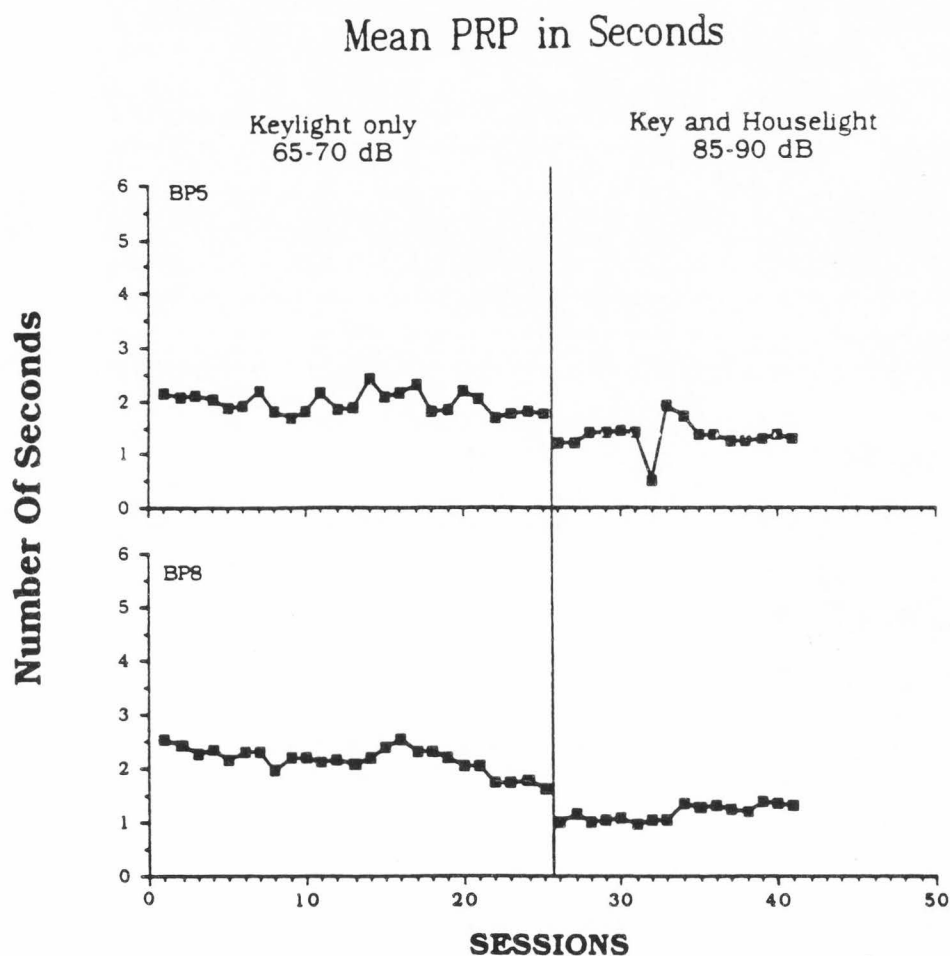


Figure 3. Mean postreinforcement pause (PRP) in seconds on a variable-ratio (VR) 20 schedule of reinforcement for control subjects BP-5 and BP-8. Both subjects were given an oral injection of 2.00 g/kg of distilled water before each session. The left panel indicates mean pause length on the VR 20 schedule with only the keylight illuminating the chamber. The right panel indicates mean pause length on the same VR schedule with the key and houselight illuminating the chamber. Additionally, the ambient noise level was increased by 15-20 dB and aluminum foil was draped over the clear sidewalls of the operant chamber.

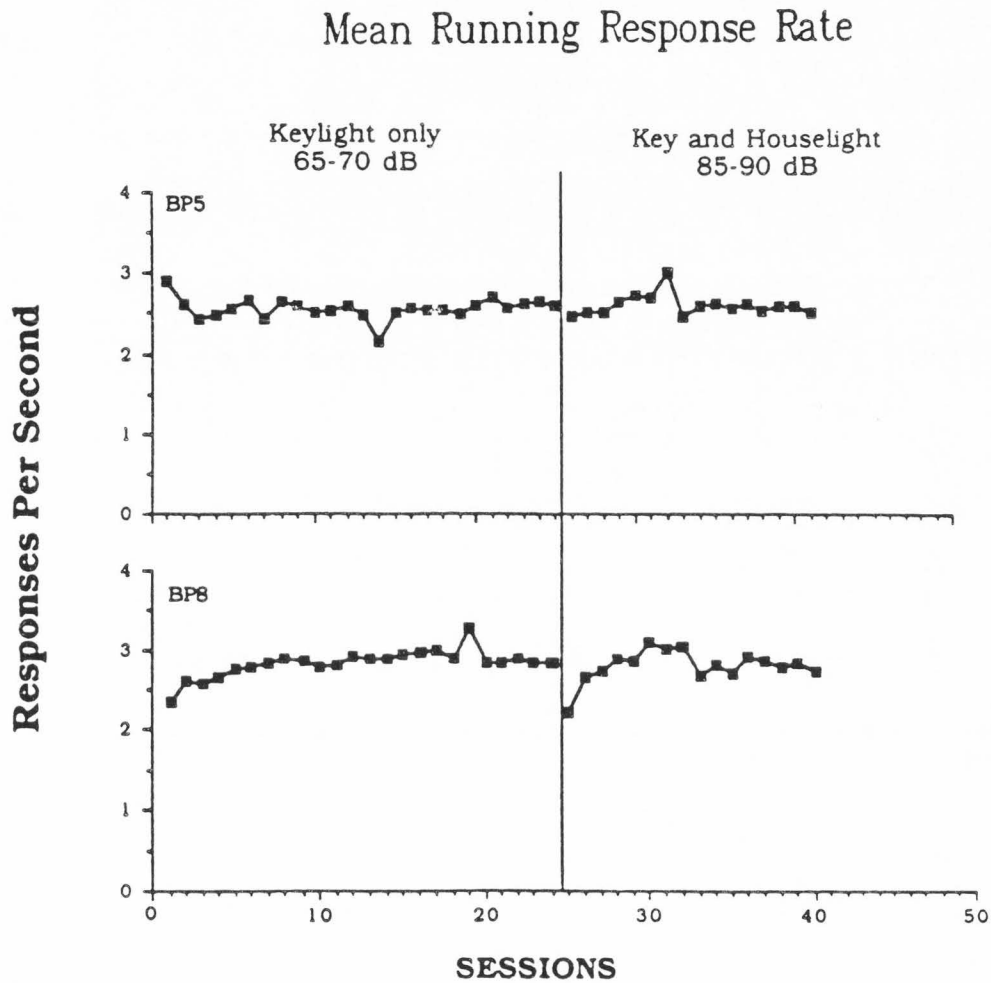


Figure 4. Mean running rate in responses per second, excluding the postreinforcement pause, on a VR-20 schedule of reinforcement for control subjects BP-5 and BP-8.

data, as in Figure 5. Again, a clear decrease can be seen in the mean PRP data over the course of all sessions for both subjects. This decrease is more evident in the data of subject BP-7.

Figure 6 illustrates the mean running response rate data. The data in Figure 6 do show an increasing trend in rate of response over all sessions for both subjects. This behavior change relates back to the decrease in mean PRP seen in earlier figures. Note the difference in the number of sessions on each condition for subjects BP-7 and BP-6 was due to an error as was the delivery of water. As a result of these findings, experiment two was implemented.

Experiment Two

The results of experiment two are presented here in terms of two different outcomes for two of the subjects relative to the remaining four. With two subjects, 2.00 g/kg of 25% V/V ethanol was sufficient to completely suppress operant responding, relative to operant responding following a dosage of water. To produce the same degree of behavioral change in the four other subjects required doses large enough to produce a taste aversion and no food intake for three to four days. These four subjects were dropped from the experiment. To counter the problem, a less rigorous criterion was adopted to define the effective dose to which tolerance developed. Instead of total response suppression, a criterion of an average PRP across the first four ethanol sessions that was at least twice the average PRP over the four preceding water sessions was adopted to be the behavior change goal from ethanol administration. This dose was determined using dose response curves. Even with this less rigorous response criterion, some

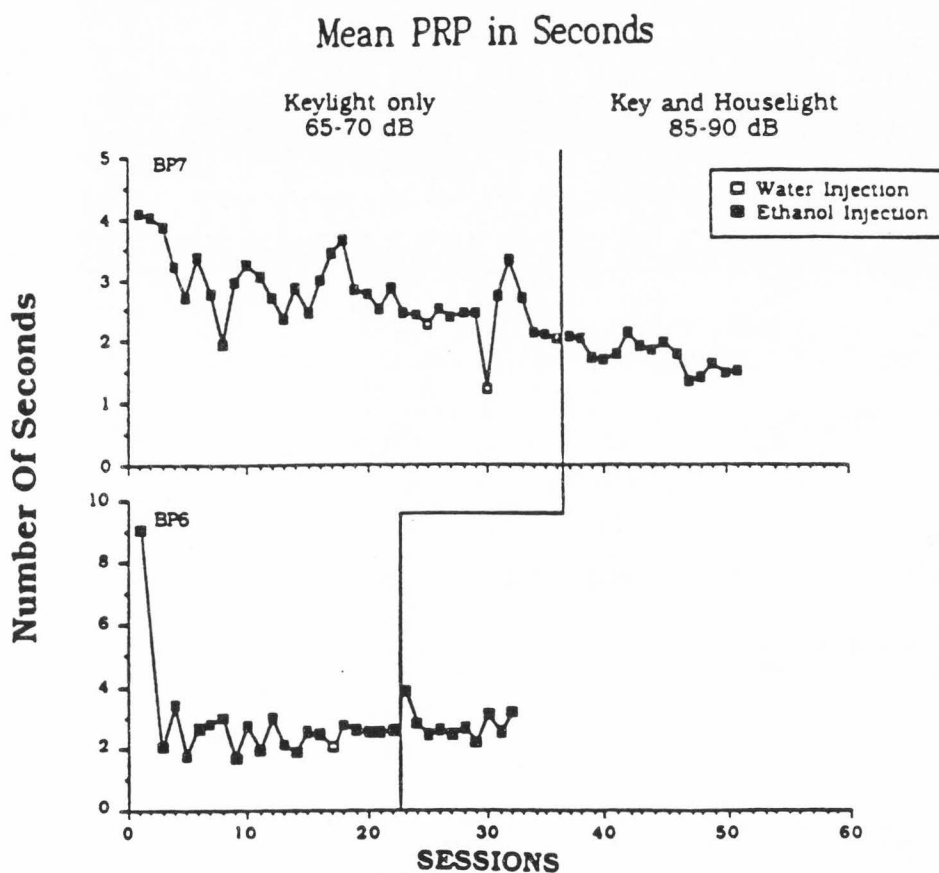


Figure 5. Mean postreinforcement pause (PRP) in seconds on a variable-ratio (VR) 20 schedule of reinforcement for experimental subjects BP-7 and BP-6. Experimental subjects were given an oral injection of ethanol (25% V/V 2.00 g/kg) before each session, as indicated by the solid squares (■). Open squares (□) indicate injection of water; these sessions were intended to probe for tolerance to the ethanol. The left panel indicates mean pause length on the VR-20 schedule of reinforcement with only the keylight illuminating the chamber. The right panel indicates mean pause length on the VR-20 schedule of reinforcement in an altered context. In the modified environment, the chamber was illuminated by both the keylight and houselight, the ambient noise level was increased by 15-20 dB and aluminum foil was draped over the clear sidewalls of the operant chamber.

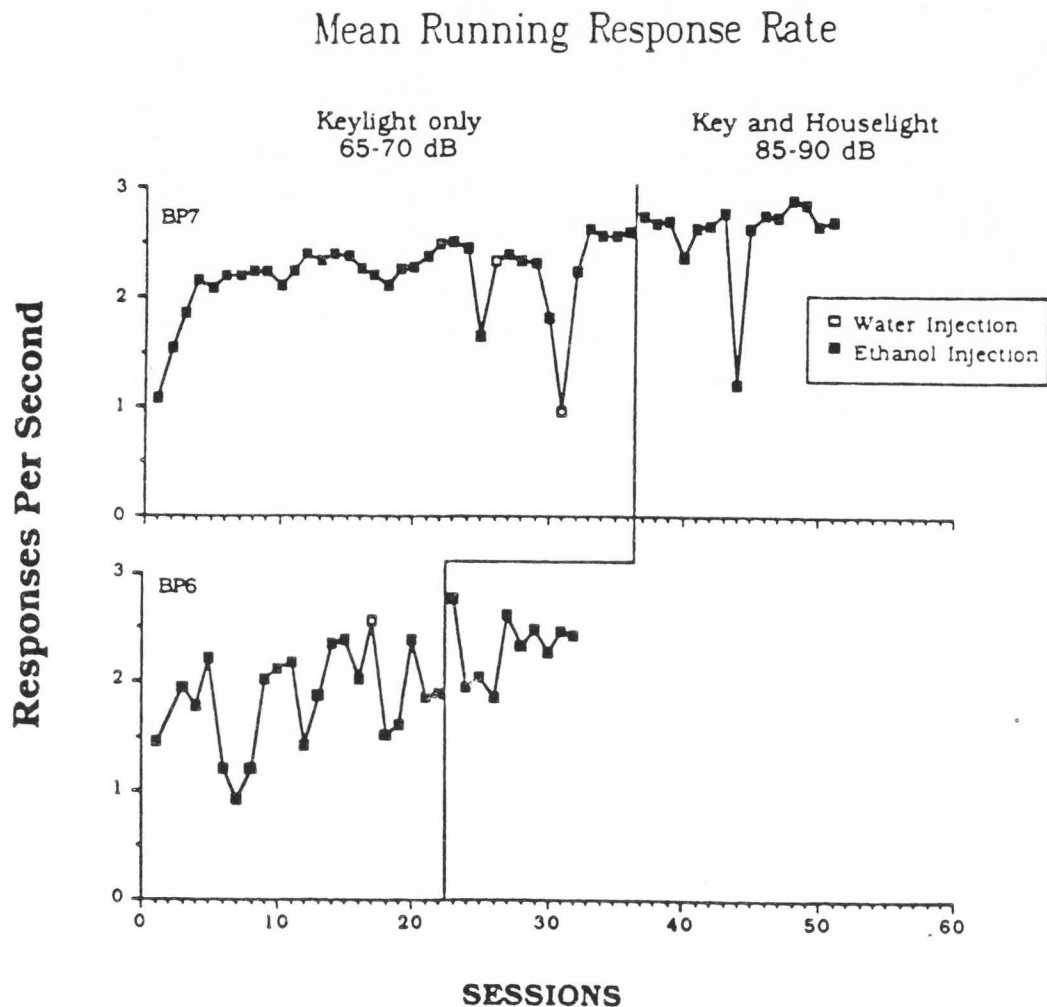


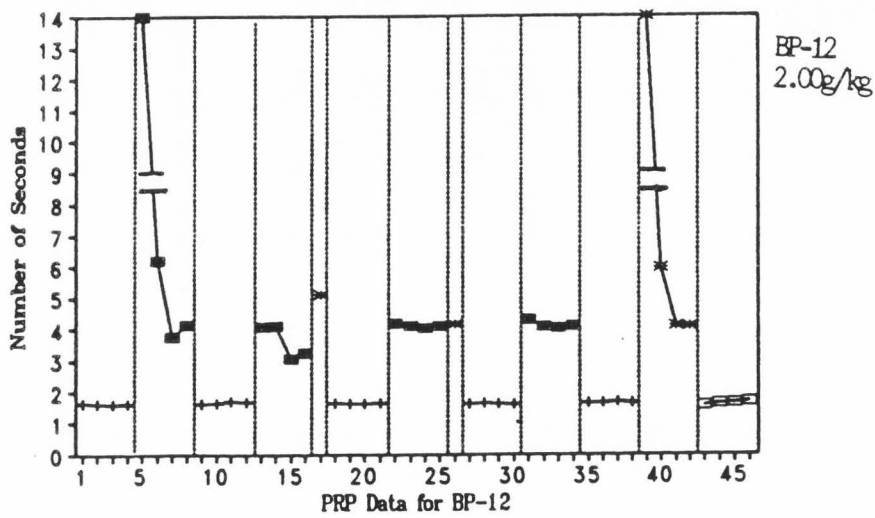
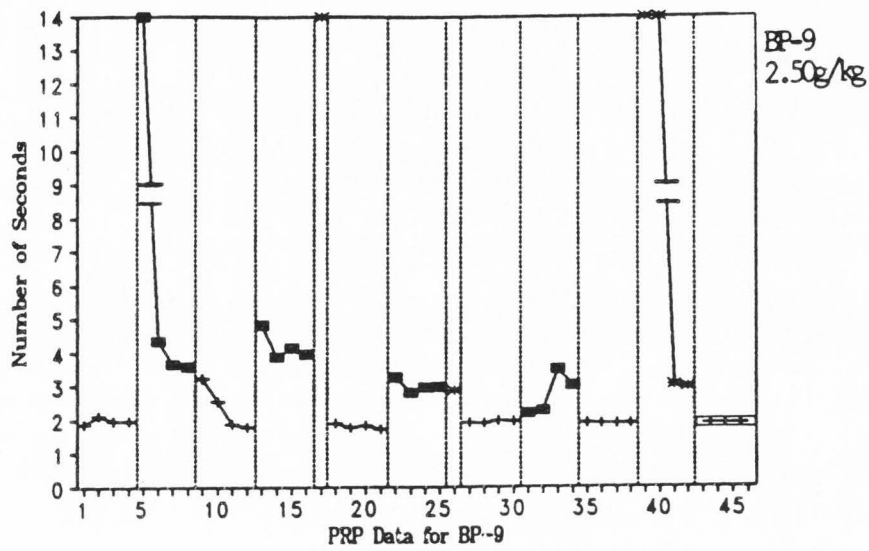
Figure 6. Mean running response rate in responses per second, excluding the postreinforcement pause, on a VR-20 schedule of reinforcement for experimental subjects BP-7 and BP-6. The descriptive labels refer to environmental conditions described in Figure 5 text.

subjects required large daily doses, which were different for every subject.

With these factors present, the results of the second experiment can be seen as showing more meaningful outcomes than experiment one. Experimental data for two subjects, BP-9 and BP-12, are shown in Figures 7 and 8. Using the conditioning procedures described, the results show a sensitivity to the operant-respondent interactions that composed the behavioral tolerance. The postreinforcement pause (PRP) indicated the most sensitivity, again, as seen in Figure 7. The initial four water sessions showed a high degree of stability, which was also true of all subsequent water sessions, for both subjects. The ethanol delivery initially suppressed responding in the first drug session completely, but responding recovered in subsequent sessions, but with slower response rates shown in Figure 8. Across subsequent series of drug sessions, the data in Figure 7 did not indicate a clear pattern of recovery towards the behavior seen after water delivery. Data from the probes for context specific tolerance did tend to show behavioral disruption as a function of ethanol delivery in the water predictive context.

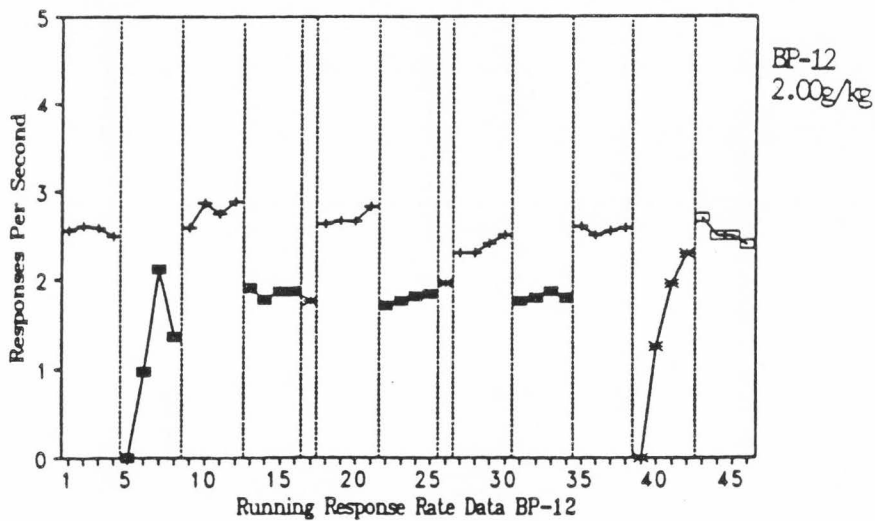
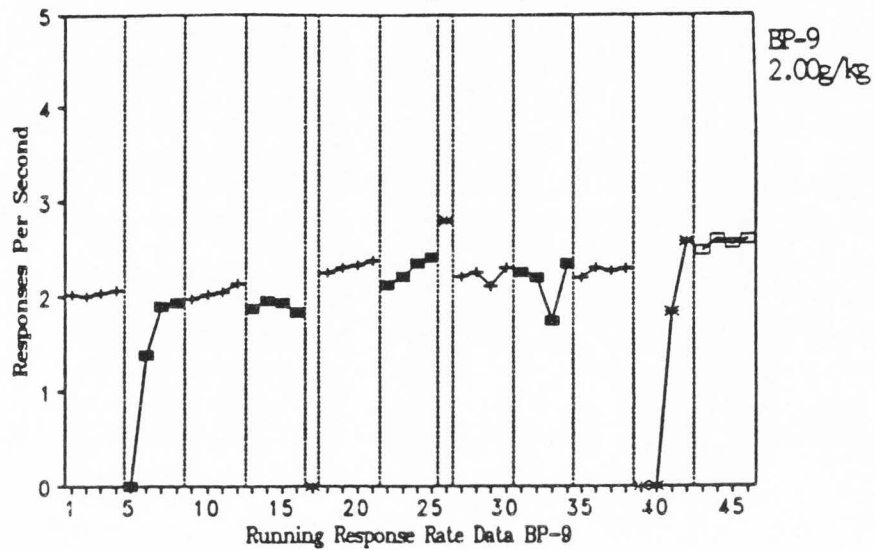
Both subjects' behavior was most affected in the very first probe session. On this occasion, both birds vomited; neither had done so previously. BP-9 did not respond at all in this session; BP-12 did respond but with a significantly longer mean PRP. In the second probe session, there were no major behavioral changes in the dependent variables, but subject BP-9 responded through 5 of the 30 hopper lifts,

Mean PRP in Seconds



—○— Light/Water —■— Darkness/Alc —*— Tolerance Pro —◇— Facilitation Pr

Mean Running Response Rate



—△— Light/Water —■— Darkness/Alc —×— Tolerance Pro —○— Facilitation Pr

Figure 8. Mean running response rate in responses per second on a VR-20 schedule of reinforcement for subjects BP-9 and BP-12. The legend and experimental conditions are described in Figure 7 text.

missing part or all of the available food. During the four consecutive probe sessions, a transient pattern of behavioral change was evident for both subjects. BP-9 was again observed to vomit during the first probe and did not respond during this or the following probe session. BP-12 was also observed to vomit and did not respond during the first probe. In the second consecutive probe, BP-12 responded but with a longer than average mean PRP and slower mean response rates. For the third and fourth probe sessions, both subjects responded at levels comparable to earlier ethanol sessions. They became tolerant in the new context. The response rate data displayed a curve depicting the response recovery across the four sessions, as shown in Figure 9. The subsequent four probes for conditioned facilitated behavior resulting from water delivery in the ethanol context did not evidence any such effect, but were instead very similar to data from other water sessions.

Experiment two PRP data for subjects O-1, BP-13, BP-14, and A-2 are shown in Figures 9 and 10. All four subjects' PRP data showed considerable stability for those sessions preceded by water injections. For those sessions preceded by ethanol delivery, some consistencies and differences can be seen in the subjects' data. Subject O-1, given 6.00 g/kg ethanol, and subject BP-13, given 3.00 g/kg ethanol, showed no significant decrease in mean PRP across consecutive series of ethanol sessions. The only exception to this generalization applies to BP-13, which displayed major increases in mean PRP in the first ethanol series of sessions, but thereafter mean PRPs remained elevated relative to the PRPs following water delivery

Mean PRP in Seconds

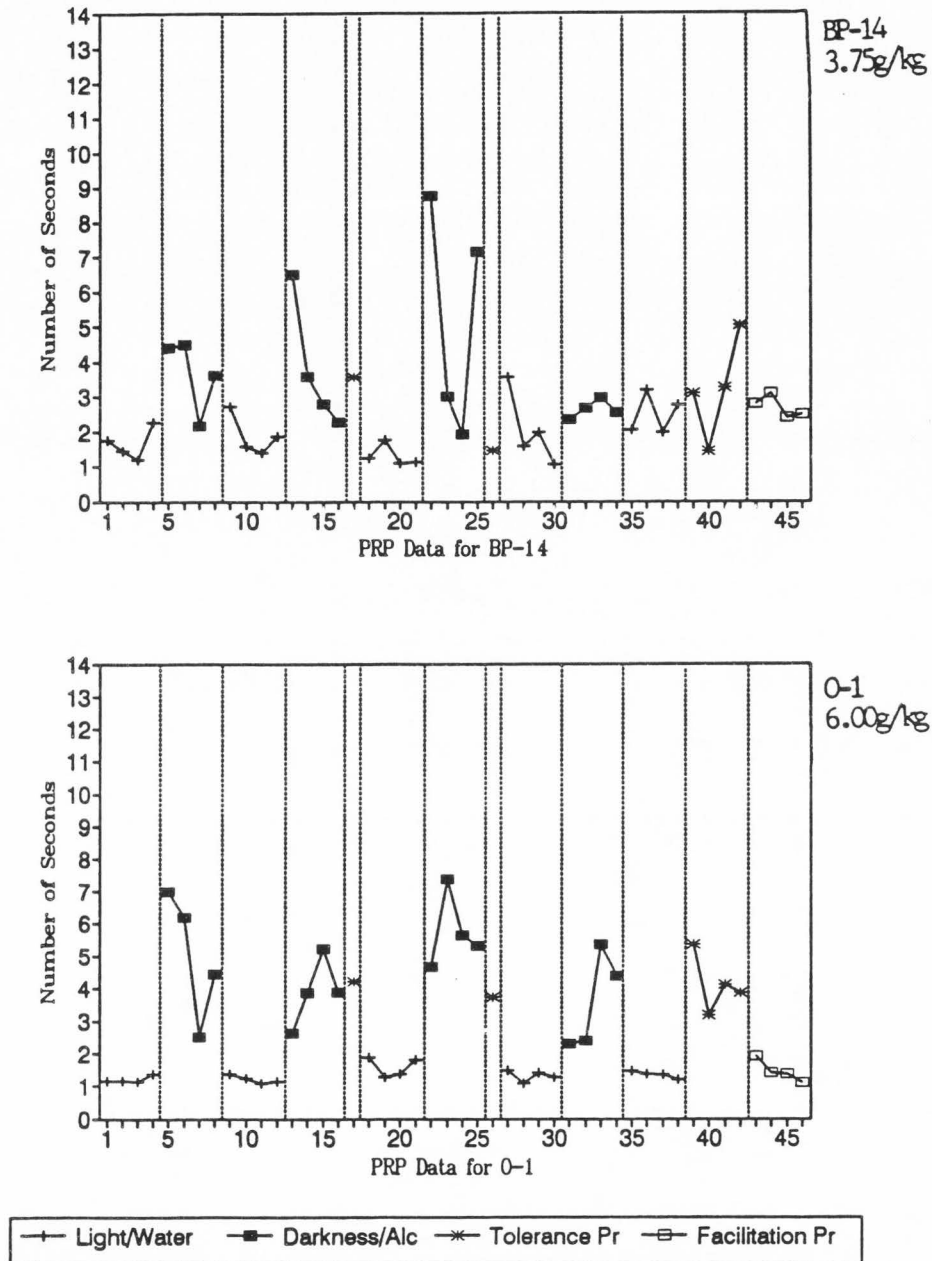
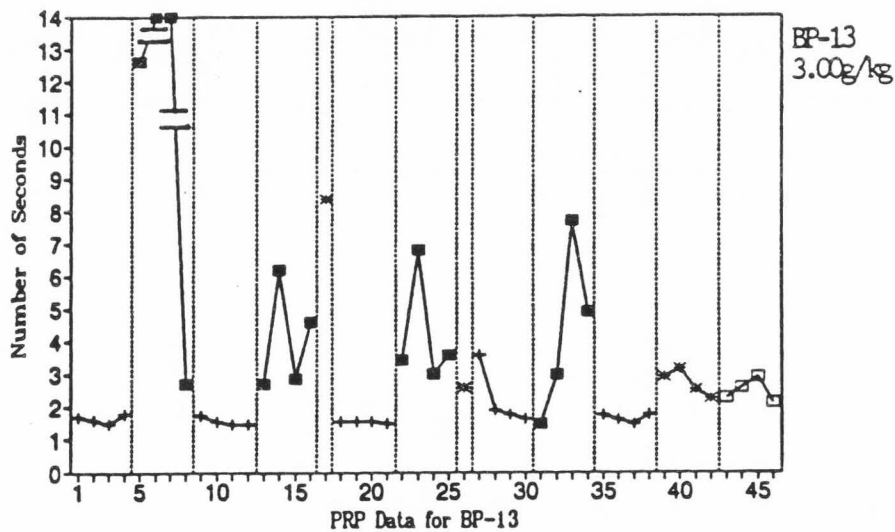
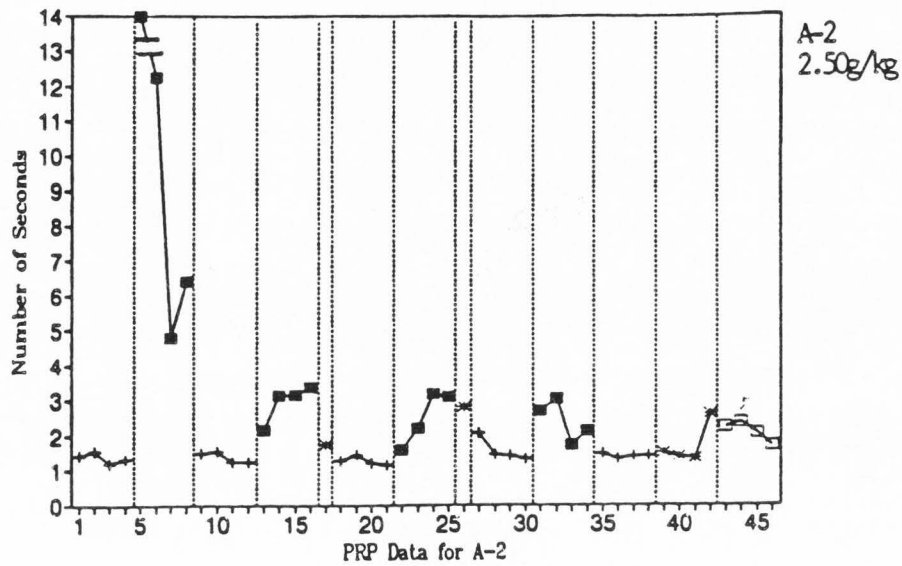


Figure 9. Mean postreinforcement pause (PRP) in seconds for subjects BP-14 and O-1 on the variable-ratio (VR-20) schedule of reinforcement. Session number is indicated along the X axis.

Mean PRP in Seconds



—+— Light/Water —■— Darkness/Alc —*— Tolerance Pr —□— Facilitation Pr

Figure 10. Mean postreinforcement pause (PRP) data in seconds for subjects A-2 and BP-13 on the variable-ratio (VR-20) schedule of reinforcement.

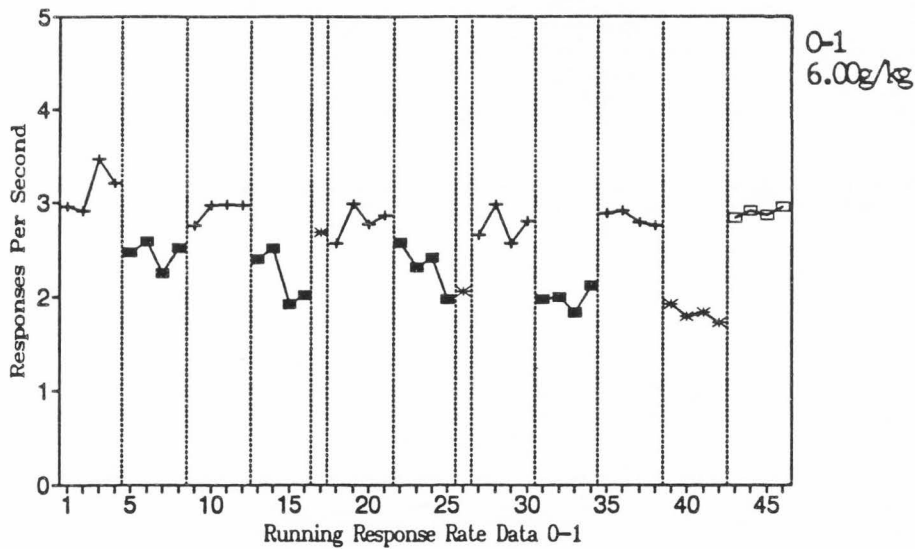
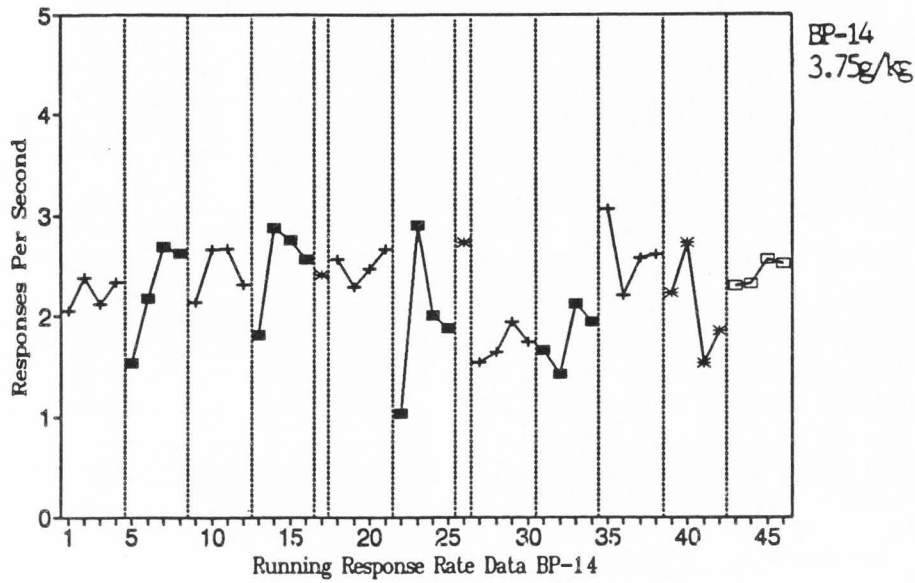
but within a broad range of values. BP-13 also displayed more overall variability in its ethanol data than other subjects. Subject A-2, who received 2.50 g/kg of ethanol, showed a very similar pattern to that of BP-13. Here, the first ethanol sessions resulted in total response suppression followed by a very long mean PRP in ethanol session two, which decreased significantly in ethanol sessions three and four. In each of the following series of ethanol sessions, the mean PRP was significantly lower and in fact, overlapped slightly with the mean PRP values from sessions preceded by water injections. Note that A-2 showed a large decrease in mean PRP between the first and second tolerance conditioning series of sessions. It is as if a large degree of tolerance was acquired between exposures to ethanol. A similar pattern can be seen for subject B-1 and in the data of BP-9 during its second tolerance conditioning experience, to be discussed later. A corresponding increase in mean running response rate can be seen in later figures. Subject BP-14, who received 3.75 g/kg of ethanol, produced a different response pattern in that the mean PRP can be seen as increasing somewhat across the first three series of ethanol sessions. By the fourth series of ethanol sessions, the mean PRP had dropped and came to overlap somewhat with mean PRP values from water sessions.

Of additional interest are the data from the tolerance probe sessions. Again, some consistent trends can be seen. For three of the four subjects, O-1, BP-14, and A-2, in those probe sessions where ethanol was delivered in environments formerly predictive of water, it appeared to make no difference in the value of the mean PRP. All of

the probe sessions fell well within the range of values from typical ethanol sessions. For two of these subjects, BP-14 and A-2, in some probe sessions the mean PRP values were either a minimum or approximated the minimum value for mean PRPs obtained following delivery of ethanol. Subject BP-13 produced a different response pattern in that the first tolerance probe resulted in a large increase in the average PRP which roughly approximated the large increase in mean PRP seen in the very first ethanol sessions. However, this outcome needs to be considered in the face of other observations that this subject displayed considerable variability in its ethanol session data. All other tolerance probes for BP-13 were well within the range of values from typical ethanol sessions. Finally, the data from the sessions wherein water was delivered in the environment predictive of ethanol showed no real difference from other water preceded sessions.

The running response rate data for these four subjects, shown in Figures 11 and 12, with the effects of the postreinforcement pause removed, showed a high degree of behavioral stability in those sessions in which water was delivered. The introduction of ethanol produced response suppression, being the most pronounced in subjects A-2 and BP-13. Subject BP-13 displayed a large degree of variability across the various sessions in which ethanol was delivered, and initially showed a high degree of response suppression in the first four ethanol sessions. The next four ethanol sessions evidenced considerable recovery of response rate, followed by another series of sessions which showed considerable response suppression, to values that approximated the degree of response suppression seen in the initial ethanol series.

Mean Running Response Rate



—+— Light/Water —■— Darkness/Alc —*— Tolerance Pr —□— Facilitation Pr

Figure 11. Mean running response rate data, in responses per second, for subjects BP-14 and O-1. This dependent variable does not include postreinforcement pause (PRP) time.

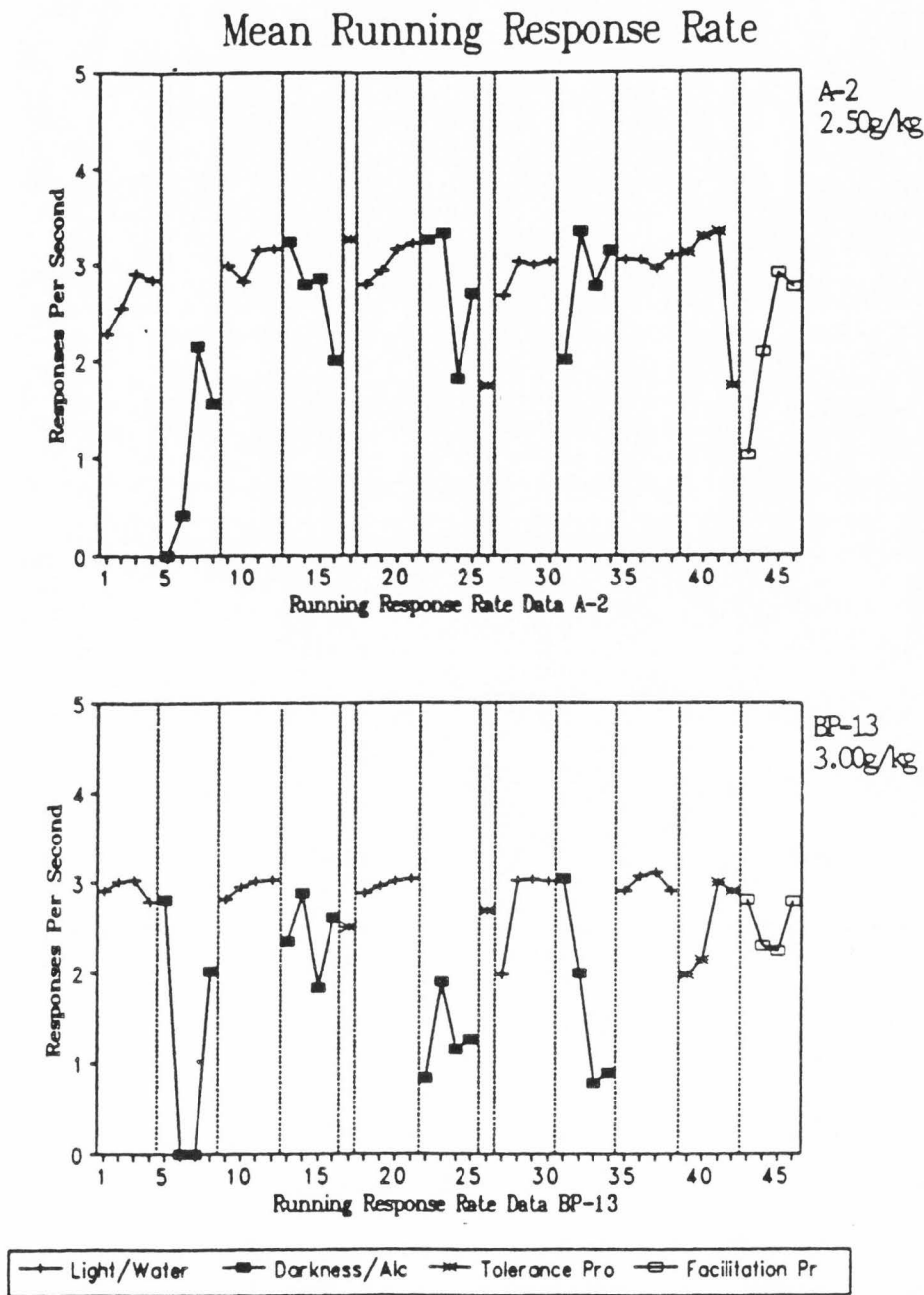


Figure 12. Mean running response rate data, in responses per second, for subjects A-2 and BP-13.

However, the tolerance probes for subject BP-13 did not provide any evidence of context specific tolerance, and in fact showed more consistency than the tolerance conditioning sessions data. The final four sessions in which water was delivered in the ethanol predictive environment cannot be seen as being distinct from other sessions involving water. Subject A-2, after showing the large initial response suppression, displayed considerable response recovery and for all ethanol sessions thereafter, mean running response rate data fell into a consistent but fairly large range of values. This subject's tolerance probes also showed no evidence of context specific tolerance as all the probe values fell within the range of values from other ethanol sessions. A possible exception was the observation that two of the tolerance probe data points, probe #2 and the final tolerance probe of the four consecutive probe sessions, constituted the minimum values of the ethanol session range of values. But both of these values were well above the degree of response suppression found in the first four tolerance conditioning sessions. Also, the facilitation probe sessions did not represent distinct data trends as seen with other birds.

Subject BP-14's data did not show a large degree of response suppression across any of the ethanol sessions, either tolerance conditioning or tolerance probe sessions. All of the tolerance probe values for the subject fell within the range of data points obtained from typical ethanol sessions.

Subject O-1's data for this parameter were very similar to the performance of BP-14 in that there was no large amount of response suppression from ethanol sessions. In general, considerably more

stability could be seen in the ethanol session data for O-1 and BP-14 than for the other two subjects. None of the tolerance probe data points showed evidence of context specific tolerance for O-1. It appears that for O-1, the difference between running response rate following water delivery relative to ethanol actually increases over the course of all sessions. It is impossible to call this decrease in response rate following ethanol injection an indication of tolerant behavior. Finally, those sessions in which water was delivered in a context predictive of ethanol were indistinguishable from other water sessions for these dependent variables. If a conditioned facilitation effect was present, either it was weak and/or the dependent variables were not sensitive to its effects.

The data from the operant baseline sessions are shown in Figures 13 and 14 for the mean PRP, and Figures 15 and 16 provide the data regarding mean running response rate. As described earlier, the subjects simply performed on the same schedule of reinforcement alternating over the same environment, in the absence of any injection for a total of 16 sessions. Again the mean PRP data show the most variability, but this variable is much more stable than earlier experimental sessions. Little can be said from these data other than that the changes from context to context did not produce functional differences in the dependent variables.

Overall, the data of the second experiment did not provide much in the way of clear evidence for context specific tolerance. It appears here that once tolerance was acquired, it remained more or less stable

Baseline Data

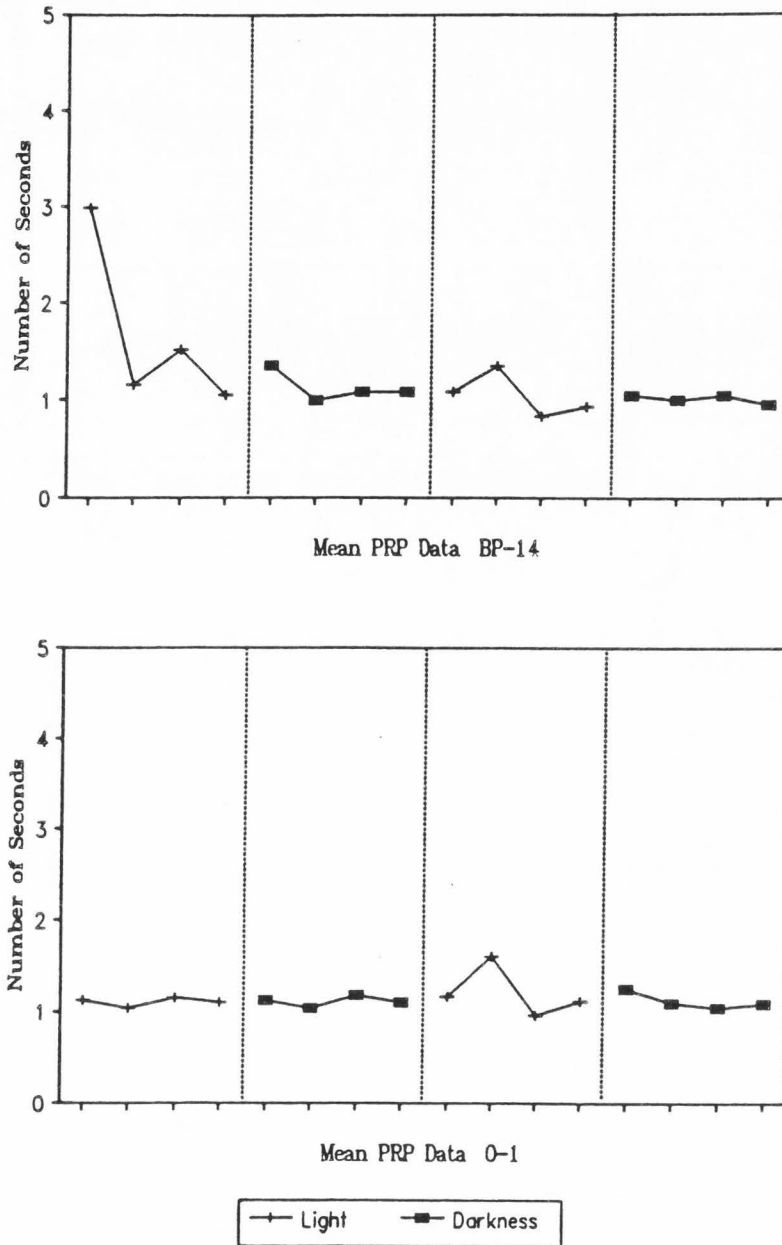


Figure 13. Baseline mean postreinforcement pause (PRP) data for subjects BP-14 and 0-1. Data shown by a plus symbol (→) indicate sessions in which the houselight was illuminated. Filled squares (■) indicate sessions in which the chamber was illuminated by only the blue response keylight. No injections were given prior to any sessions in baseline. Session numbers are indicated along the X axis.

Baseline Data

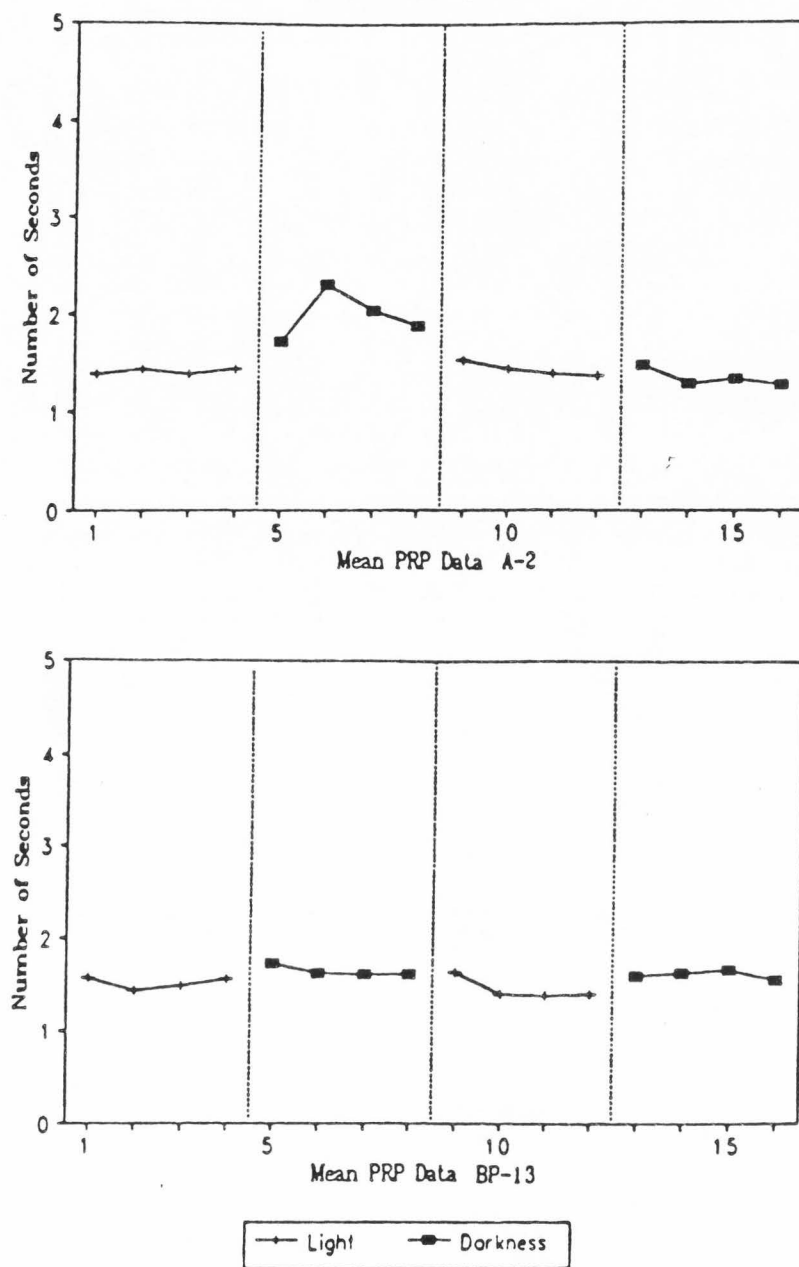


Figure 14. Baseline mean postreinforcement pause (PRP) data in seconds for subjects A-2 and BP-13.

Baseline Data

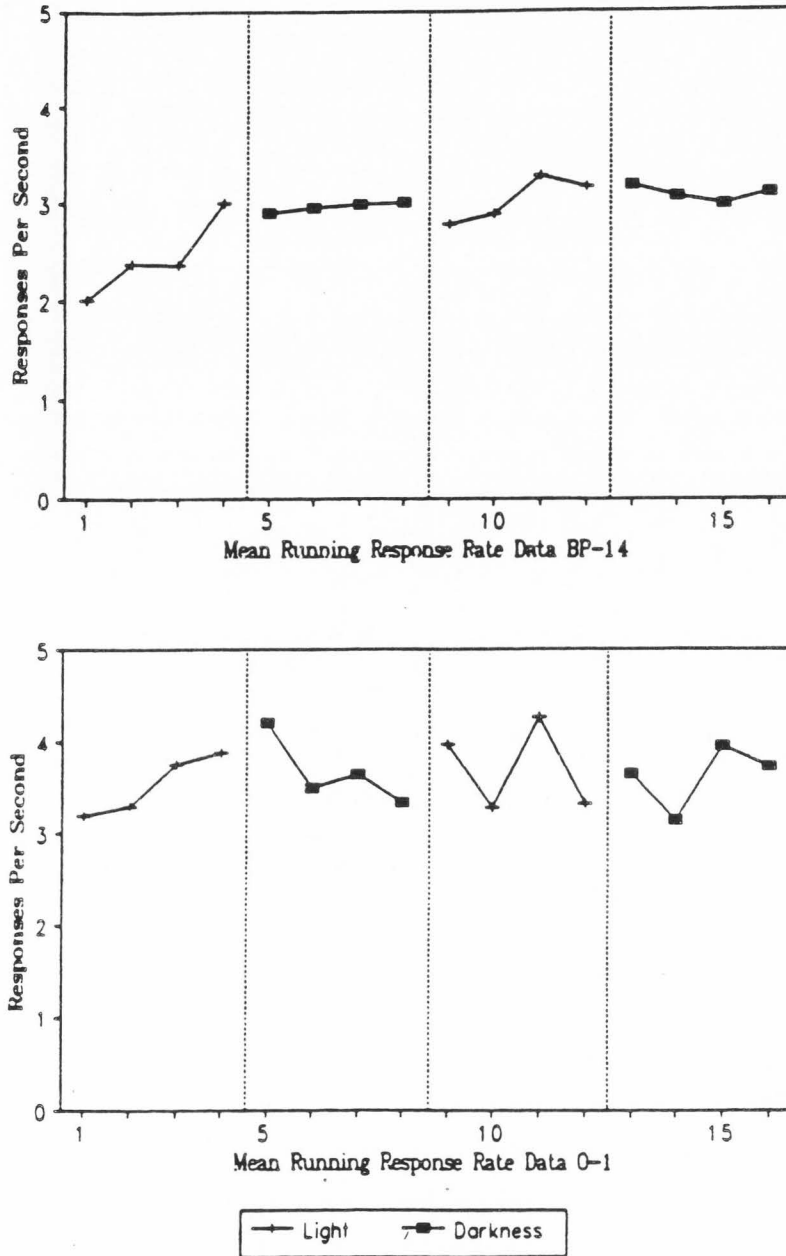


Figure 15. Baseline data for the dependent variable mean running response rate, excluding PRP time, in terms of responses per second. Data shown is for BP-14 and O-1.

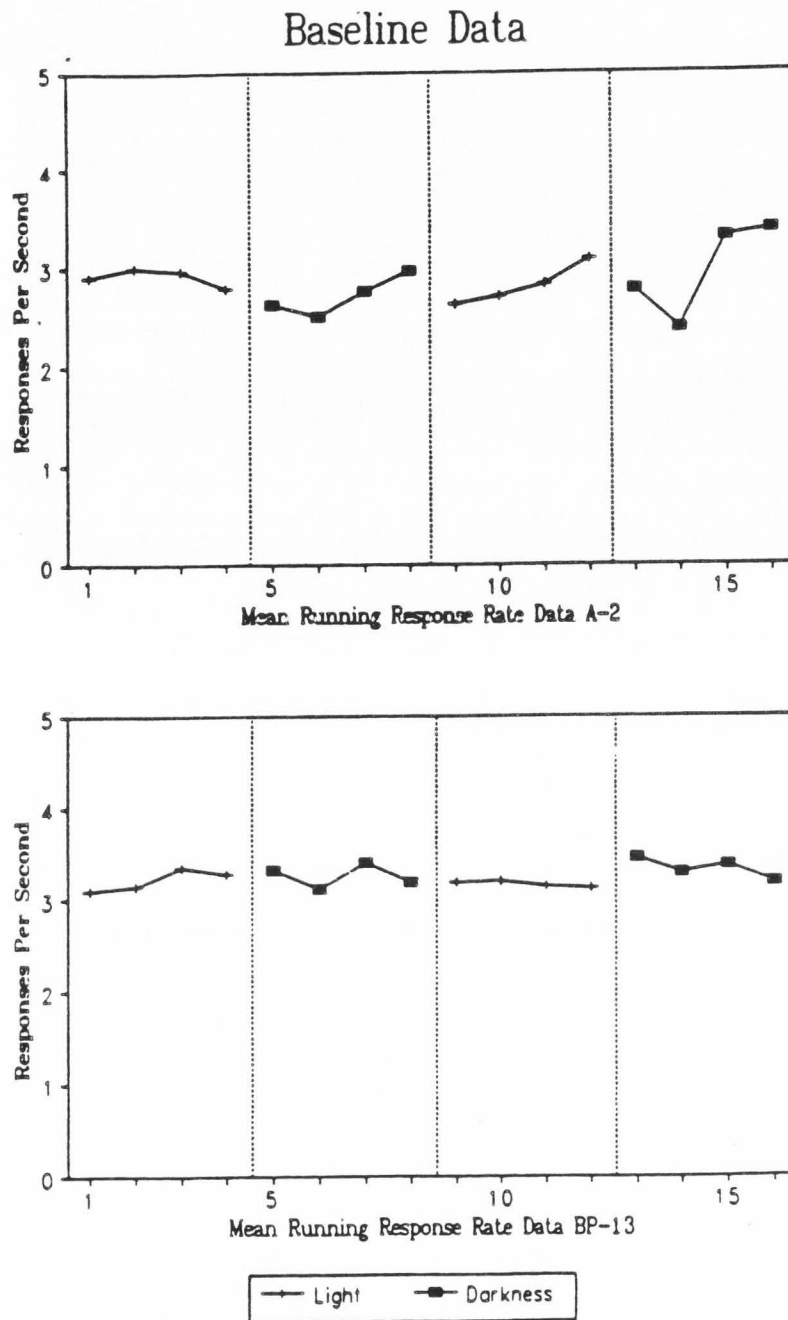


Figure 16. Baseline data for mean running response rate in responses per second for subjects A-2 and BP-13.

across different contexts for most subjects. However, the degree of tolerance found here is limited at best. It might be better to say that once the initial disruption of behavior due to ethanol is no longer present, behavior remained relatively stable. This initial disruption is not strongly present for all subjects. Namely, BP-14 and O-1 do not show the clear perturbation of behavior that A-2 and BP-13 show. And this outcome could lead one to conclude that while respondent and operant processes interact to produce tolerance, evidence could be seen that either process could overwhelm the other, under appropriate antagonistic conditions. Other conclusions are also possible. One possibility is that the contexts were not "different enough" for all subjects to cause a failure of context dependent tolerance. While lighting, noise levels, and the physical appearance of the chamber were altered, the same blue response key was a constant stimulus across all sessions. It is possible that this unchanging stimulus allowed for context specific tolerance to be present in all sessions, including the tolerance probe sessions. In that case, the tolerance probes were, in fact, no different to the subjects with the possible exception of BP-13's first tolerance probe for the mean PRP parameter. As a result, no strong evidence was found for context specific tolerance being absent because the respondent tolerance process was still viable.

To conduct a functional analysis of the possibility that both operant and respondent processes were still in effect in the tolerance probe sessions, an additional experiment was conducted. The functional analysis of experiment three attempted to sort out the conditions under

which operantly conditioned tolerance would be primarily in effect from the conditions under which respondently conditioned tolerance would be in effect. The simplest way to pursue a functional analysis of the question at hand was to run additional subjects with still further differences being present from context to context, that is to include a change in the stimulus present on the response key. Higgins et al. (1989) stated that increasing the role of discriminative control by exteroceptive stimuli should diminish the extent of behavioral changes produced by a drug. Based on this logic, the experimental changes proposed next were expected to facilitate tolerance due to either conditioning process. Again, individual subject dosages had to be arrived at, but a smaller range of doses was found to be needed, ranging from 3.00 to 4.00 g/kg of 25% V/V ethanol. The actual doses were, for subject A-4, 3.00 g/kg; subject D-2, 3.25 g/kg; subject B-3, 3.75 g/kg; and subject D-1, 4.00 g/kg.

Experiment Three

The results of experiment three again showed that mean PRP data was the most sensitive to the experimental manipulation, as can be seen in Figures 17 and 18. For all four subjects, the water sessions showed a high degree of stability, and most values fell within a relatively narrow range of values. The initial ethanol sessions showed considerable variability for all four subjects, but with some other trends being apparent in the data. Subjects D-1 and D-2 did not show a trend across consecutive series of ethanol sessions indicative of significant tolerance development; it could be seen for both subjects that a greater degree of response suppression was present in later

Mean PRP in Seconds

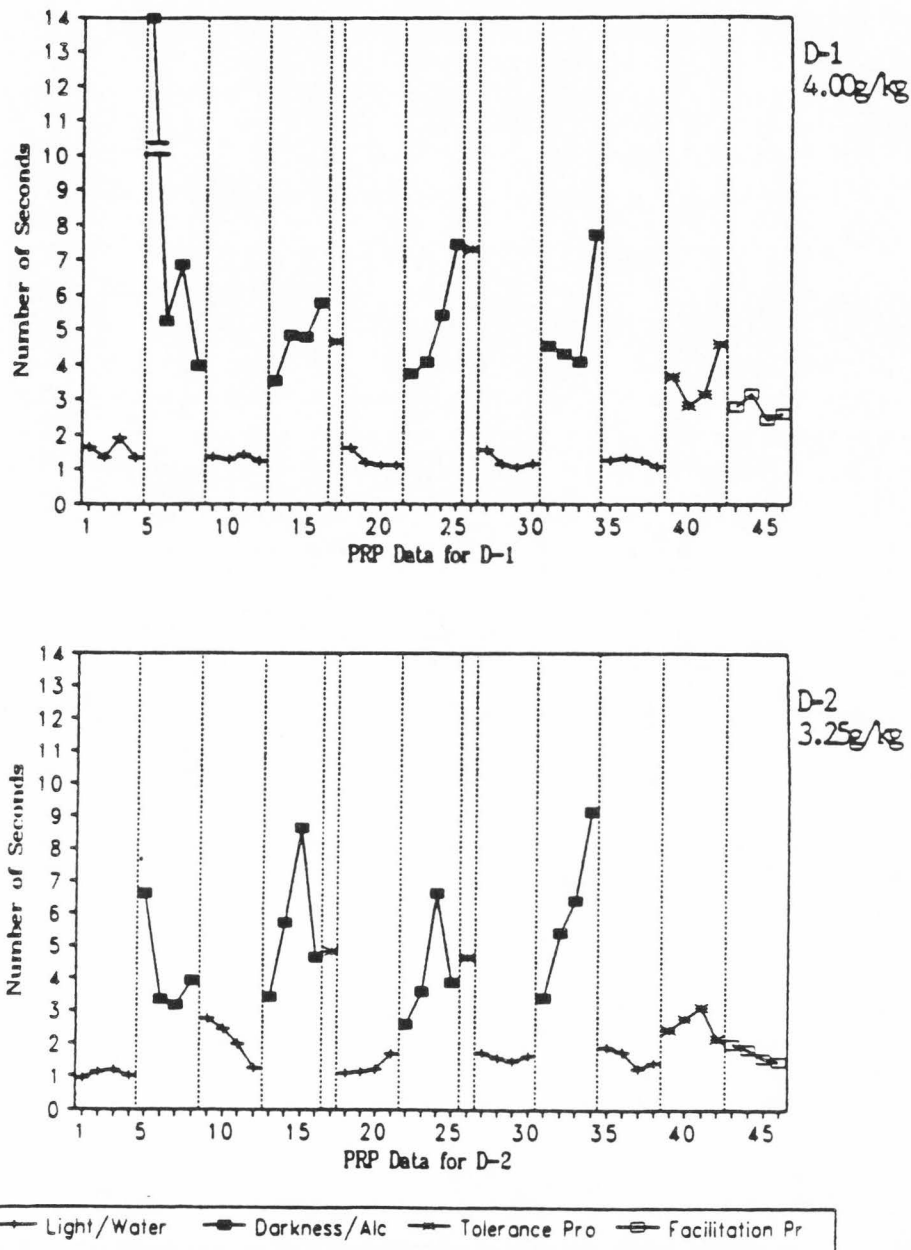
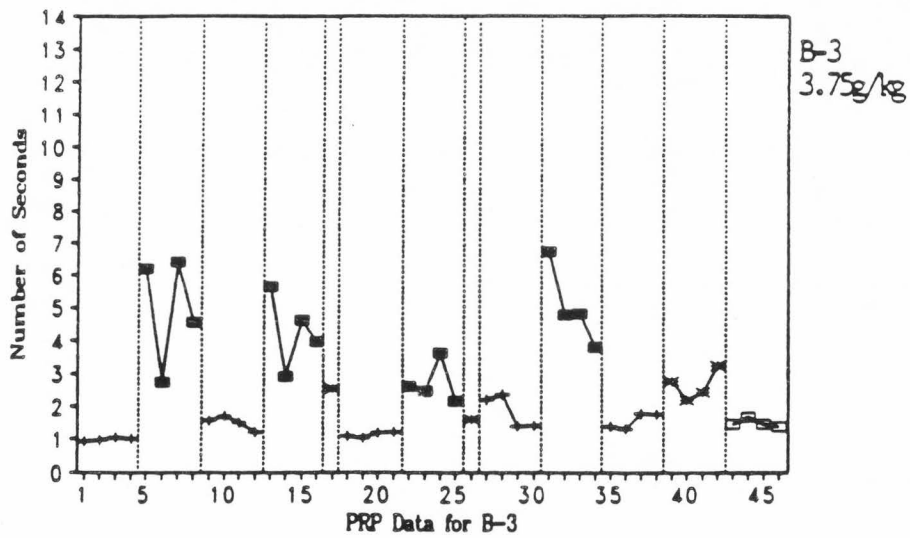
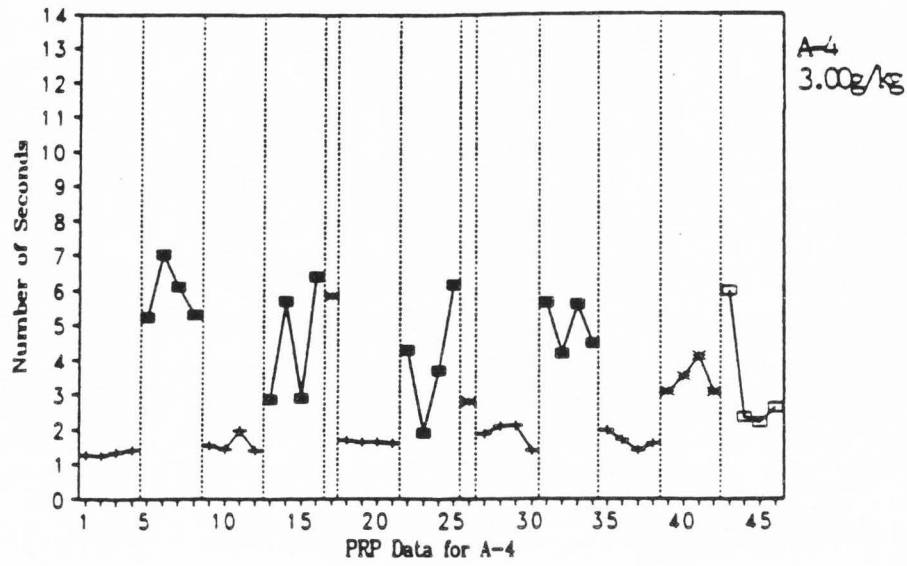


Figure 17. Mean postreinforcement pause (PRP) data in seconds for subjects D-1 and D-2 on the VR-20 schedule of reinforcement. Data shown by a plus symbol (+) indicate sessions preceded by water delivery, blue response keylight, houselight illumination and increased noise levels. Data shown by filled squares (■) indicate sessions preceded by ethanol delivery, and in which the chamber was dark except for a red keylight and ambient noise levels. Asterisks (*) indicate sessions in which ethanol was given in the water predictive context, and open squares (□) indicate sessions in which water delivery occurred in the ethanol context. Sessions are indicated on the X axis.

Mean PRP in Seconds



—○— Light/Water —■— Darkness/Alc —▲— Tolerance Pro —◇— Facilitation Pr

Figure 18. Mean postreinforcement pause (PRP) data in seconds for subjects A-4 and B-3.

ethanol sessions than in earlier ones. An exception to that generalization is that the initial ethanol session for subject D-1 resulted in complete response suppression. Except for this extreme data point, the maximum value for PRP length occurred in later ethanol tolerance conditioning sessions; for subject D-2, the most response suppression occurred in the final session of the last ethanol session. In fact, an increasing trend was evident in all four sessions of this last ethanol series. A fifth data point from an additional ethanol session which was not shown on the graph indicated that the increasing trend did not continue but instead declined to a value comparable to other ethanol session data. D-2's data in Figure 18 show an interesting trend over the course of the tolerance conditioning sessions. For the last three series of these sessions, the data fall into the pattern of an inverted U. For the very last series, the ungraphed fifth data point is needed to form the inverted U pattern. The significance of this pattern is not immediately apparent and this pattern is not evident in the data of any other subject.

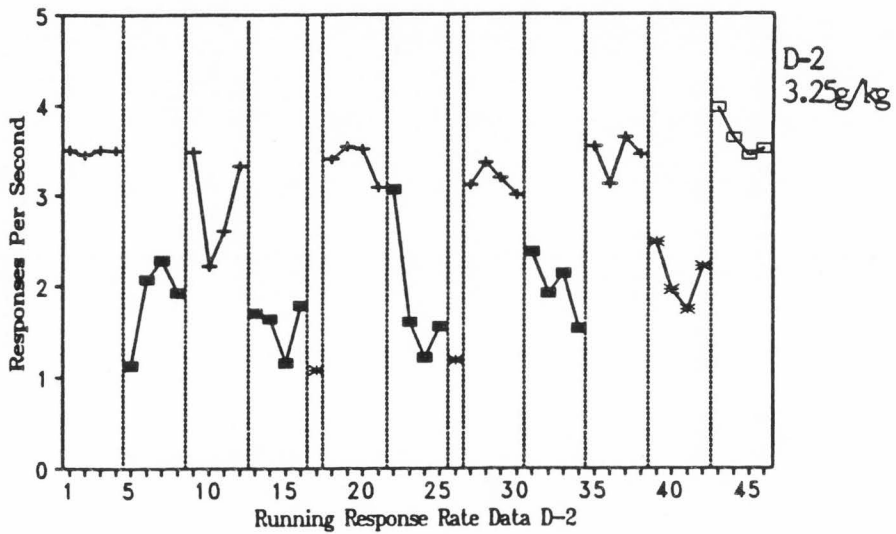
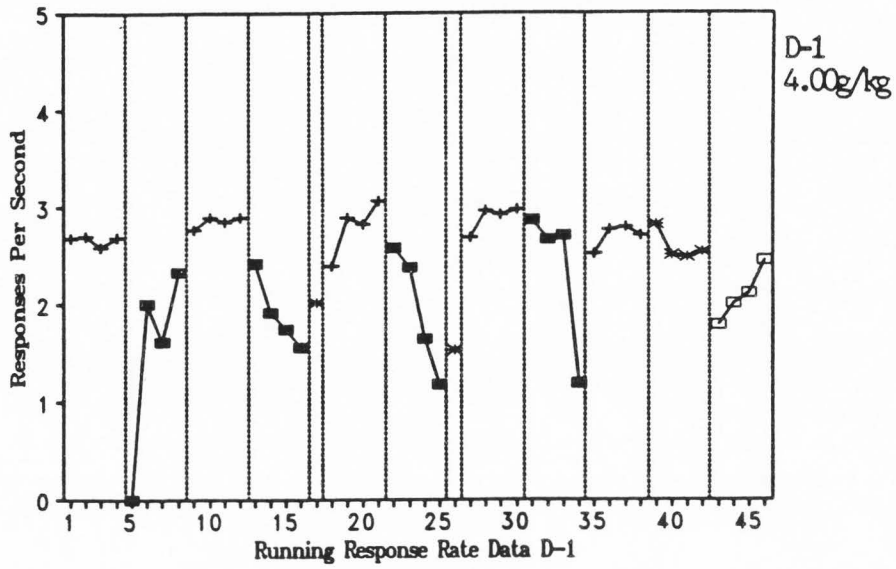
On the other hand, the ethanol tolerance probe sessions for these subjects all fell within the range of values from the tolerance conditioning sessions. The experimental sessions in which water was delivered in the midst of conditions predictive of ethanol were, for the most part, indistinct from other water sessions. Subjects A-4 and B-3 also showed a high degree of consistency across different water delivery sessions. For those sessions in which ethanol was delivered, considerably more variability was found in PRP values. Both of these subjects' data also appeared to show a slight trend of decreasing PRP

values except for an increase for both birds in the fourth series of tolerance sessions. But again for both birds, all of the data points for the tolerance probes for context specific tolerance fell within the range of values from ethanol sessions that showed response recovery relative to the initial ethanol sessions. Finally, the data from the last four sessions in which water was delivered in an ethanol paired context were, with the exception of one data point for A-4, not different from other water session data.

The data for the running response rate dependent variable, shown in Figures 19 and 20, showed some apparent trends. The data from water sessions, including sessions in which water was delivered in the ethanol context, were very stable and consistent. The data from tolerance conditioning sessions fell within two general trends. Subjects D-1 and D-2's data showed some degree of increasing response recovery across consecutive tolerance sessions, but with a high degree of variability. All of the tolerance probe data points for D-2 fell within the range of the values from other ethanol sessions. While it can be said that subject D-2 showed a slight increasing trend in its running response rate data, the subjects' first and second tolerance probe data points represented minimum or near minimum points of response rate. Other tolerance probes fell within the range of values from other ethanol paired sessions.

For subjects B-3 and A-4, the data from later tolerance conditioning sessions relative to earlier tolerance conditioning sessions did not show a strong trend of response rate recovery but instead generally showed a stable direction, falling within a similar

Mean Running Response Rate



Light/Water
 Darkness/Alc
 Tolerance Pro
 Facilitation Pr

Figure 19. Mean running response rate data excluding PRP time in terms of responses per second for D-1 and D-2.

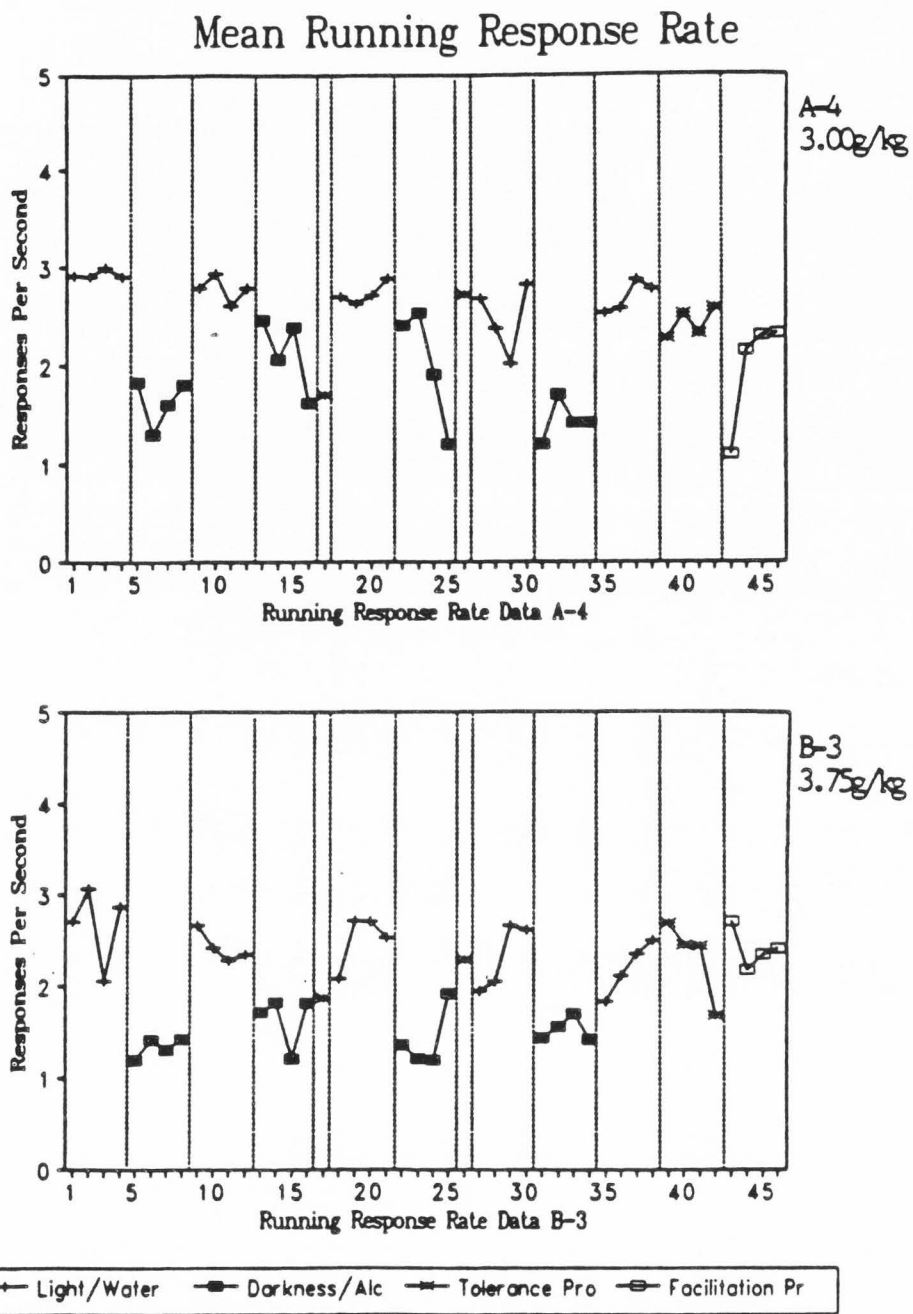


Figure 20. Mean running response rate data in responses per second for subjects A-4 and B-3.

range of values. The data from the tolerance probe sessions were noteworthy because they represented, in the case of a few data points, the maximum or near maximum values of running response rate. Subject B-3 showed a high value in terms of response rate recovery for probe session two, and for the first three sessions of the four consecutive sessions of tolerance probes. Some of these data points approximated or exceeded running response rate values from water sessions. For subject A-4, tolerance probe two represented a value approximating data from water sessions.

Overall, the results of this experiment tended to solidify the conclusion that once the restricted tolerant behavior developed that was seen here, it remained more or less constant across different contexts. This experiment also served to clarify and replicate the results of the second experiment by having represented a more adequate test of operantly conditioned versus repondently conditioned tolerance. Here the contexts were made even more different but the outcomes were very similar to the second experiment. While some data could be taken to indicate a loss of tolerance to some degree with context shifts, again nothing approaching the behavioral changes seen with the data of the two subjects BP-9 and BP-12 could be found here.

Even with the greater differences across contexts, little evidence for a "context effect" was found. As to why this outcome occurred again, the most straightforward answer would be to refer to the control of the reinforcement schedule. The operant schedule would favor behavioral momentum and regularity across contexts. In the probes for context specific tolerance, the main source of behavioral

variation would be from the internal drug state. All of the contextual stimuli had been experienced prior, all except for the internal drug stimuli in the presence of a nonpredictive context. Higgins et al. (1989) again stated that increasing the control of behavior by exteroceptive stimuli (by adding to its saliency) would decrease the control of behavior by drug stimuli. That appears to encapsulate the observed effects here.

Another question that could be asked here is why there is no clear evidence for behavioral tolerance to the ethanol for much of these subjects' data. Obviously, it could be due to a number of uncontrolled variables, such as the sex, health, and histories of these subjects. Associated with these variables is the possibility that tolerance would have been seen after a greater number of ethanol exposures than conducted here. In the very first experiment, EP-7 showed a gradual decrease in mean PRP over the course of over 30 consecutive ethanol preceded sessions. Subject EP-6 showed an initial large decrease in mean PRP but thereafter showed no clear decrease in mean PRP over approximately 20 consecutive tolerance conditioning sessions. Tolerance will clearly develop at different rates for different subjects due to a number of factors. Also, if these subjects had to rely on the reinforcement schedule for all their food as in a closed economy, tolerance might have more clearly emerged. As it were, the subjects were maintained at roughly 80% of their free feeding weights by post session feedings.

Finally, the results of the behavioral baseline sessions are shown in Figures 21-24. As is evident from the graphed data, the subjects'

Baseline Data

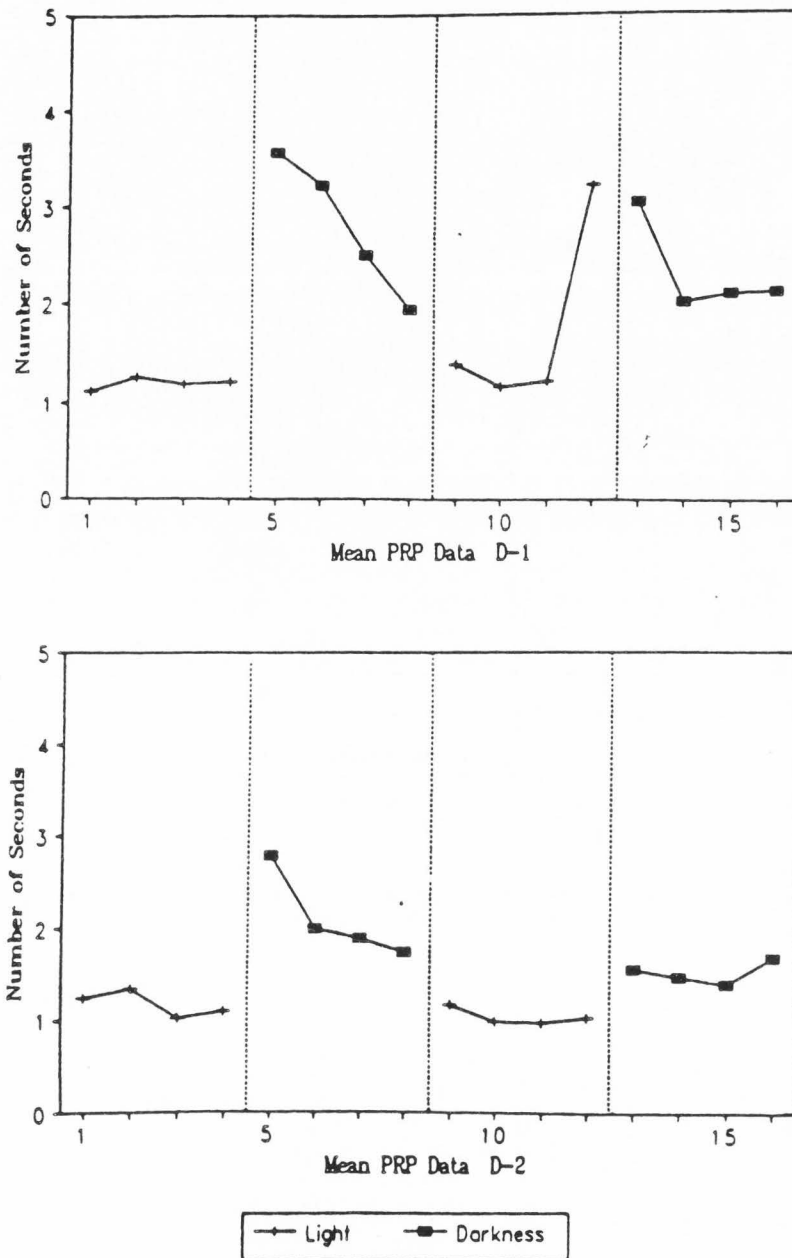


Figure 21. Baseline mean postreinforcement pause (PRP) data in seconds, for subjects D-1 and D-2. Data points indicated by plus symbols (—+) are for sessions in which the chamber was illuminated by the houselight, red keylight, and increased noise levels. Filled squares (—■) indicate sessions in which the chamber was illuminated by the red keylight alone. No injections were given prior to baseline sessions on the VR-20 schedule of reinforcement.

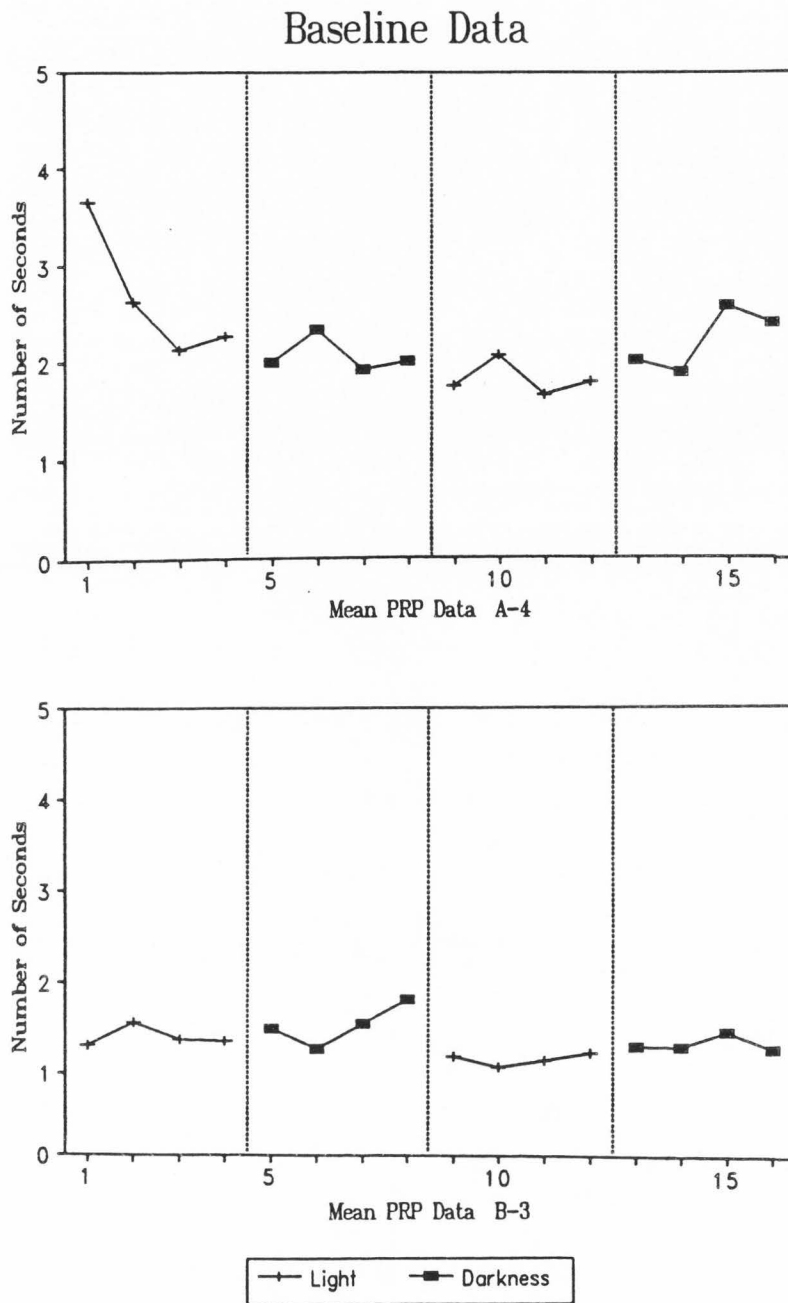
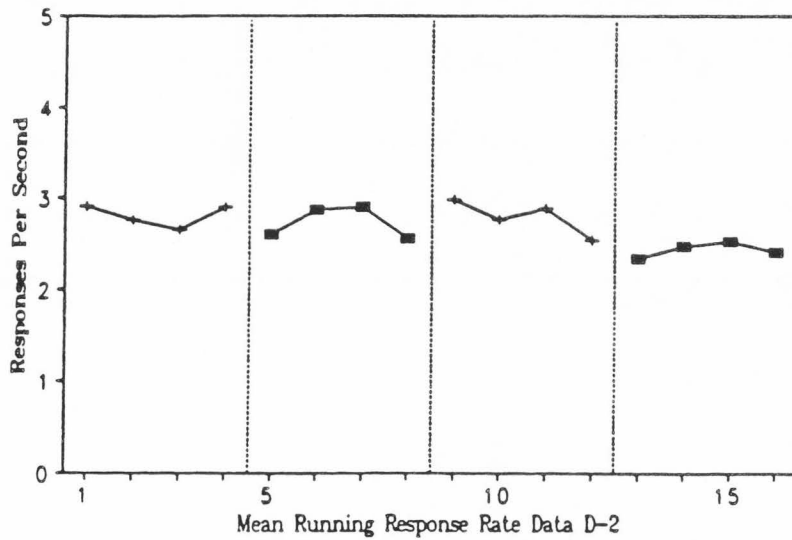
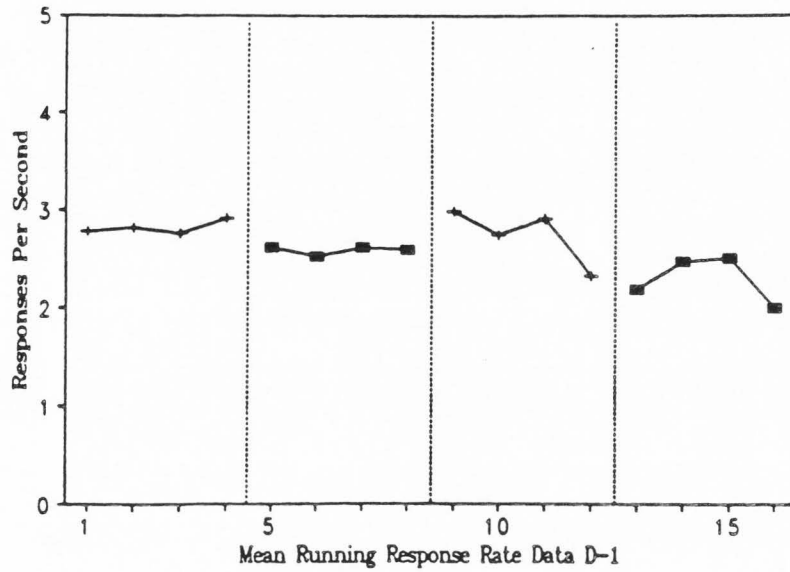


Figure 22. Baseline session data for mean postreinforcement pause (PRP) in seconds from subjects A-4 and B-3.

Baseline Data



—△— Light —■— Darkness

Figure 23. Baseline mean running response rate data in responses per second for subjects D-1 and D-2. As before, the PRP time is not included in the calculation of this dependent variable.

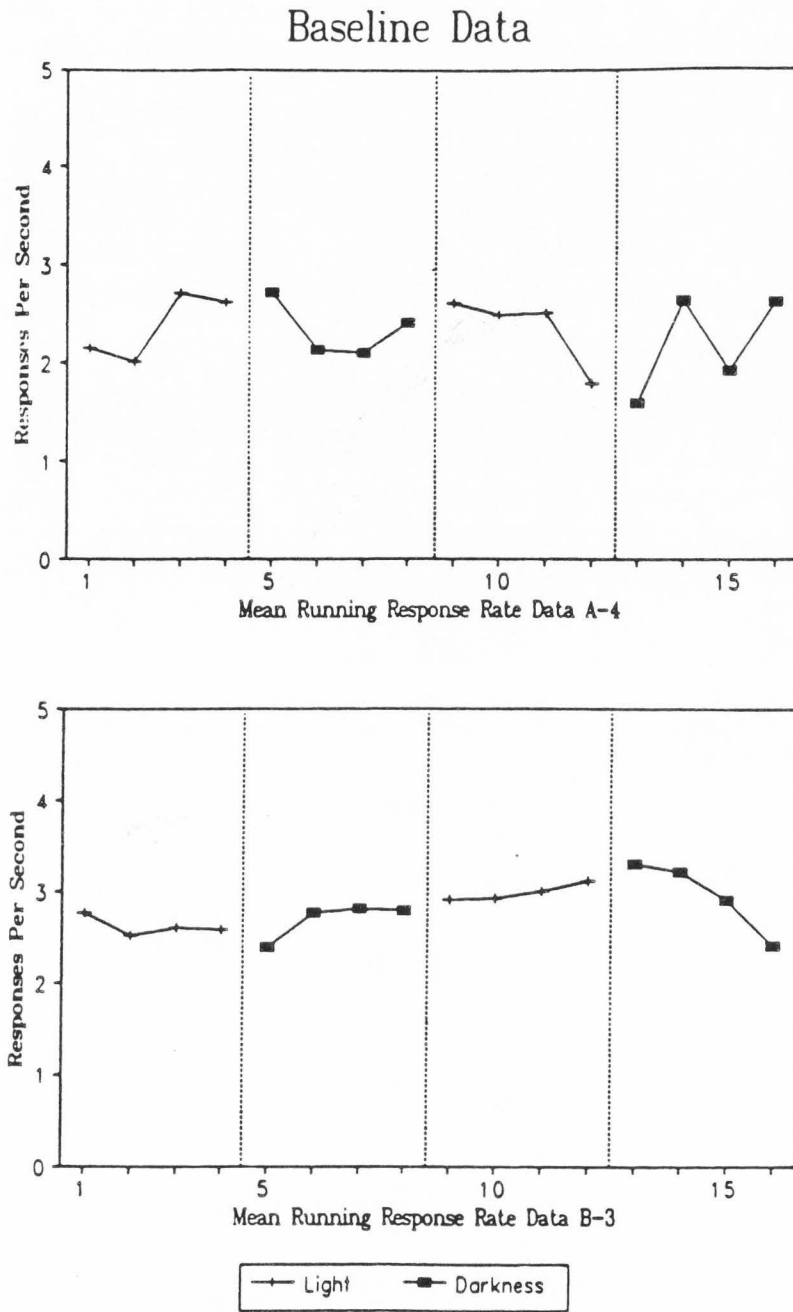


Figure 24. Baseline mean running response rate data in responses per second for subjects A-4 and B-3.

behavior tended to show stability for all three dependent variables, across the different contexts. Subject D-1, however, showed more fluctuations than the other subjects, seen mostly in the mean PRP data, Figure 21. But considering that by this point the subjects were very familiar with the contextual manipulations, a high degree of stability in the absence of any injected agent was not surprising.

Experiment Four

The results of the final experiment were not surprising in light of the outcomes obtained so far. The last experiment was intended to add clarification to the interaction between the operant and respondent processes by having used latent inhibition or preexposure to a potential CS to limit that stimulus's efficacy to serve as a CS. This was done by putting the subjects of this experiment through a behavioral baseline series of sessions prior to tolerance conditioning sessions. Since little evidence had emerged to argue for any hegemony by a respondently conditioned tolerance under conditions closer to what could be considered optimal, manipulation to hinder the development of respondent tolerance also produced little evidence for its effects. However, all of the experimental subjects so far had shown a much different response pattern to the ethanol in that a larger dosage was required to produce an actually decreased behavioral change, relative to the two experiment two subjects. The differences in dosage ranged from .50 g/kg more to as much as three times the dosage given subjects BP-9 and BP-12. For two of the four subjects of the final experiment, a similar picture was seen in that subject B-2 required a dosage of 6.00 g/kg and S-1 required a dosage of 3.50 g/kg of the ethanol to

produce the specified behavioral changes. The remaining subjects, B-2 and A-3, both required approximately 2.25 g/kg of ethanol to cause behavioral change significant enough to meet the experimental criteria. Based on the earlier data, for subjects whose behavior is suppressed by lower doses of ethanol, the respondent process showed a strong influence countermanding an operant schedule of reinforcement for tolerant behavior. Based on this conclusion, latent inhibition should tend to negate or minimize the influence of the respondent process in such subjects.

The results of the last experiment supported this conclusion. The results are presented in Figures 25-28 for the initial baseline sessions and later experimental sessions are shown in Figures 29-32. As can be seen in the graphs of the baseline data, there was considerable consistency for all measures for all subjects with some exceptions. Subject S-1 showed the most variability with all three measures showing some degree of change, within the first four sessions, as in Figures 26 and 28. The initial exposure to the altered context, with dark chamber and red response key, produced an increase in mean PRPs and slowed response rates for all subjects, but the variations fell within a small range. These behavior changes were absent for the most part, in the second exposure to the dark and red key context.

The first four experimental sessions in which water delivery preceded the bright and noisy context were also essentially lacking in significant response variation. The introduction of ethanol at the requisite dosage produced major increases in PRP duration for all

Baseline Data

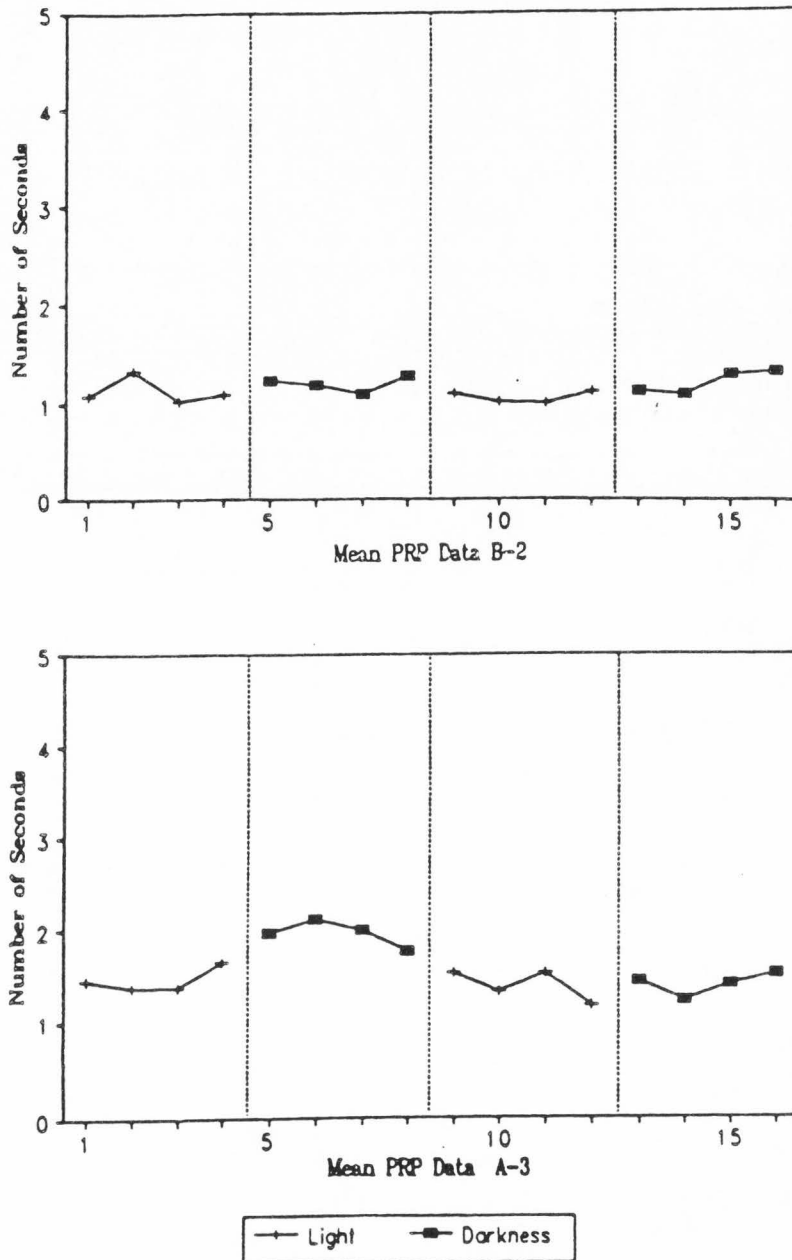


Figure 25. Baseline mean postreinforcement pause (PRP) data in seconds for subjects B-2 and A-3. The experimental conditions in effect are the same as in other baseline sessions but this data was collected prior to the ethanol and water preceeded experimental sessions for these subjects and subjects B-1 and S-1. Sessions are indicated along the X axis.

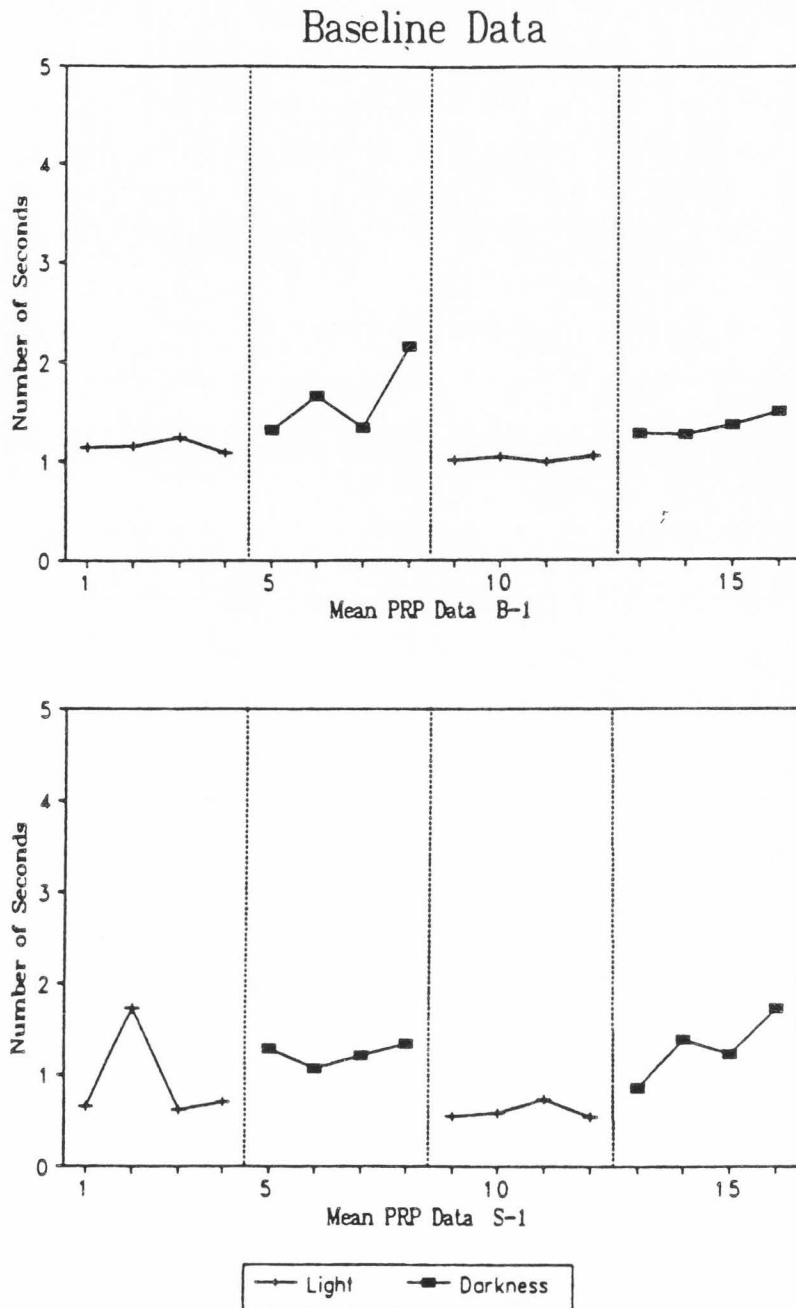


Figure 26. Baseline mean postreinforcement pause (PRP) data in seconds for subjects B-1 and S-1.

Baseline Data

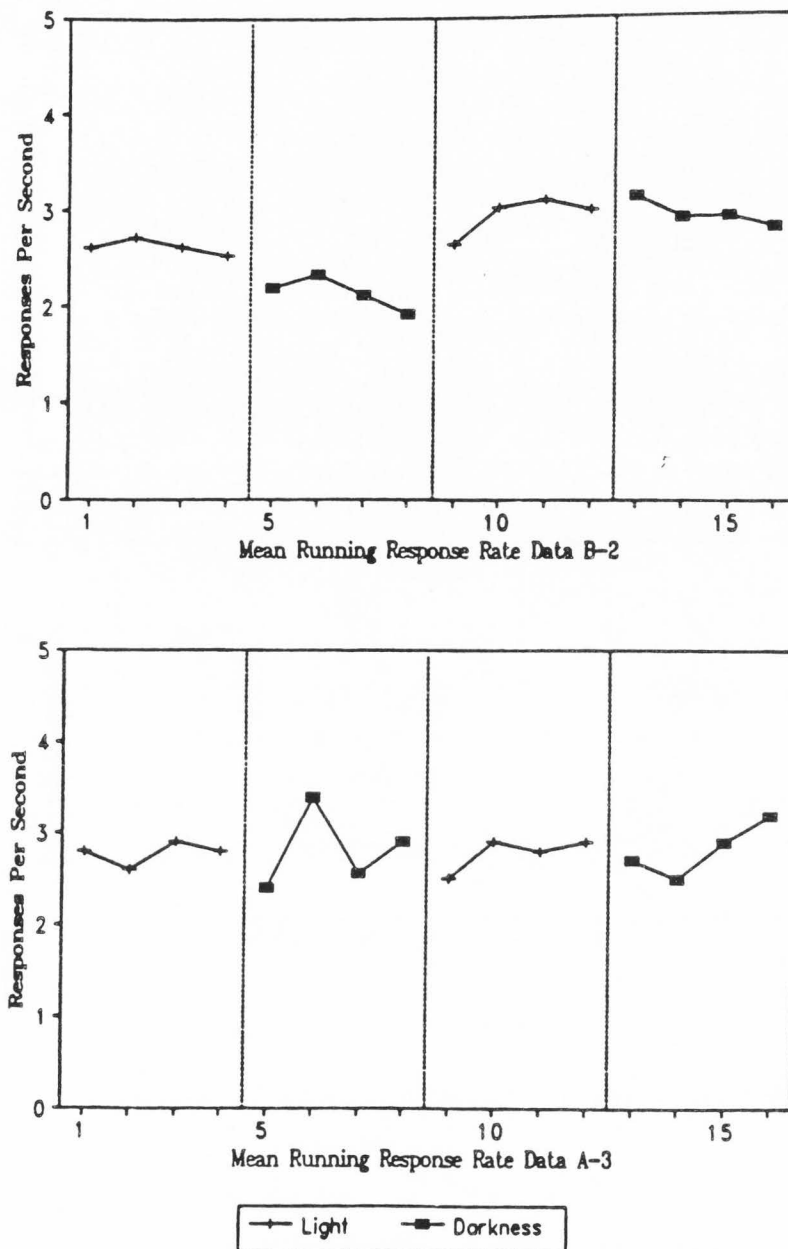


Figure 27. Baseline mean running response rate data in responses per second for subjects B-2 and A-3. This data excludes the PRP time in calculation of responses per second.

Baseline Data

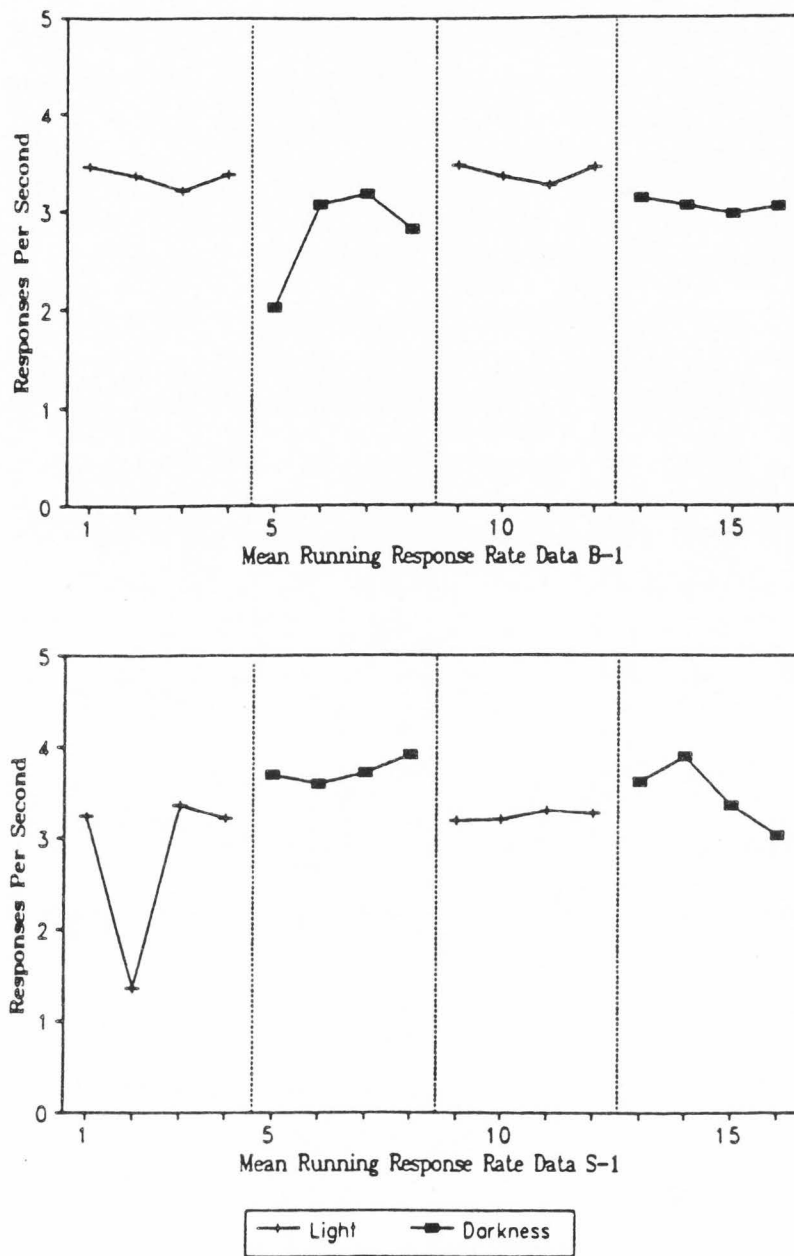
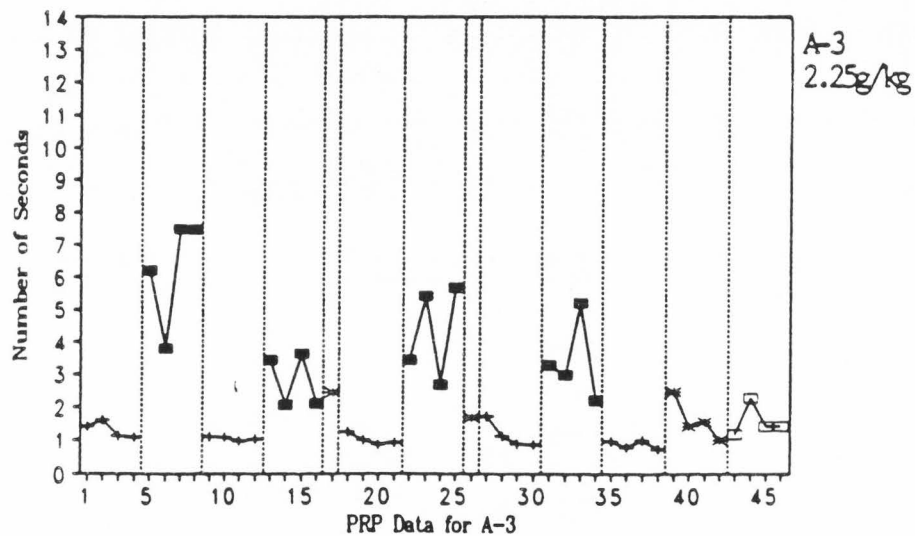
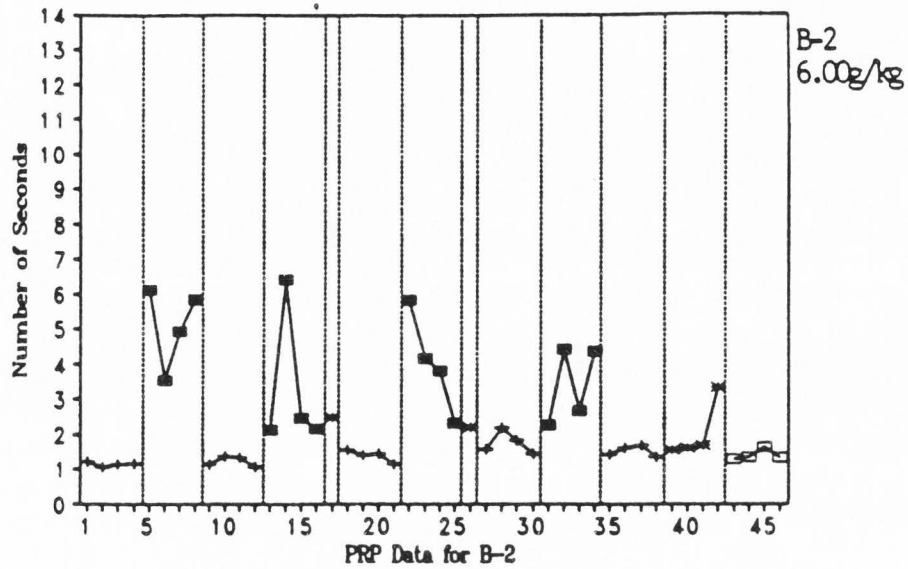


Figure 28. Baseline mean running response rate data in responses per second for subjects B-1 and S-1.

subjects; accompanied with increases in response variability. Subject B-2, which received the largest dosage of ethanol, 6.00 g/kg, actually showed the smallest range of PRP values across the first four sessions as shown in Figure 29. Subjects B-1 and A-3, which both received 2.25 g/kg of ethanol, had average PRPs falling roughly within the same range as seen in Figures 29 and 30. Subject S-1, which received 3.50 g/kg of ethanol, displayed the widest range of average PRP values, shown in Figure 30. The succeeding water sessions for all subjects showed slightly more variability of mean PRP than the initial four sessions but all values fell within a narrow range. The mean PRP data for subject B-1 (Figure 30) showed a large decrease between the first and second series of tolerance conditioning sessions. This same pattern was noted in the mean PRP data of A-2 in Figure 10 and in EP-9's second data set. All of these subjects' subsequent data did not show a distinct decrease across subsequent tolerance conditioning sessions after this initial decrease. Also, the mean running response rate data for each of these subjects showed a corresponding increase in between the first and second series and little change thereafter, as seen in earlier and later figures. Conversely, for subject S-1, the largest behavioral change in the way of tolerance occurred not between series of sessions but between the very first and second tolerance conditioning sessions as shown in Figure 30. Following that change, a slight decreasing trend could be seen across tolerance conditioning sessions. With the tolerance probe data included, the downward trend is more apparent. For subject B-2 and A-3 (Figure 29), a trend of

Mean PRP in Seconds



—○— Light/Water —■— Darkness/Alc - - - × - - - Tolerance Pro —◇— Facilitation Pr

Figure 29. Mean postreinforcement pause (PRP) data in seconds for subjects B-2 and A-3. Experimental conditions and graphic details are the same as indicated in the prior experiment.

Mean PRP in Seconds

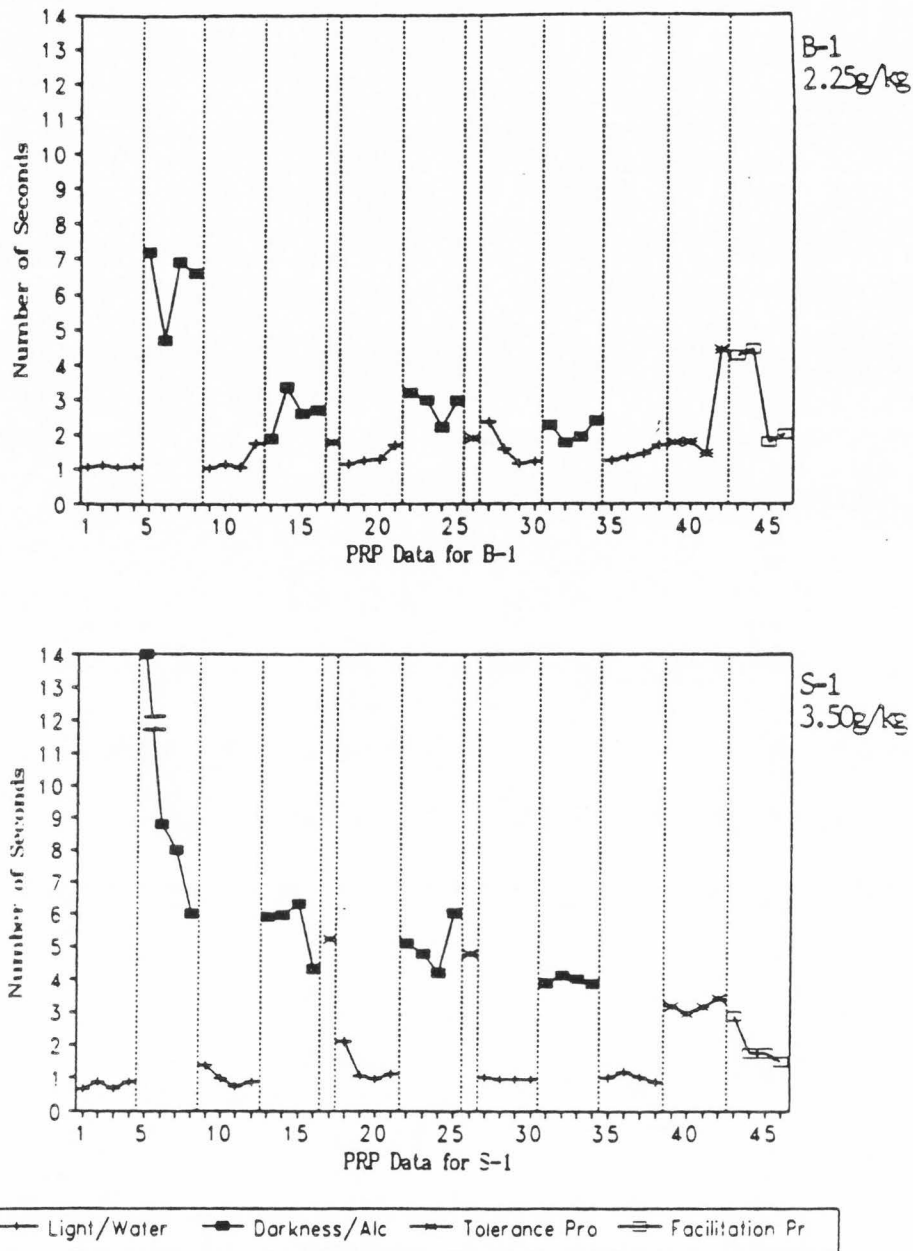


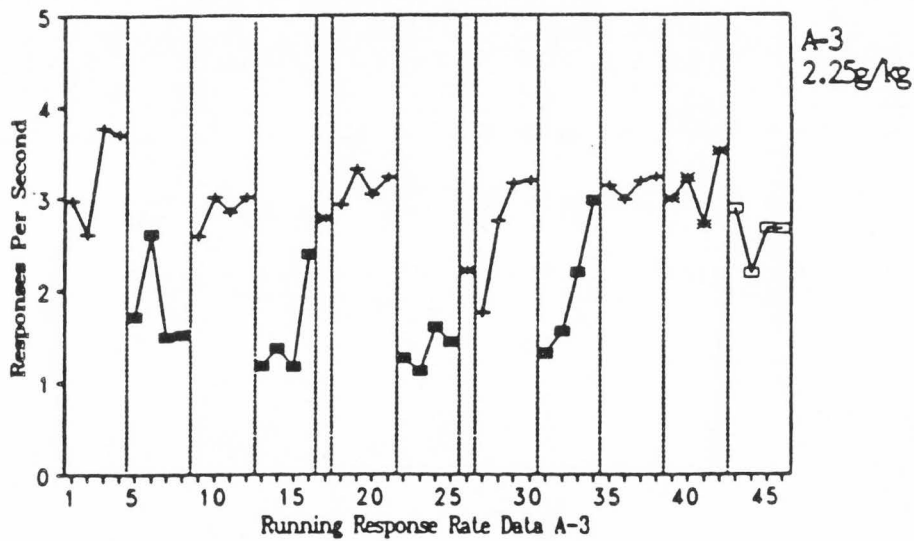
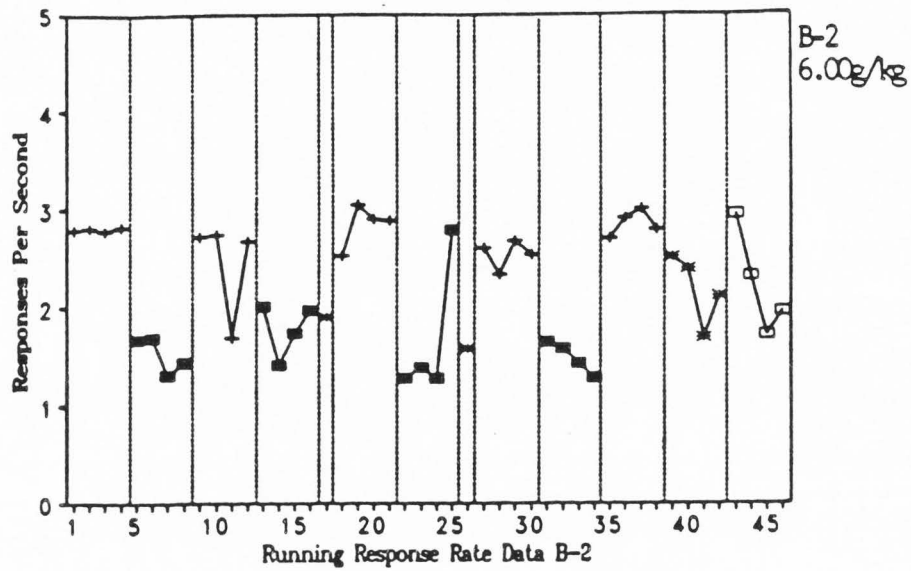
Figure 30. Mean postreinforcement pause (PRP) data in seconds for subjects B-1 and S-1.

decreasing PRPs indicative of tolerance was seen to a much smaller degree than with the other subjects. However, this conclusion may be argumentative.

All of the tolerance probe sessions data points for all subjects fell within the range of values from later ethanol sessions and did not approach the extreme values from the initial sessions. However, B-2 did not show any distinct or extreme behavioral data as a result of ethanol administration. Finally, one subject, B-1, showed an increase in the initial values of those sessions in which water was delivered in the context predictive of ethanol. These variations represented the largest average PRP values of any sessions in which water was delivered. For subject B-1 this relatively large jump in mean PRP followed a large increase in average PRP in the very last tolerance probe session. Subject B-2 showed the same increase in the final tolerance probe session but not the accompanying increase in the water sessions. Why these patterns occurred is not known, nor is its significance. In summation, the mean PRP data from the final experiment were not divergent from the earlier outcomes and tended to show that once tolerance to ethanol emerged, it tended to remain more or less constant across different environments.

The average running response rate data are shown in Figures 31 and 32. For all subjects, the water-preceded sessions showed the most stability, but all subjects displayed some degree of variation in either the typical water sessions or the sessions in which water was given in the ethanol context. The administration of ethanol resulted in a decrease in response rate relative to the water sessions

Mean Running Response Rate



—△— Light/Water —■— Darkness/Alc —×— Tolerance Pro —○— Facilitation Pr

Figure 31. Mean running response rate data in responses per second for subjects B-2 and A-3. The PRP time has been excluded in the calculation of responses per second for this dependent variable.

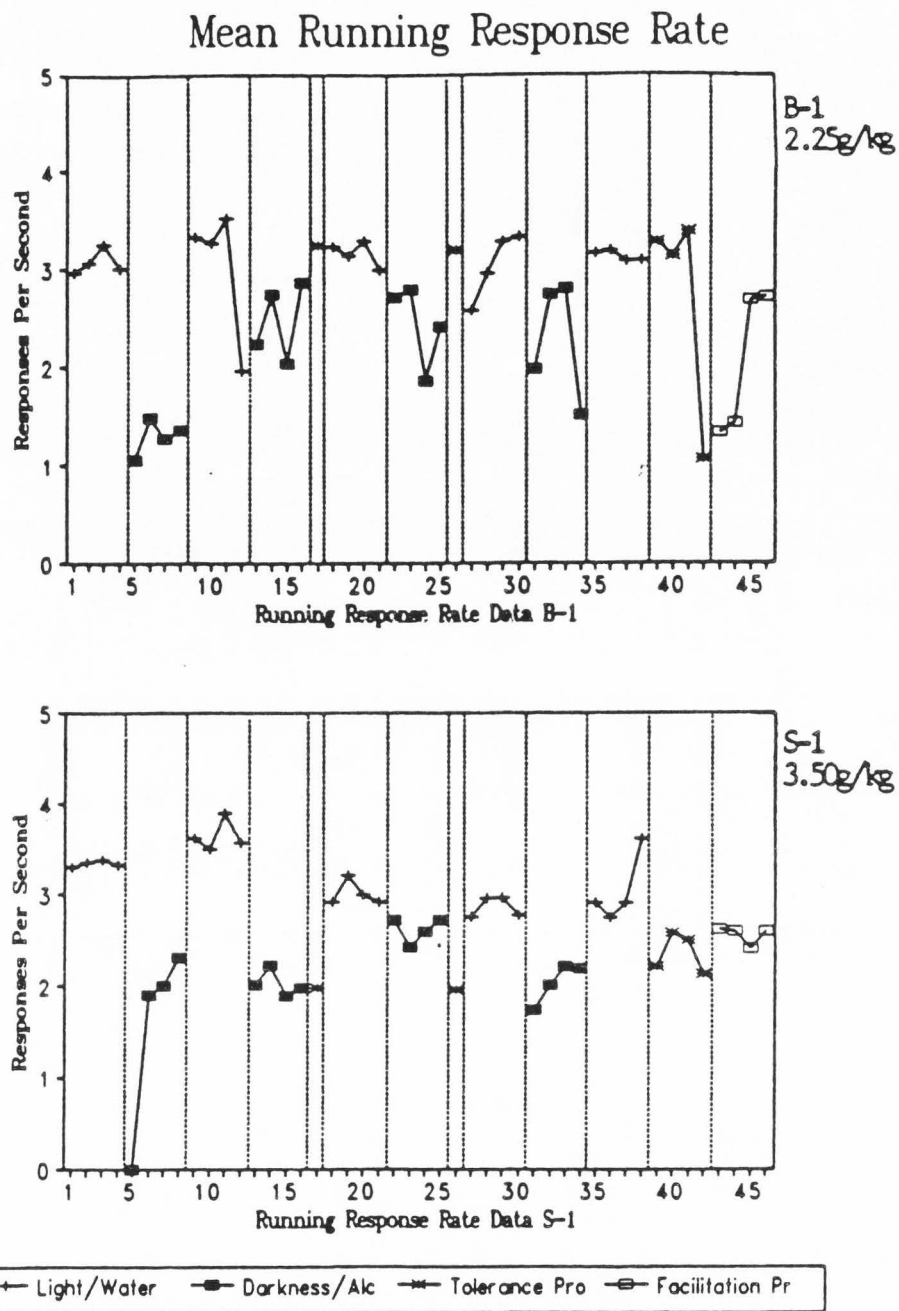


Figure 32. Mean running response rate data in responses per second for subjects B-1 and S-1.

for all subjects. No subjects showed a strong trend of increasing response rate over the series of consecutive tolerance conditioning sessions with one exception, B-1, to be discussed below. Subject A-3 (Figure 31) showed a more or less stable pattern of response rate across consecutive ethanol series. The same generalization applied to A-3, also shown in Figure 31. Subject B-1 showed an increase in mean response rate that occurred between the first and second series of tolerance conditioning sessions, shown in Figure 32. Thereafter, little change in response could be seen for this subject. The data of S-1, also in Figure 32, showed an increase in response rate that took place across the very first and second tolerance conditioning sessions and minor response rate change after those sessions.

Considering the tolerance probe data next, for B-2, these data points represented maximum or near maximum values of response rate, with the exception of the very first tolerance probe. A similar pattern occurred for subject A-3 with two exceptions being the very first and the very last tolerance probes, both shown in Figure 31. The tolerance probe data points of B-1 (Figure 31) likewise exceeded the values from other ethanol sessions with one notable outlier, the very last tolerance probe, as seen in Figure 32. For subject S-1, the tolerance probes fell within the range of data from other ethanol exposure sessions and did not show an indication of increasing response rate indicative of tolerance. The analysis of this dependent variable adds clarification to the conclusion that once tolerant behavior develops, it remains intact despite changes in the environment.

In the section that preceded the discussion of this experiment it was argued that the data of two subjects here, B-1 and A-3, would be of interest since they showed a high degree of response suppression to dosages very similar to the dosages required to completely suppress responding in subjects BP-9 and BP-12. However, following the baseline sessions, the data of B-1 and A-3 represented little in the way of a replication of subjects BP-9 and BP-12. Either the baseline sessions minimized the effect found with the low dosage subjects or a still unidentified factor could explain the difference between the BP-9 and BP-12 and all of the latter subjects. One way of further clarifying the results of these experiments would be to put BP-9 and BP-12 through the procedures of the final experiment. That is, after obtaining the results of the earlier experiment, the subjects would be run across a series of baseline sessions and then have those subjects reacquire tolerance to a higher dosage of ethanol in a still different context. Unfortunately, one of these subjects, BP-12, had to be sacrificed as a result of an infection. The remaining subject, BP-9, was put through the procedure described above.

The baseline mean PRP data and mean running response rate data are shown in Figures 33 and 34, respectively. For these dependent measures, there is little difference in behavior across the different contexts in baseline in that a high degree of stability is evident here. It should be pointed out again that the dark context now includes the response key illuminated with red. Baseline was continued for two alternations across both contexts, for a total of 16 sessions.

Baseline Data

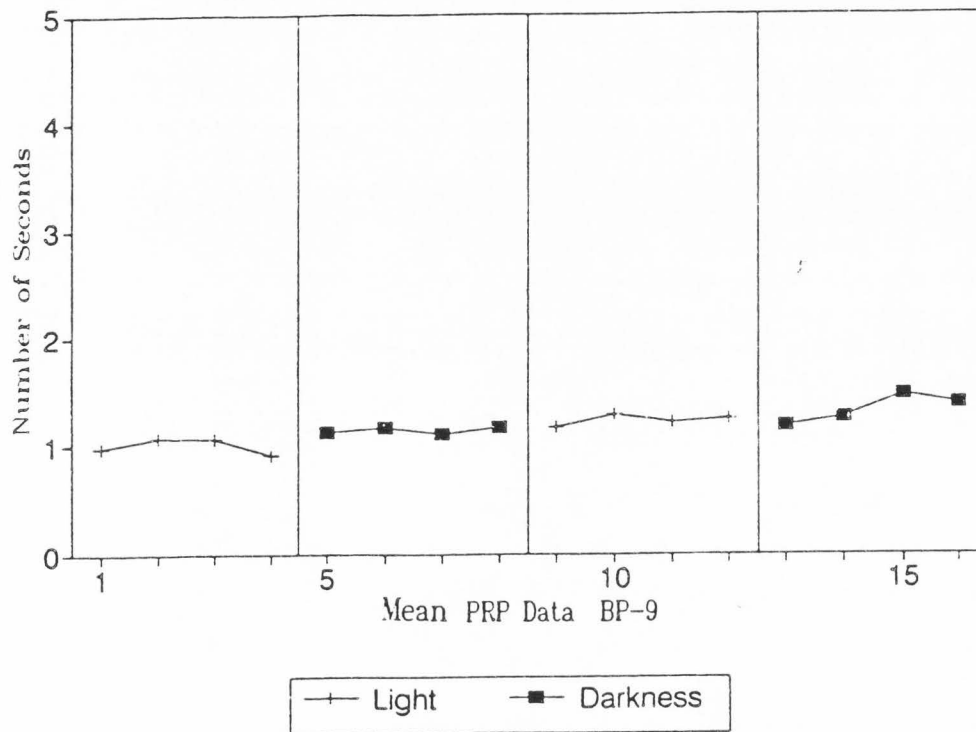


Figure 33. Baseline mean postreinforcement pause (PRP) for subject BP-9 on the VR-20 schedule of reinforcement. Plus symbols (—+) represent data from sessions in which the chamber was illuminated by the houselight, the red response keylight, and with increased noise levels. Filled squares (—■) symbolize data from sessions in which the chamber was illuminated by the keylight alone at ambient noise levels. No injections were given prior to any sessions, which are indicated along the X axis.

Baseline Data

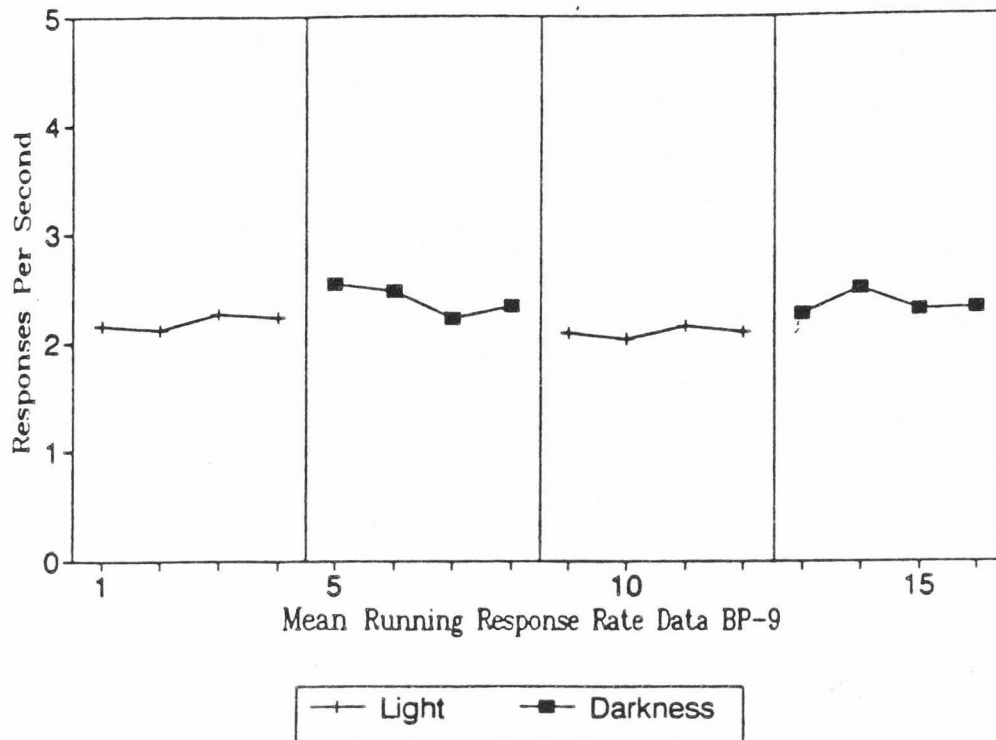


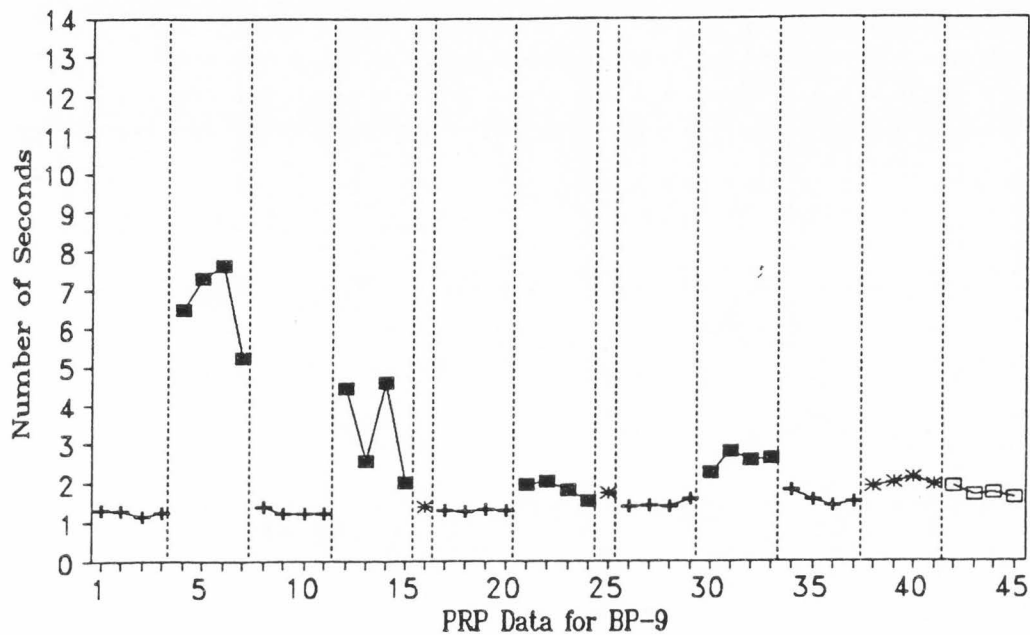
Figure 34. Baseline mean running response rate in responses per second for subject BP-9.

In the experimental session data, Figures 35 and 36, the initial delivery of water resulted in little change in BP-9's behavior relative to baseline for any of the behavioral parameters. The average PRP data from the water sessions was very consistent and all fell within a small range of values. The largest exception to this generalization occurred in the final sessions in which water was delivered in the environment formerly paired with ethanol. This pattern had been seen with most of the subjects of the earlier experiments.

The delivery of the larger dose of ethanol, 2.50 g/kg, determined from a dose response curve, resulted in large increases in average PRP, particularly across the first four tolerance conditioning sessions. The increase seen in the second ethanol series was substantially reduced. The reduction occurred between ethanol series as noted earlier, and by the third ethanol series the average PRP values approximated the data from water sessions. All of the tolerance probe data points fell below the data points from other ethanol sessions as seen in Figure 35. In terms of this parameter, it appears that tolerance developed quickly and remained very constant across changes in context. This data did not provide support for a context dependent tolerance effect. The mean running response rate data, Figure 36, did not display strong response rate differences from either the ethanol or a context dependent tolerance effect.

In summation, having the subject reacquire tolerance to a higher dose of ethanol in another altered environment was an additional manipulation intended to clarify the mechanisms of tolerance

Mean PRP in Seconds Series 2



—+— Light/Water —■— Darkness/Alcohol —*— Tolerance Prob —□— Facilitation Pro

Figure 35. Mean postreinforcement pause (PRP) data in seconds for subject BP-9. This data is from a second tolerance conditioning session, in addition to this subject's experiment two data. Sessions are indicated along the X axis. Symbols used are the same as in earlier graphs.

Mean Running Response Rate Series 2

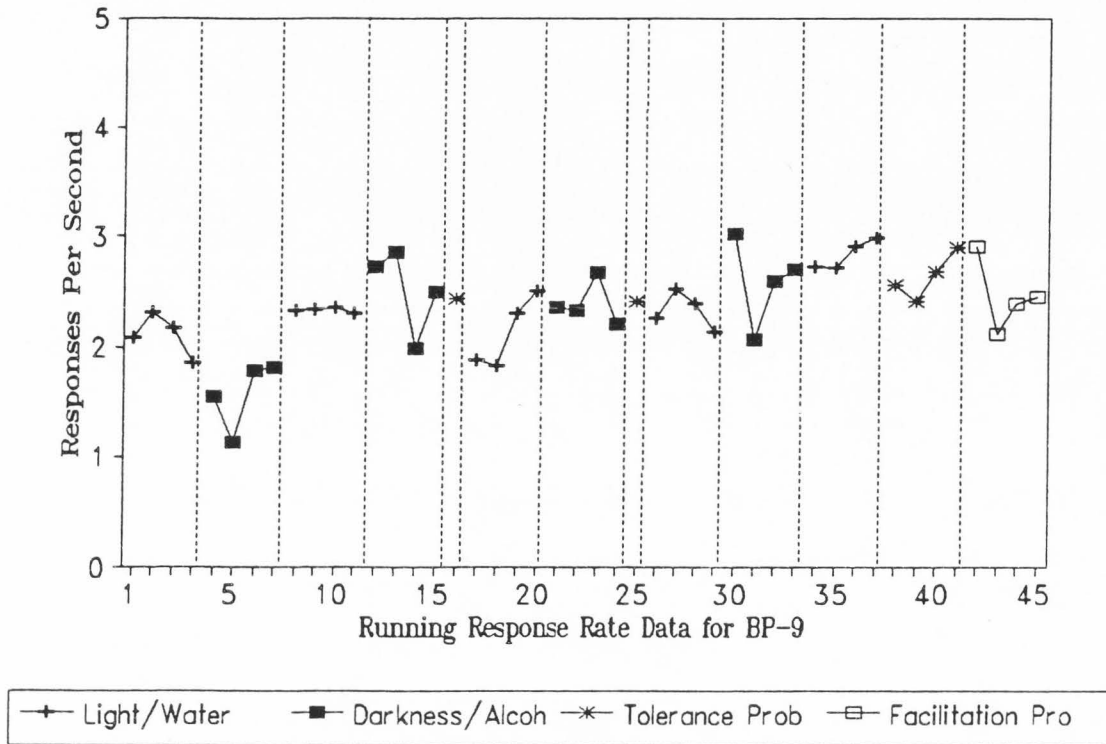


Figure 36. Mean running response rate data in responses per second for subject BP-9. Data shown is from a second tolerance conditioning series.

acquisition. On the surface, this additional data again favored the conclusion that once tolerance developed on an operant reinforcement schedule, it remained a constant across contexts. The results of the functional analyses involving the additional contextual stimuli changes also favored the above conclusion. All of the results acquired after the first two subjects, EP-9 and EP-12, have supported this conclusion. One other largely unrelated conclusion could be drawn. Ethanol appears to increase the variability in responding on a schedule of reinforcement. Cohen, Neuringer, and Rhodes (1990) reported that doses of ethanol impaired the ability of rats to emit repetitious response sequences but not response sequences that were varied. In that study, as in the present, ethanol served to increase response variability. But this conclusion is subsidiary to the empirical question posed in this investigation. With respect to the conclusion that once tolerance develops via reinforcement of behavior on a schedule of reinforcement and it remained a constant across contexts, the results of two subjects represented a contradiction. A reconciliation and discussion of the contradiction follows in the discussion section.

DISCUSSION

In formulating the statement of the problem, this author argued that the nature of the interaction of operant and respondent processes in developing tolerance to ethanol is not understood. Both processes are individually supported as being the primary process in acquiring tolerance by abundant literature. While both processes are no doubt jointly present, various studies tend to indicate a hegemony by one of the paradigms. The emphasis on one process over the other could be seen as being the result of the type of behavioral parameters measured. Studies that examine interactions between the two processes are fewer in number, and for the most part, very similar to other studies. That is, depending upon the type of behavioral measures taken, those studies indicated that either process can be crucial in the acquisition of tolerance to ethanol. Grilly (1989), for example, proposed that most of the tolerance to ethanol is acquired through operant means. He presents no empirical evidence to support this conclusion, however.

The present experiment did add to the existing literature, in terms of the methodology and the results which replicate and complement other studies. Table 2 summarizes the results for the mean postreinforcement pause data and Table 3 provides a summary of the mean running response rate data. Only the data from tolerance probe sessions are shown in these tables. In Table 2, an equal (=) sign

Table 2

A Summary of the Tolerance Probe Data Points for All Subjects From the Mean Postreinforcement Pause Data

Subject	Probe#1	Probe#2	Probe#3	Probe#4	Probe#5	Probe#6
BP-9	HIGH	=	HIGH	HIGH	=	=
BP-12	HIGH	=	HIGH	HIGH	=	=
BP-14	=	LOW	=	=	=	=
O-1	=	=	=	=	=	=
A-2	=	=	=	=	=	=
BP-13	HIGH	=	=	=	=	=
D-1	=	=	LOW	LOW	LOW	=
D-2	=	=	=	=	=	LOW
A-4	=	=	=	=	=	=
B-3	=	LOW	=	=	=	=
B-2	=	=	LOW	LOW	LOW	=
A-3	=	LOW	=	LOW	LOW	LOW
B-1	=	=	=	=	LOW	=
S-1	=	=	LOW	LOW	LOW	LOW
BP-9#2	=	=	=	=	=	=

Here, an equal sign (=) indicates that the probe was equal to the range of prior tolerance conditioning sessions. LOW and HIGH indicate that the tolerance probe was either less than or greater than the prior tolerance conditioning sessions by at least one-half second. In terms of this dependent variable, only HIGH is indicative of a context dependent tolerance effect in this summarization.

Table 3

A Summary of the Tolerance Probe Data Points For All Subjects From the Mean Running Response Rate Data

Subject	Probe#1	Probe#2	Probe#3	Probe#4	Probe#5	Probe#6
BP-9	LOW	HIGH	LOW	LOW	=	=
BP-12	=	=	LOW	=	=	=
BP-14	=	=	=	=	=	=
O-1	=	HIGH	=	=	=	LOW
A-2	HIGH	=	=	=	=	=
BP-13	=	=	=	=	HIGH	=
D-1	=	=	HIGH	=	=	=
D-2	LOW	LOW	=	=	=	=
A-4	=	HIGH	=	=	=	=
B-3	=	HIGH	HIGH	HIGH	HIGH	=
B-2	=	HIGH	=	=	=	HIGH
A-3	HIGH	HIGH	HIGH	HIGH	HIGH	=
B-1	HIGH	HIGH	HIGH	HIGH	HIGH	LOW
S-1	=	=	=	=	=	=
BP-9#2	=	=	=	=	=	=

Here, an equal sign (=) indicates that the probe was equal to the range of prior tolerance conditioning sessions. LOW and HIGH indicate that the tolerance probe was either less than or greater than the prior tolerance conditioning sessions by at least one-half second. In terms of this dependent variable, only LOW is indicative of a context dependent tolerance effect in this summarization.

indicates that a tolerance probe data point was equal to the range of prior tolerance conditioning sessions. The same convention holds for an equal sign in Table 3. In Table 2, the word High indicates that a tolerance probe exceeded the values of prior tolerance conditioning sessions by at least one-half second. The word Low indicates a tolerance probe was less than the prior tolerance conditioning sessions by at least one-half a second. Hence, High is indicative of data verifying a context specific respondent tolerance effect while Low contradicts any context specific tolerance effect. In Table 3, the terms High and Low are assigned opposite meanings, since response rate is now the dependent variable of interest. Here, High represents a faster rate of response for a tolerance probe than for earlier tolerance conditioning sessions and Low points to a slower rate of responding on a tolerance probe, relative to prior ethanol sessions. Both Tables 2 and 3 confirm the conclusions presented in the results section.

This study evaluated dependent variables of operant behavior, and found, for most subjects, that tolerance developing due to operant reinforcement of compensatory behaviors was immune to contextual stimuli changes associated with respondently conditioned tolerance, or lack thereof. The data summary of Tables 2 and 3 overwhelmingly shows that the tolerance probe data points were mainly equivalent to tolerance conditioning sessions and favored the operant tolerance effect over the respondent effect. That is, the most common outcome showed the tolerance probe data to be equivalent to tolerance conditioning sessions. The second most common outcome was the result

that the tolerance probe data points actually represented behavioral improvement--shorter PRPs or faster response rates--rather than tolerance conditioning sessions. The least likely outcome to occur was the behavioral disruption that indicated respondent, context specific, tolerance. Overall, these data are contradictory to the respondent tolerance hypothesis. Here, contextual variations more often than not resulted in either no change, or a facilitation of the dependent measures examined. However, these results must be couched within the terms of the qualifications stated above, because, for a minority of subjects, tolerance developed but was subject to extreme disruption by changes in contextual stimuli, presumably due to a breakdown in respondently conditioned tolerance. These same subjects also showed more impairment due to a relatively smaller dose of ethanol than those subjects whose behavior was immune to any contextual manipulations. Clearly, something was different about this subset of subjects and their behavior. It should also be noted here that the ethanol regimen could have produced long-term physiological changes in all subjects. (In later experimentation by others, virtually all of these subjects were difficult to stabilize in weight under food deprivation conditions. This was not a problem during this study, however.) One possible difference is that of an idiosyncratic drug response, a term used to describe an unexpected response or an unusual effect of a drug (Grilly, 1989). Such a response can be independent of dosage and implies more than just hyporesponsiveness or merely sampling error. Also, this is merely a description, not an explanation, of the observed results. Instead of focusing on some vaguely defined individual

difference, a few studies discussed here again point to differences in susceptibility to the effects of ethanol and the presence or absence of tolerant behavior due to respondent processes, results that are very similar to those of the present study.

As presented above, Baker and Tiffany (1985) reported that tolerance to morphine was highly context specific at small doses, such as .50 mg/kg. However, with significantly larger doses, tolerance tended to decrease over successive probes. By the third such trial, no context specific tolerance was present. With larger drug doses, the amount of tolerance that was context dependent clearly decreased.

Le et al. (1987) extended similar findings to include tolerance to ethanol. Again using rats in a Pavlovian conditioning paradigm, tolerance to ethanol's hypothermic effects were highly context dependent at a relatively low dose of ethanol, 2.00 g/kg. At twice that dosage, significant tolerance could be found in the context predictive of ethanol and in a radically altered environment. Both of these studies point to a dosage-related variable in context dependent tolerance in studies examining autonomic factors.

Le et al. (1989) studied operant dependent variables and found a similar dosage-related factor. They measured tolerance to the motor impairment from ethanol with rats on an active avoidance task. In rats that performed while intoxicated from a low dose of ethanol, (2.00 g/kg), tolerance was highly context specific. Rats that received intoxicated practice from a larger dose of 4.00 g/kg displayed tolerance that generalized to different contexts.

Goudie and Demellweek (1986) proposed that, based on earlier studies in which this same outcome occurred, at higher doses, nonassociative or dispositional tolerance becomes a more important factor. Dispositional factors would include altered drug distribution, metabolism, excretion, and physiological changes at receptor sites. However, Vogel-Sprott (1992) argued that changes in dispositional factors only contribute a minor role in ethanol tolerance. Chronic ingestion of ethanol will only slightly increase the capacity to metabolize ethanol (Hawkins, Kalant, & Khanna, 1966; Isbell, Fraser, Wikler, Belleville, & Eisenmann, 1955; Mendelson, Stein, & Mello, 1965) in that elimination rates of alcoholics are within the range obtained from normals. And any inherent assumption that dispositional tolerance is a constantly increasing factor is not necessarily valid. Jones (1974) found that circadian rhythms could be a factor in afternoon versus evening drinking with tolerance being more pronounced in the evening. Jarvik and Henningfield (1988) reported that tolerance for nicotine is lost during sleep as smokers report the first cigarette of the day is the strongest. More exposure does not always mean more tolerance (Vogel-Sprott, 1992).

However, Poulos and Cappell (1991) stated that the intensity and persistence of what they called an unconditioned adaptation would be proportional to the magnitude of the drug disturbance instigated. A prolonged unconditional adaptation (or UR) could give rise to a backward conditioning procedure. Large drug doses serve to extend the activity of the UR and in effect decrease the interdose interval (IDI), leading to ineffective backward conditioning. These researchers argue

that the degree and duration of a UR are directly related to dose and indirectly to IDI. As a result, associative tolerance is less pronounced (and nonassociative tolerance more so) when large doses and short IDIs are used.

Poulos and Cappell (1991) stated that a 48-hour period is a moderate IDI, hence the 24-hour IDI in the present study is a short IDI period. This helps to explain the lack of context specificity for classically conditioned tolerance and presumably facilitates (or at least not hinder) the operant acquisition of tolerance since more of an organism's operant behavior and controlling contingencies would still be in effect. An argument could be made for the facilitatory effect in that a larger dose could remain in the organism's system longer and provide for extended periods of operant responding while intoxicated or "intoxicated practice."

In summary, a small number of studies had found a dose effect in that tolerance, due to respondent conditioning cues, was very likely to be present to smaller doses of morphine and ethanol, both of which are behavioral depressants. With higher doses, tolerance which was context dependent tends to be decreased or absent, including behavioral situations in which tolerance due to operant processes was still functional. In addition, Kalant, LeBlanc, and Gibbins (1971) argued that the larger drug effects from a specific dose would result in more rapid or greater development of tolerance. This supposition has not been supported by more recent research (Le & Kiianmaa, 1990).

The present study mirrored these outcomes and the similarity to earlier studies added clarification to the present study. A viable

conclusion is that tolerance acquired on an operant schedule of reinforcement to lower doses of ethanol is subject to disruption by contextual changes associated with respondently conditioned tolerance. With experience to higher doses of ethanol, contextual manipulations had minimal effects on operantly acquired tolerance. That is, either process can be a more potent behavioral tolerance mechanism, as a function of dosage. One question that arises is why this outcome is so rarely found. The parsimonious answer is that differential outcomes occur only with differential dosages. If one's subjects all receive the same dosage, this effect is not found. Differential dosages are most likely used to arrive at specific criteria of behavioral changes, in light of individual differences to a given drug.

Another important question surrounds the nature of tolerance acquired through operant conditioning. So far, the means by which tolerance is acquired has been through some vaguely defined behavioral compensation. More specifically, if a drug's effects caused a loss or reduction of reinforcement frequency, the subject would learn to emit some behavior to regain or recover the pre-drug reinforcement frequency. The exact nature of this behavioral compensation is not understood. Based on the present study, a possible explanation could very well be the selective effect of reinforcement on operant behavior. That is, whatever behaviors were successful in leading to reinforcement would be selected for continuation and increased frequency. Those behaviors that were not effective will occur less frequently. The subjects of the present study could have learned selective behavioral immobility. Subject B-3 in particular displayed this behavioral

tendency. Upon completion of the time interval allowing for drug absorption and distribution, the key light became illuminated and the schedule of reinforcement was in effect. Following ethanol injections, the subjects would rarely begin responding immediately. B-3 would typically pause for several minutes before beginning to respond and could typically be seen with its head leaning into a corner of the chamber. Since the first pause was not included in the data analysis, this did not alter the mean values of the dependent variables, but it did lengthen the total session time. To counter this, I sometimes raised the hopper once with a handheld switch. This was done after a minimum of 60 seconds after session onset. The presentation of the hopper was often sufficient to induce this subject to begin responding. Subject A-2 would consistently pause for approximately half of the 30 minute session before beginning to respond. On a number of occasions, A-2 paused the entire or nearly the entire session and as a result, obtained few if any of that session's available reinforcers. Those sessions were not included in the data; admittedly, this may constitute a confounding variable to this subject's data. After a sufficient number of missed sessions, A-2 began responding soon enough to obtain all available reinforcement. One might argue that the adaptive value of delaying responding is analogous to a human waiting to become less intoxicated before attempting a behavioral sequence. A short-term delay is experienced, but in the long term, responding is accomplished successfully with greater ease. When returned to the home cage, all subjects were seen to stumble and fall about the cage, with sufficient force to cause possible head injury. The only way subjects could

maintain physical stability was to lean into a corner. While no objective data are available for this behavior, it appeared that the ability to stand immobile in the chamber and in the home cage developed along with tolerance measured on the dependent variables. Other studies have found related data. Mellanby (1919) and Newman and Card (1937a, 1937b) both reported that intoxicated dogs showed decreased alcohol-induced impairment of walking gait with repeated intoxicated practice.

With repeated experience Goldberg (1943) found that alcoholics had greater tolerance in terms of decreased ataxia while walking or standing than normals. Both groups were equally impaired at tasks such as coding or subtraction. The former tasks were behaviors that the alcoholics had no doubt performed repeatedly while intoxicated. Grilly (1989) predicted behavioral generalization along this line of hypothesizing.

Another possible explanation of some of the observations here arises from the observations of the effects of hopper operation on B-3. A single hopper operation was sufficient to induce this subject to begin responding. It could be that the presentation of an unconditioned stimulus (food) and stimuli associated with it, and the sound and sight of the hopper operating elicited species specific appetitive responses (unconditioned responses) such as approach, investigatory, and consummatory behavior (Carlsen, 1991). These elicited behaviors as directed towards other associated stimuli, such as the key light, result in contingent reinforcement of responding at

the key and resultant behavioral compensation. This may be a likely scenario considering the debate focusing on operant and respondent aspects of pigeon's directed pecking behavior (Davey, 1990). The two processes can never be truly separated as both are always present.

As stated earlier, Grilly (1989) made a number of predictions pertaining to behavioral generalizations of tolerance acquired through operant conditioning. Some of these pointed to possibilities for further research. Grilly argued that in order for tolerance to occur, the organism must perform or emit behavior while under the influence of a drug. From the viewpoint of operant researchers, this is an obvious requirement, but it is not completely accepted by others (Le et al., 1989).

The results of Smith (1991a, 1991b) also add complexity to the question. In those studies, which were very similar to the present study, context specific tolerance overrode performance on an operant schedule of reinforcement. No differential dosages were used and as mentioned earlier, the drugs were given before and after sessions. This would be expected to hinder context dependent tolerance but could also facilitate dispositional tolerance. The complexity of the experimental question is not yet resolved. Grilly also argued that tolerance of this type would tend to be task specific. For example, learning to compensate for ethanol's effects on walking behavior would not necessarily alter ethanol's effects on typing behavior. However, if two tasks involve similar behavioral repertoires, behavioral generalizations would be expected from one task to another. The rate of tolerance acquisition should be a function of the difficulty of the

task, interacting with the availability of reinforcement for compensatory responding. In other words, situations in which the availability and frequency of reinforcement were abundant would lead to a faster acquisition of tolerance. More difficult tasks will induce tolerance more slowly but this could be facilitated with increases in reinforcement density. In support of Grilly's predictions, LeBlanc, Gibbins, and Kalant (1975) showed that rats with acquired tolerance to ethanol on a moving belt task did in fact show cross tolerance to ethanol's effects on a circular maze task. Drug-naive rats showed no such transfer of training between the tasks.

While the reinforcement-loss operant paradigm is supported by considerable literature, there are anomalous findings that do not fit this hypothesis. Goudie and Demellweek (1986) proposed that a modified form of the reinforcement loss hypothesis can explain such anomalous outcomes. They argued that the stimulus for the development of tolerance was not reinforcement loss per se but was better put as response cost. That is, tolerant subjects tend to respond so that reinforcement was maximized for minimal energy expenditure (Branch, 1979). Such a cost hypothesis would predict that tolerance would develop to drug-related increases in response rate, even if this does not cause reinforcement loss, since increased energy expenditure would occur. Some evidence is available in support of this proposition. Dworken and Branch (1982) reported that morphine reduced the response rate in rhesus monkeys on a continuous shock avoidance schedule, which increased shock frequency. Following a chronic drug regimen, tolerance developed to morphine's rate suppressant effect such that shock

frequency approximated a return to baseline levels. Response rate did not recover to baseline but only showed tolerance to the extent that shocks occurred very infrequently. Dworken and Branch (1982) concluded that behavior was more efficient after drug treatment since response cost was minimized. This revised view of the operant tolerance paradigm is attractive because it represents an extension from behavioral economic theory (Hursh, 1980; 1984). It also is compatible with the belief that animals are adapted by natural selection to minimize energy expense by generating optimal foraging strategies (Pulliam, 1981).

Another possible effect here which has not been considered is that of state dependent learning, the phenomenon by which animals or humans learn a task under the influence of a drug; subsequently, retention and performance of the task will be facilitated under the same drug state and hindered in a nondrug state. The same effect occurs for learning in a nondrug state (Grilly, 1989). State dependent learning could be relevant here because Overton (1985) stated that while state dependent learning (SDL) is more frequently a weak effect, it is only produced by some drugs at the highest doses that will allow sustained behavioral responding. The two anomalous subjects in the present study showed a context (or state) dependent tolerance after having their behavior abolished by ethanol. However, Overton (1985) also pointed out that a very well learned response will tend to generalize to other contexts and states. As a result, the contribution of state dependent learning to the present results is worth noting but the precise role of state dependent learning is not clear.

In conclusion, more research is needed in this area. An obvious extension of the present work would be to have the subjects more dependent on acquiring tolerance to ethanol's impairment of their operant behavior; that is, to have the subjects perform in a closed economy where all food was available from only the reinforcement schedule. It might be argued that subjects of the same age and sex from a laboratory breeding colony are needed to control for differences in the rate of metabolizing alcohol. Under conditions such as these, the interactions between operant and Pavlovian processes in developing behavioral tolerance might be more clearly elucidated.

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APPENDIX: Figures Displaying Mean

Overall Response Rate Data

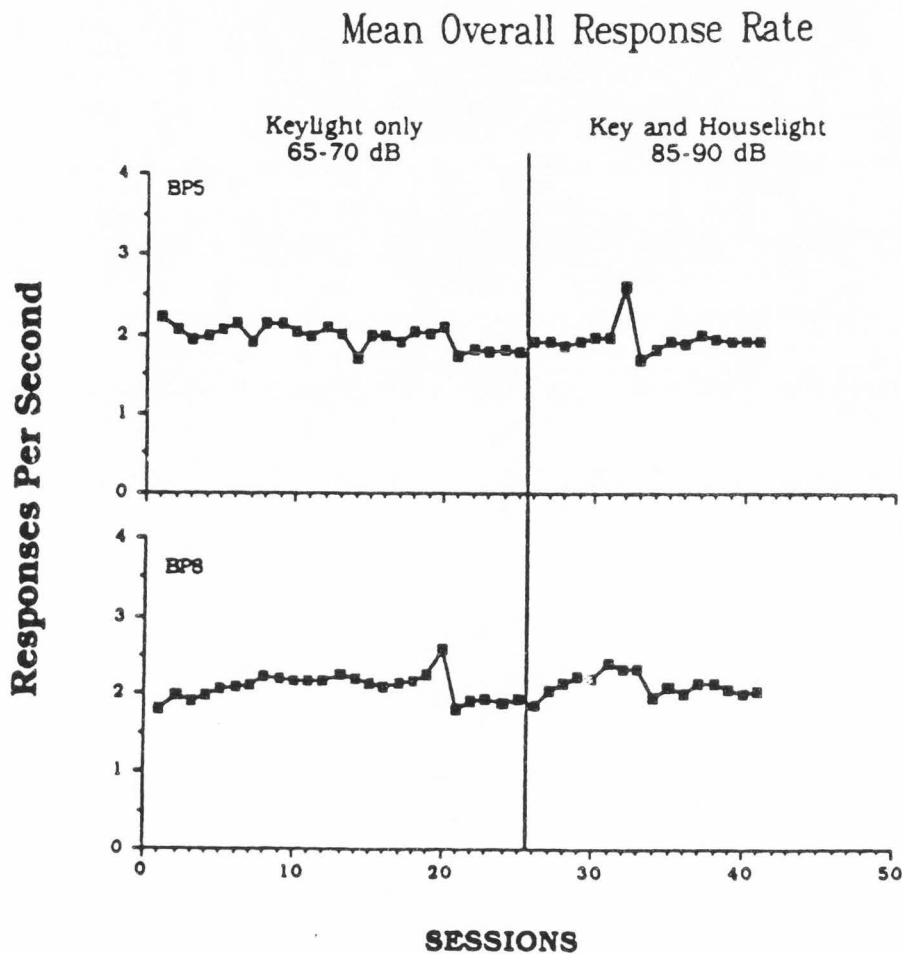


Figure 37. Mean overall response rate in responses per second for control subjects BP-5 and BP-8 on a variable-ratio VR 20 schedule of reinforcement. Both subjects received an injection of 2.00 g/kg of tapwater prior to each session. Data from the left half of the graph are from sessions in which the chamber was illuminated by the keylight alone. Data from the right half are from sessions in which the chamber was illuminated by the key and a houselight, reflective foil was draped over the sidewalls of the chamber, and ambient noise levels were increased.

Mean Overall Response Rate

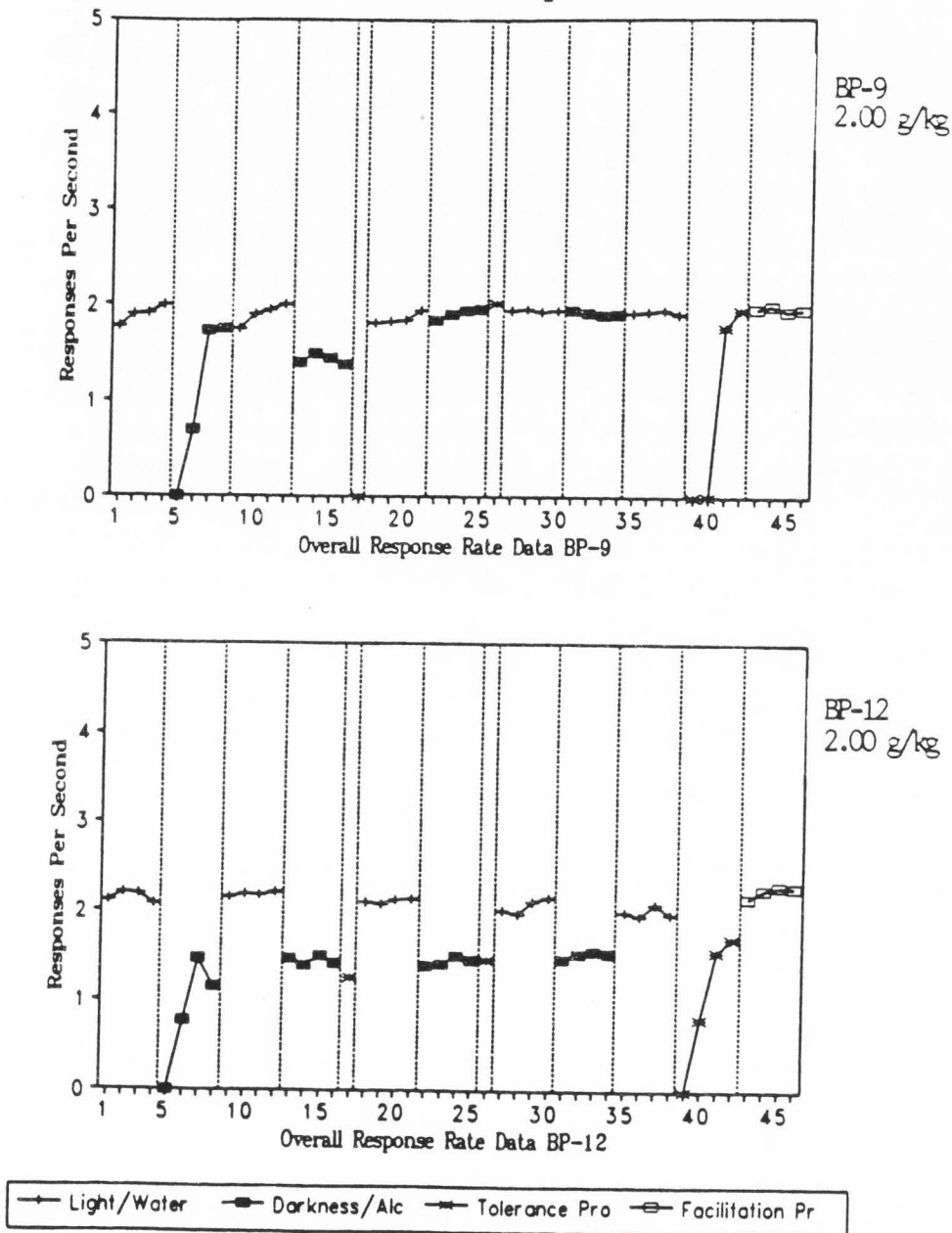
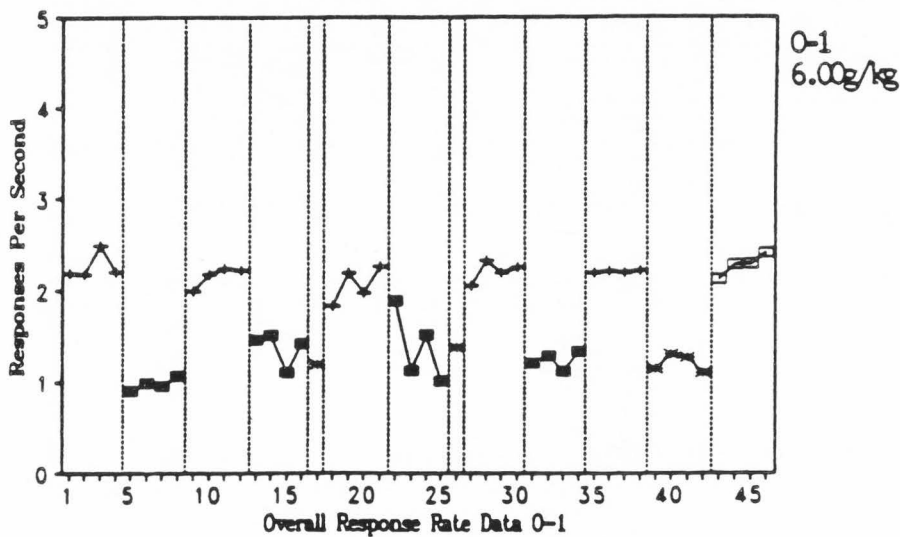
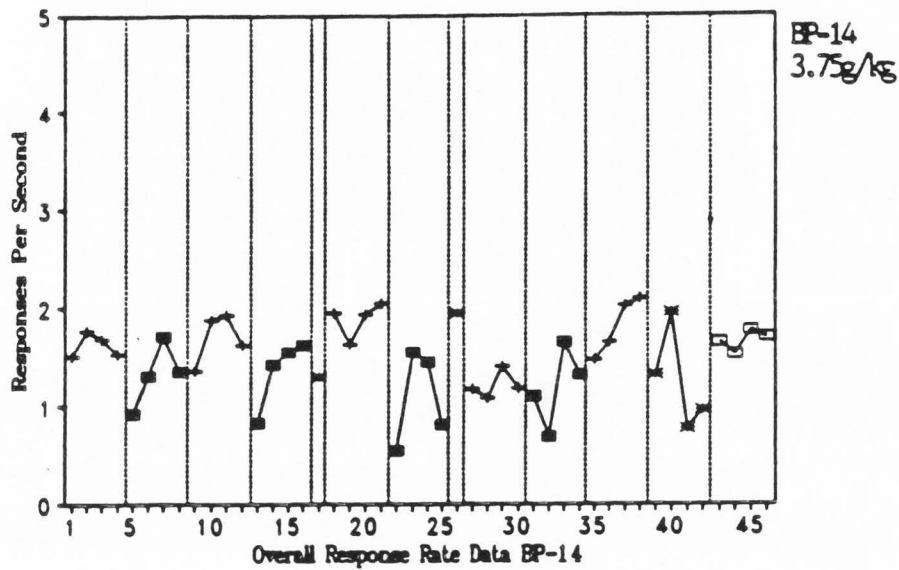


Figure 39. Mean overall response rate in responses per second on a VR 20 schedule of reinforcement for subjects BP-9 and BP-12. The legend and experimental conditions are described in Figure 7 text.

Mean Overall Response Rate



—•— Light/Water —■— Darkness/Alc —▲— Tolerance Pro —□— Facilitation Pr

Figure 40. Mean overall response rate in responses per second, for subjects BP-14 and O-1. This dependent variables includes the post-reinforcement pause in the computation of response data. Details of the experimental conditions are provided in the text and the legend is described in Figure 39 text.

Mean Overall Response Rate

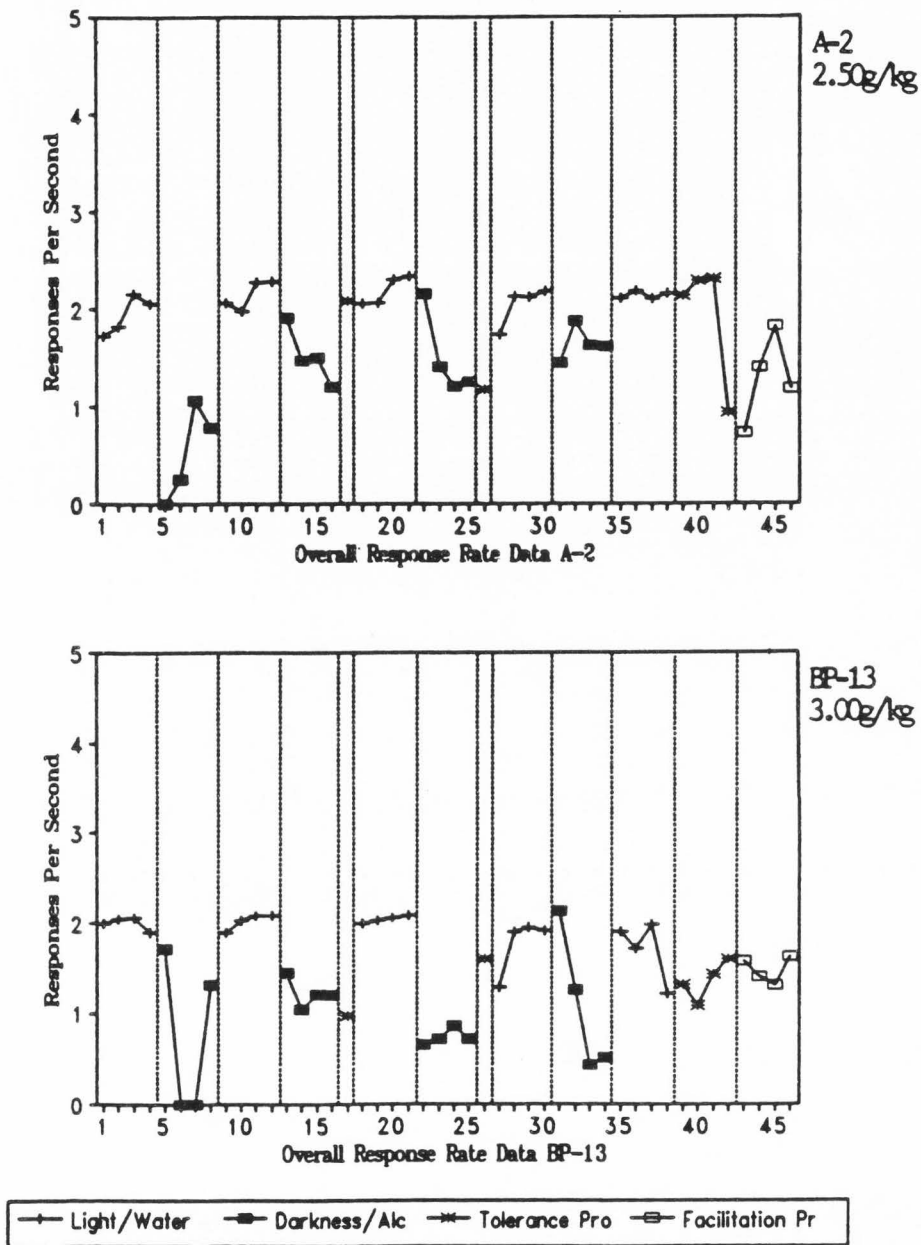


Figure 41. Mean overall response rate data for subjects A-2 and BP-13 in terms of responses per second. Session numbers are indicated along the X axis.

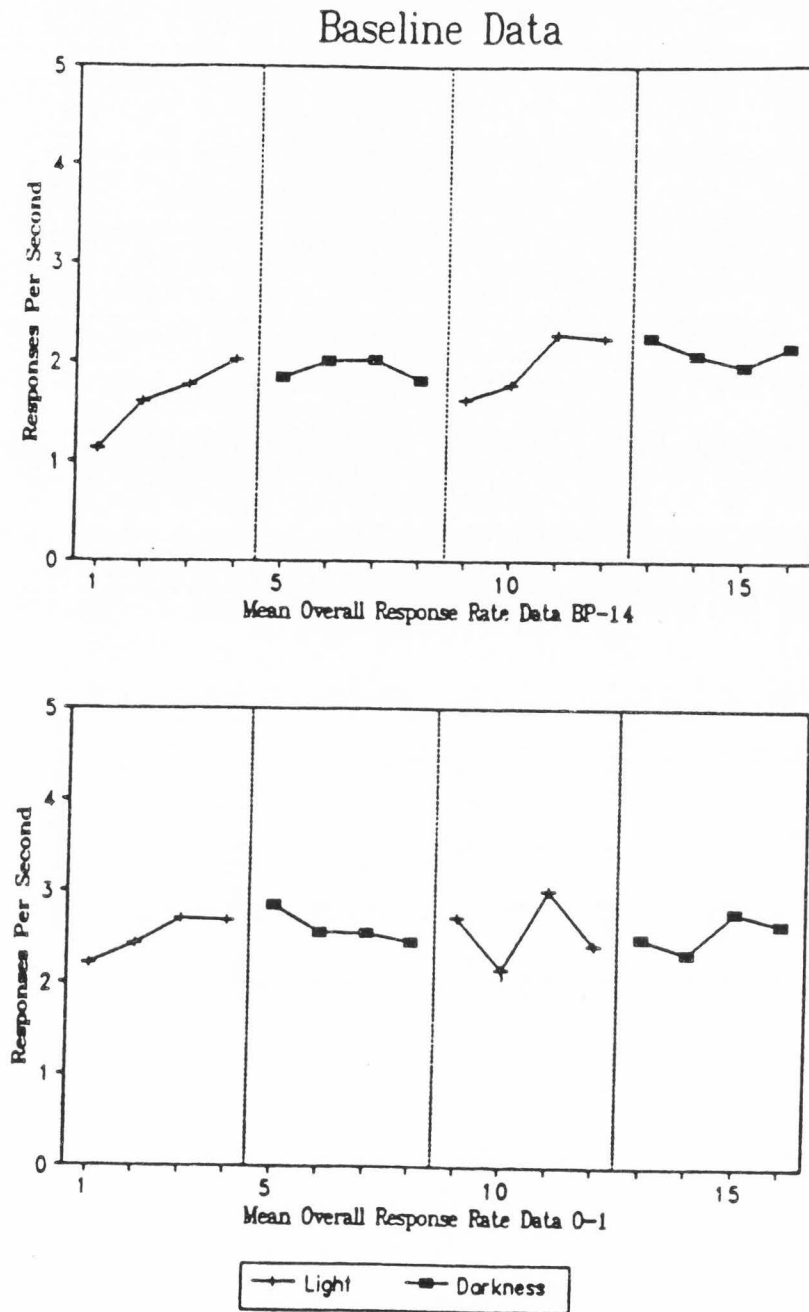


Figure 42. Baseline mean overall response rate data in responses per second, including PRP time, for subjects BP-14 and O-1.

Baseline Data

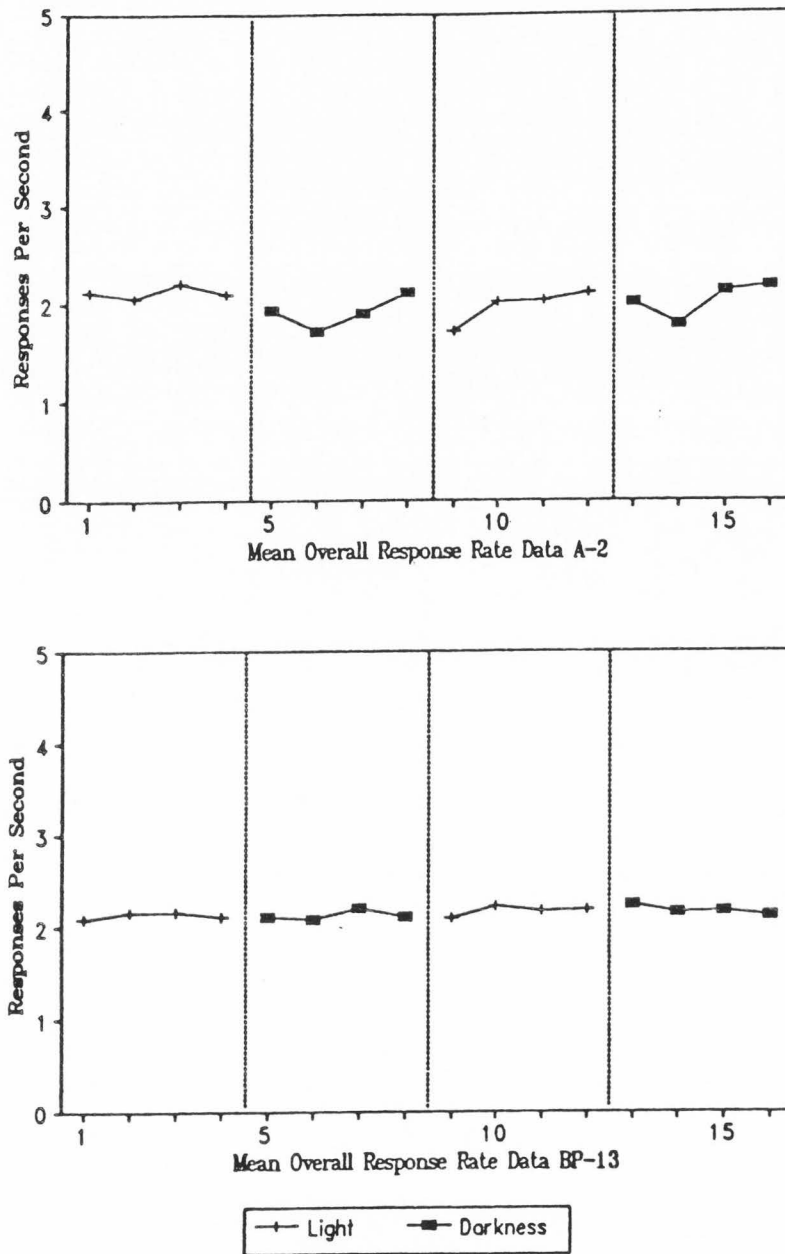
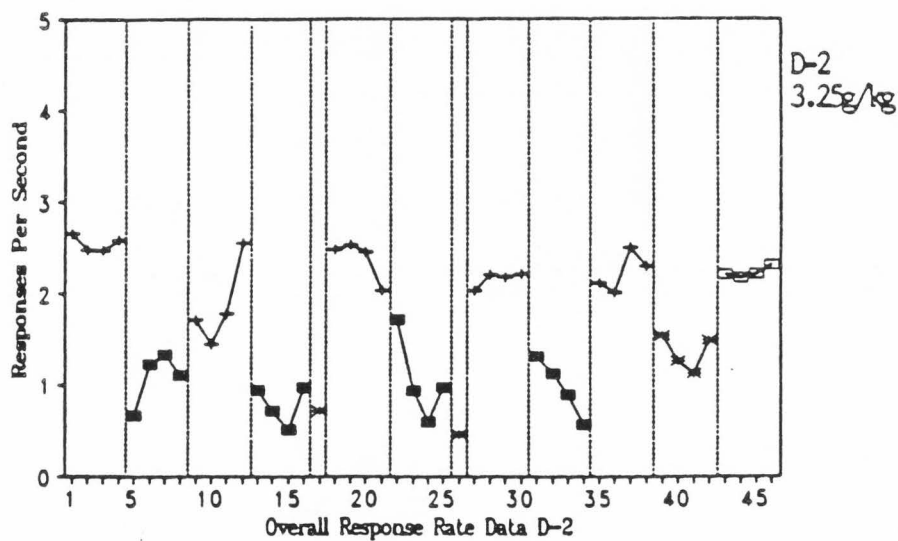
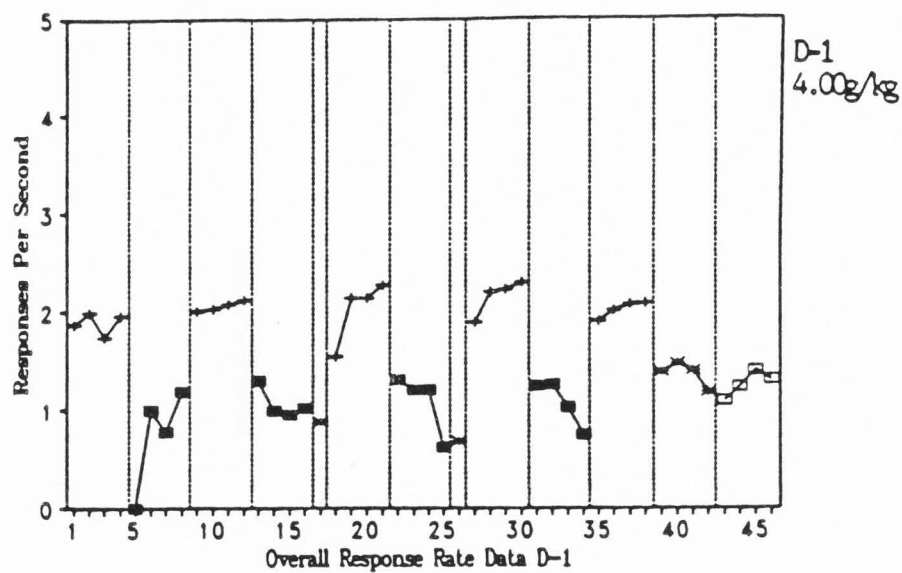


Figure 43. Baseline data for overall response rate in responses per second for subjects A-2 and BP-13.

Mean Overall Response Rate



—△— Light/Water —■— Darkness/Alc —×— Tolerance Pro —○— Facilitation Pr

Figure 44. Mean overall response rate data in responses per second for subjects D-1 and D-2. The legend is described in Figure 23 text.

Mean Overall Response Rate

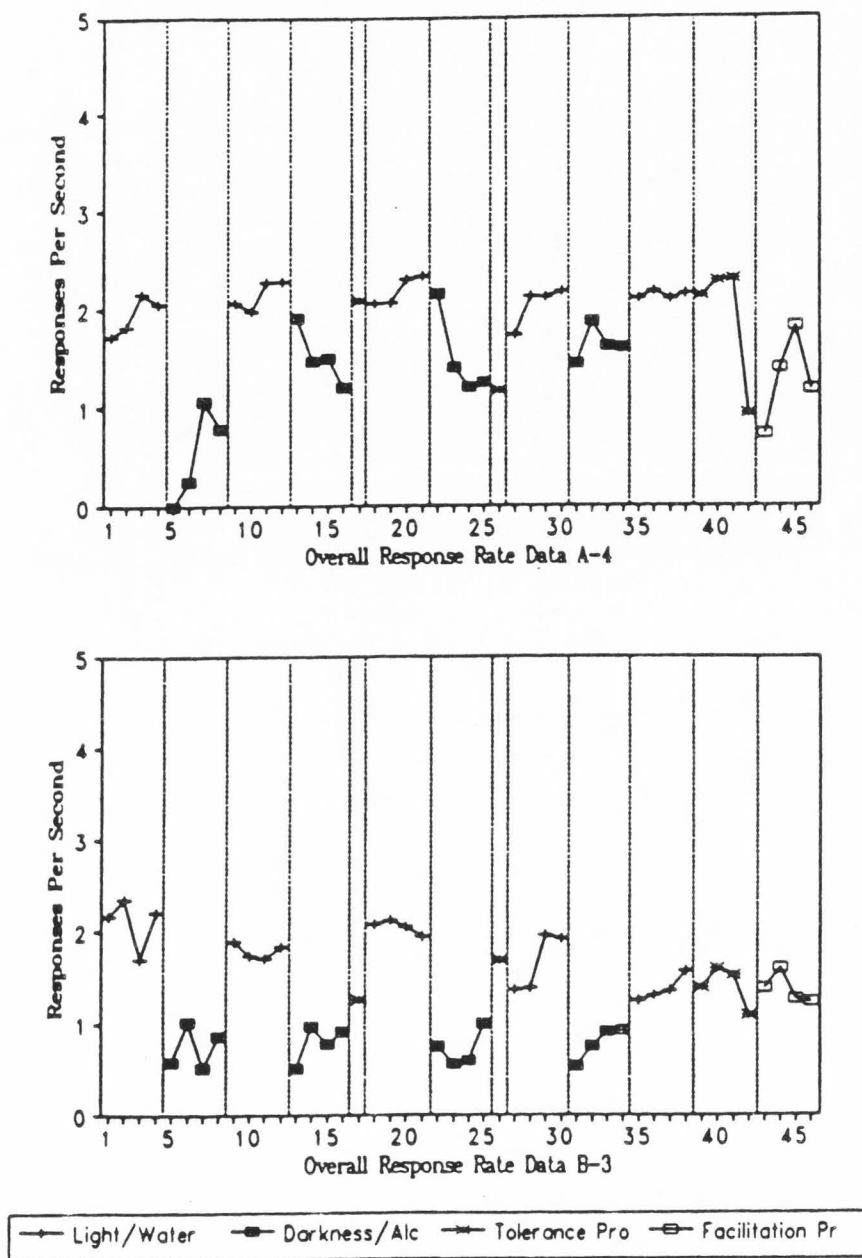


Figure 45. Mean overall response rate data in responses per second for subjects A-4 and B-3.

Baseline Data

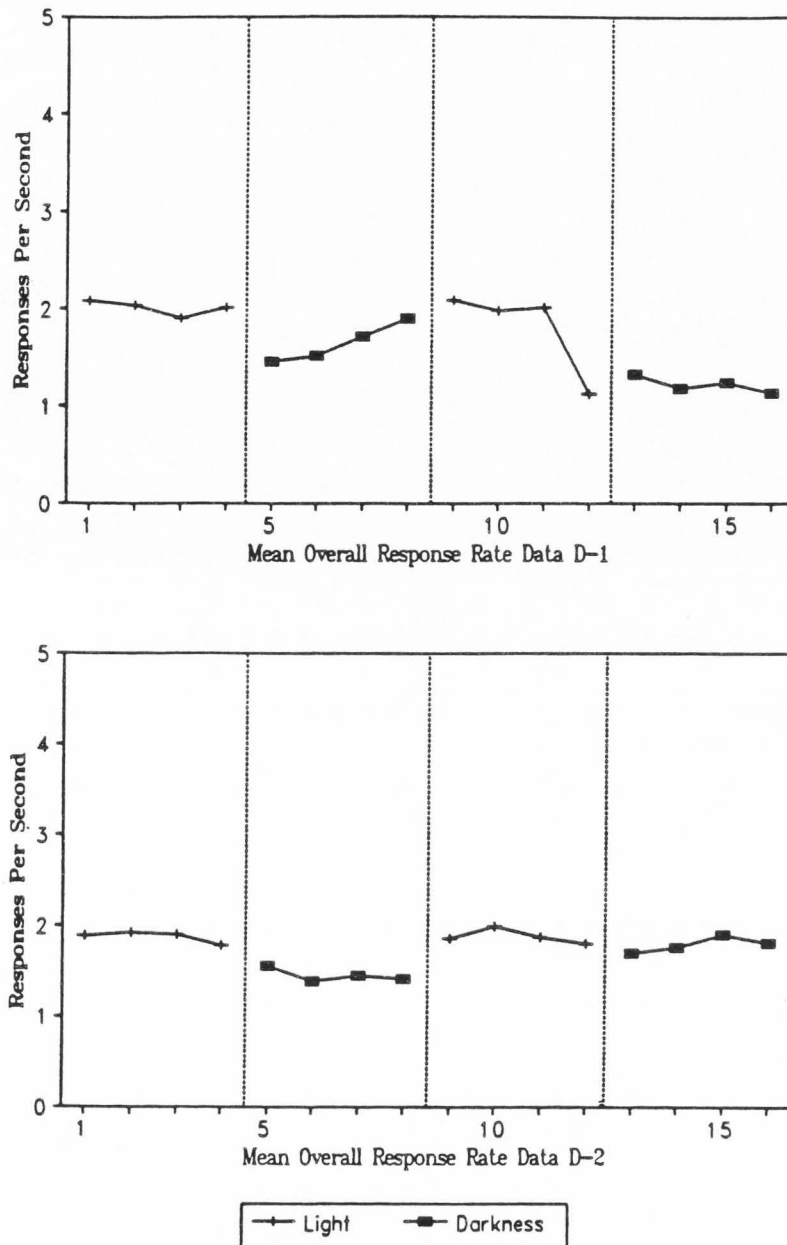


Figure 46. Baseline data for the dependent variable mean overall response rate in responses per second for subjects D-1 and D-2.

Baseline Data

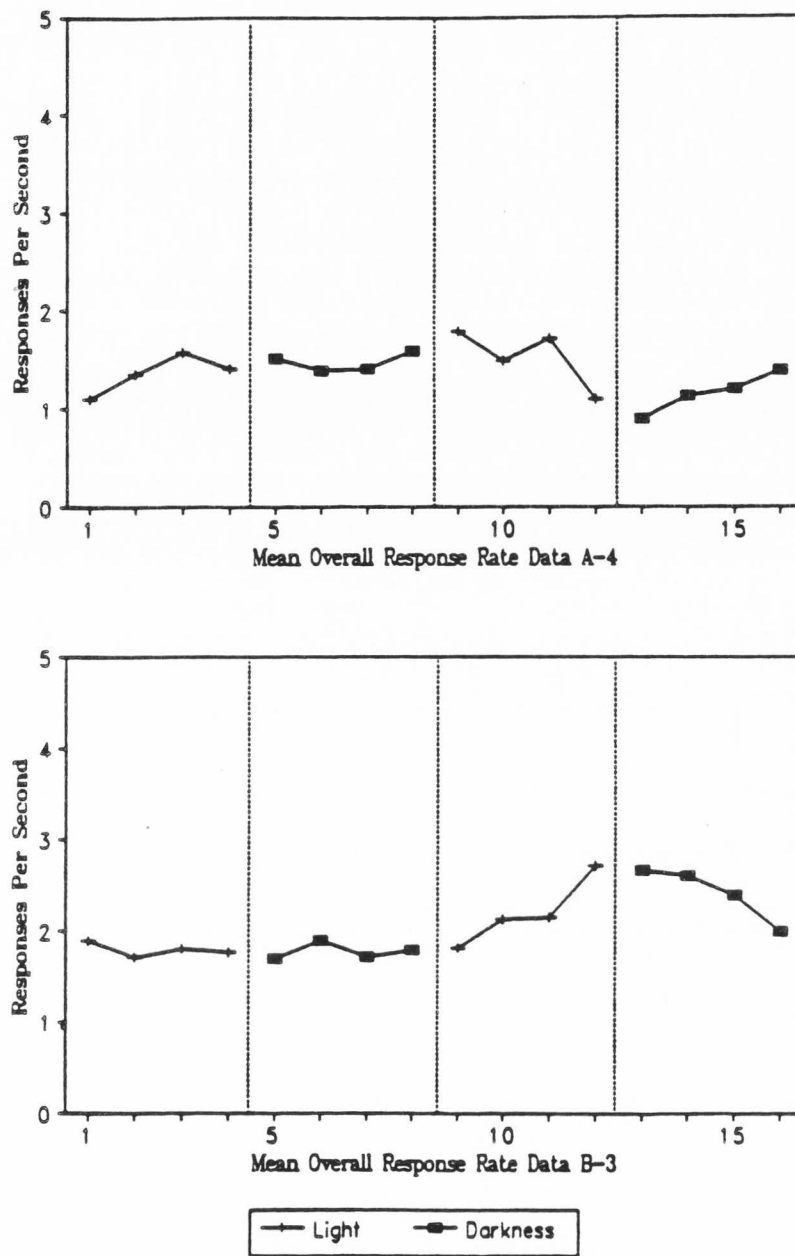


Figure 47. Baseline mean overall response rate data in responses per second for subjects A-4 and B-3.

Baseline Data

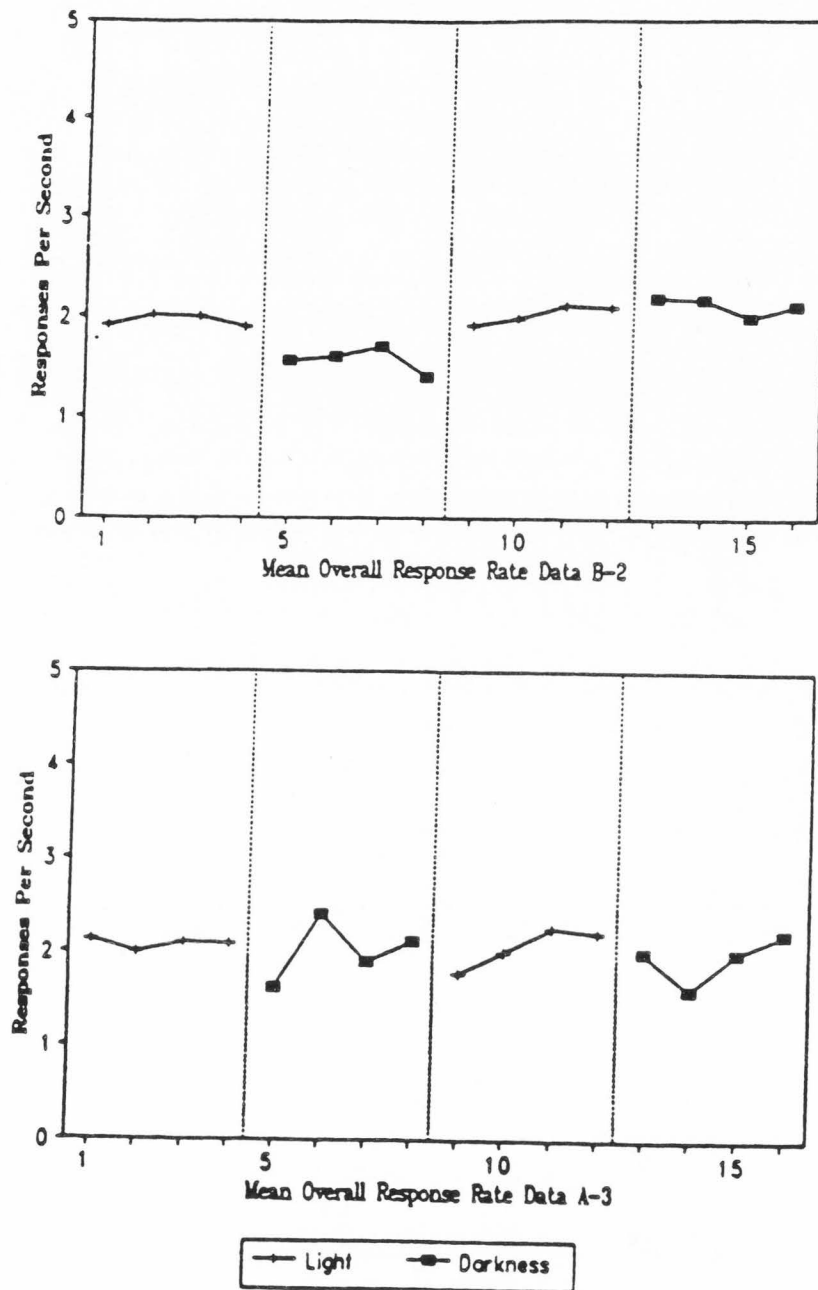


Figure 48. Baseline mean overall response rate data in responses per second for subjects B-2 and A-3.

Baseline Data

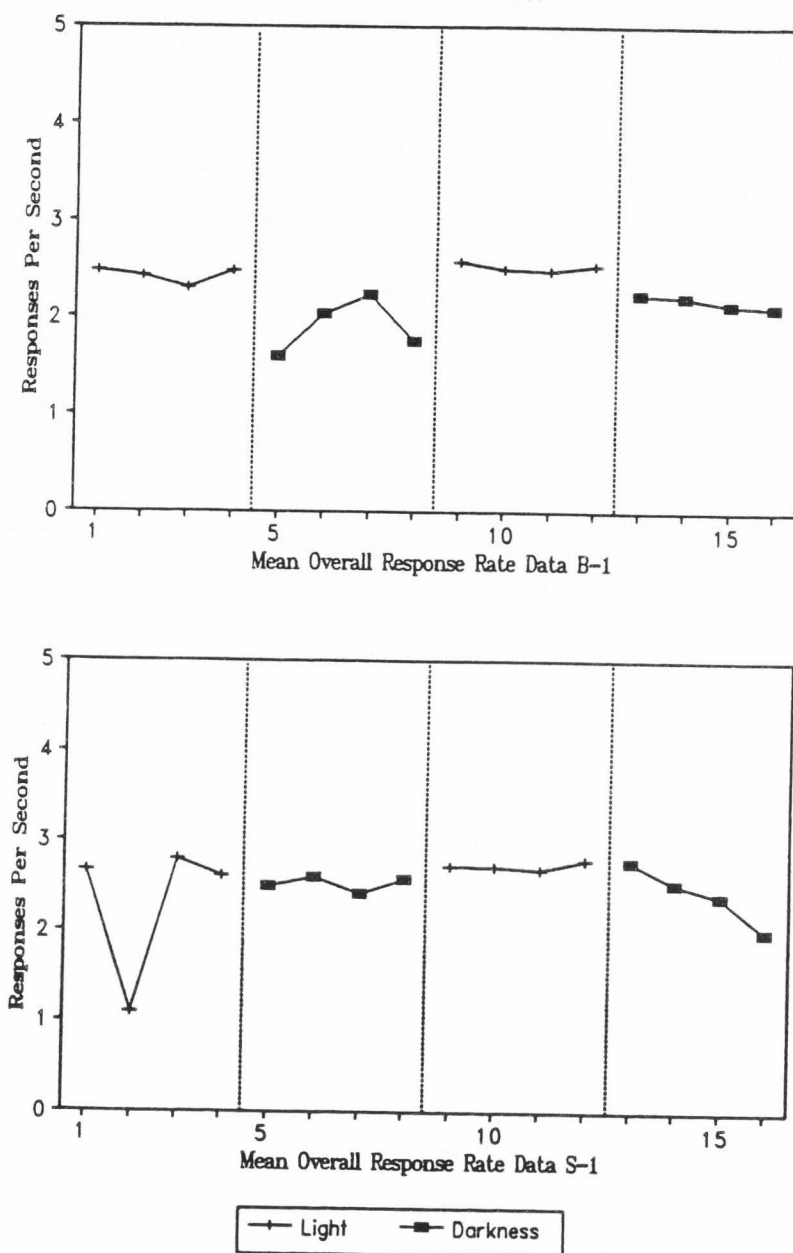


Figure 49. Baseline mean overall response rate data in responses per second for subjects B-1 and S-1.

Mean Overall Response Rate

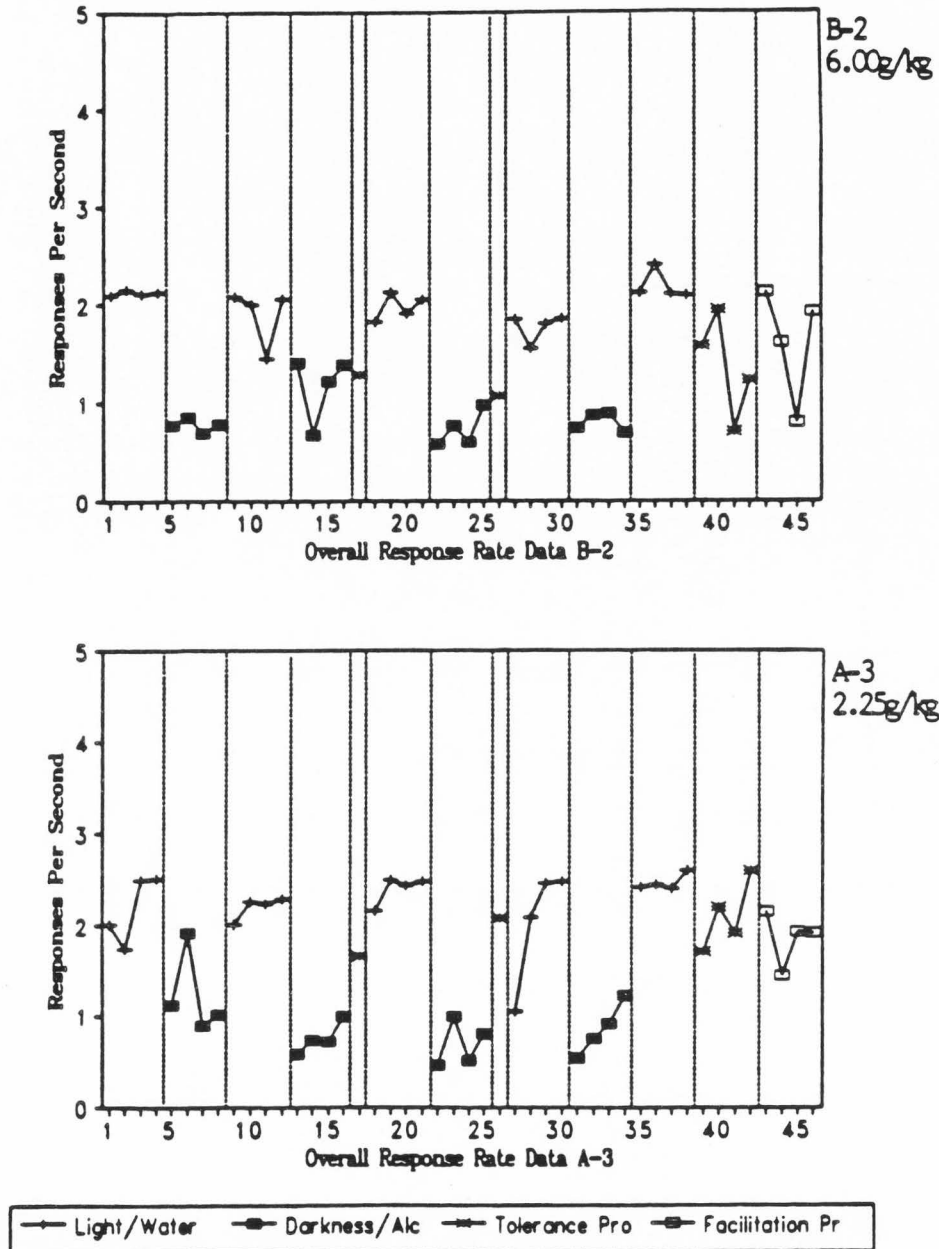
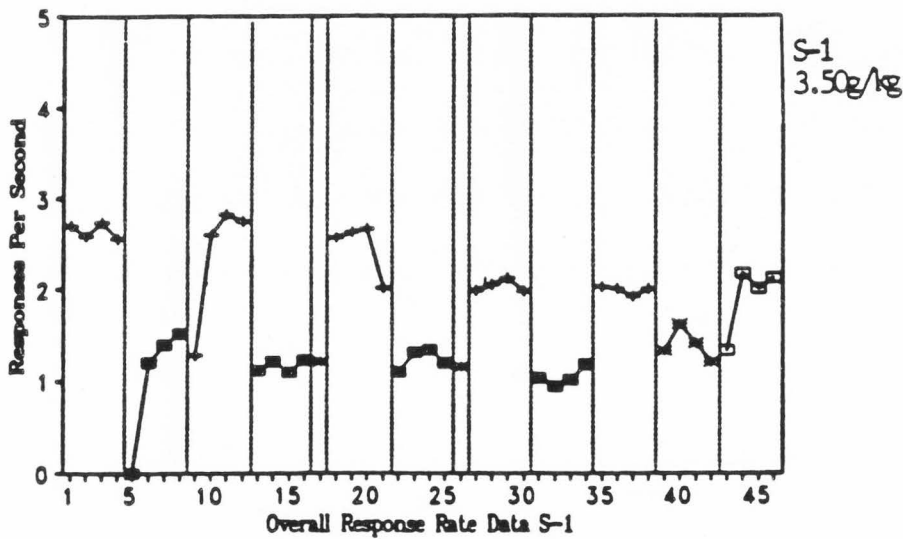
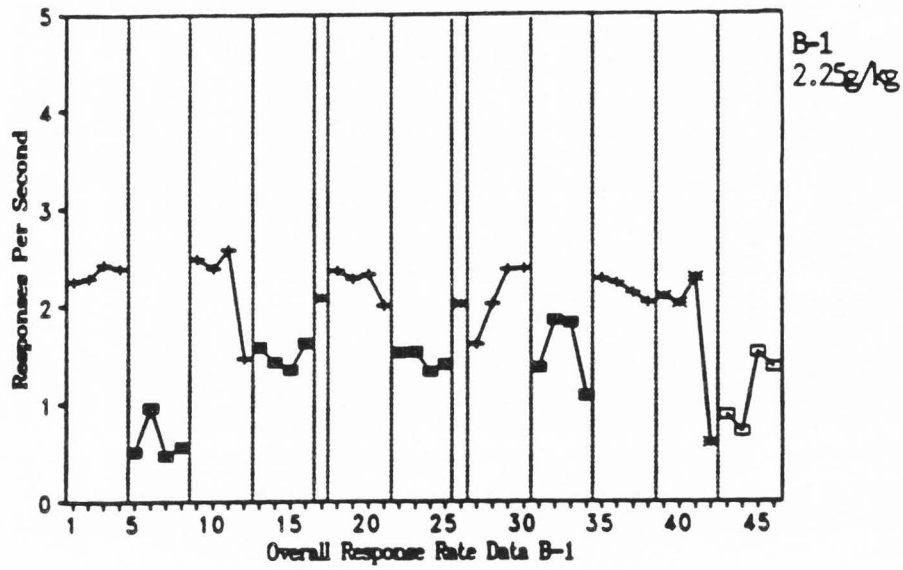


Figure 50. Mean overall response rate data in responses per second for subjects B-2 and A-3.

Mean Overall Response Rate



—△— Light/Water —■— Darkness/Alc —×— Tolerance Pro —○— Facilitation Pr

Figure 51. Mean overall response rate data in responses per second for subjects B-1 and S-1.

Baseline Data

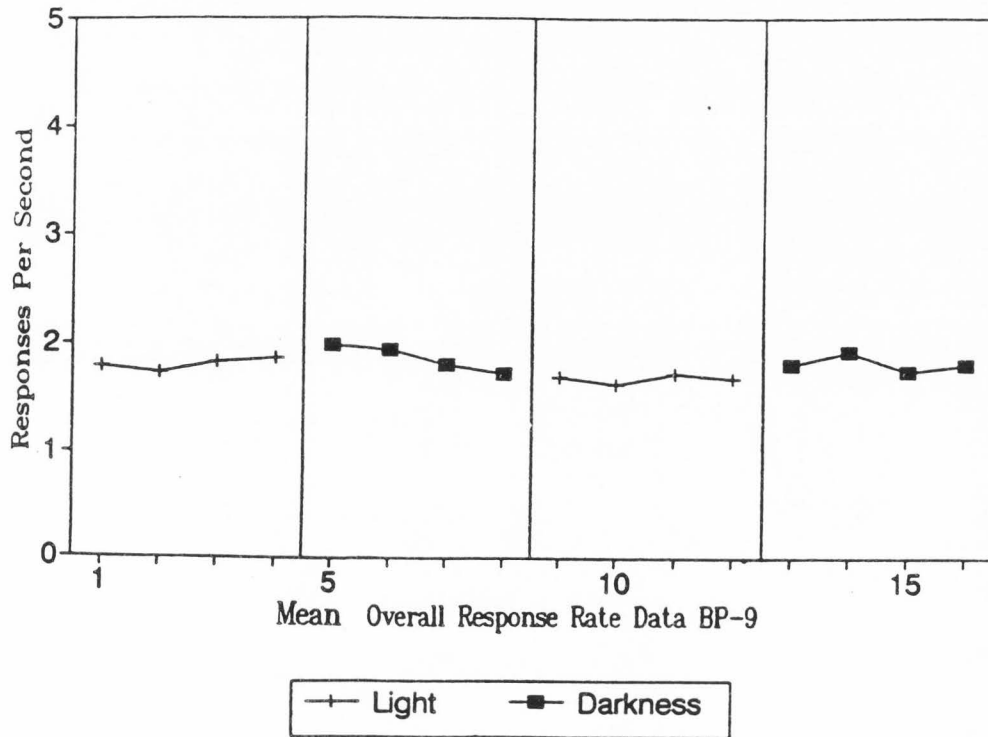


Figure 52. Baseline mean overall response rate in responses per second for subject BP-9.

Mean Overall Response Rate Series 2

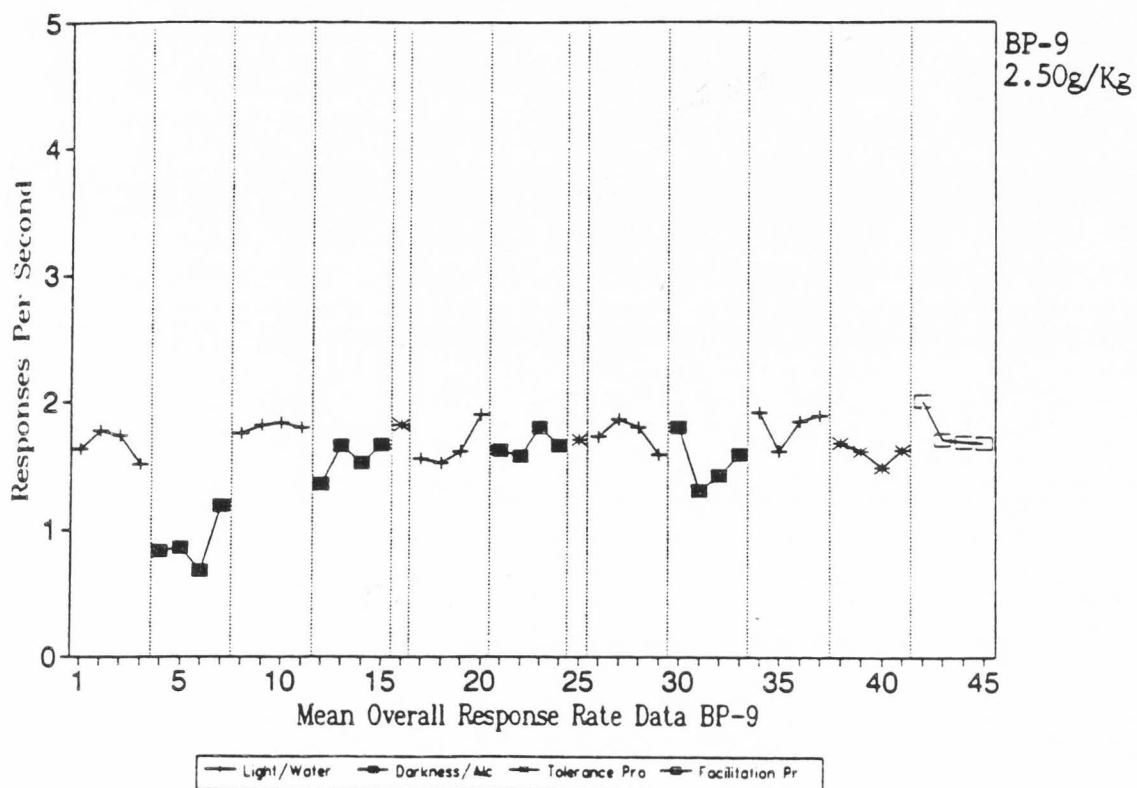


Figure 53. Mean overall response rate data in responses per second for subject BP-9. Data shown is from this subject's second conditioning series.

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Psychology 140, Analysis of Behavior: Basic Processes; (6 quarters)
Psychology 321, Abnormal Psychology (1 quarter)
Psychology 346, Physiological Psychology (3 quarters)
Psychology 351, Social Psychology (1 quarter)
Psychology 510, History and Systems (2 quarters)

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Exum, M.E., Osborne, J.G., Lignugaris/Kraft, B., & Phelps, B.J. (1991). Teaching Picture Reading Skills to Developmentally Disabled Adults in the Assembly of Complex Vocational Skills. Poster presented at the Association for Behavior Analysis, Atlanta, Georgia.

Cheney, C.D. & Phelps, B.J. (1990). Factors Predisposing to Drug Abuse. Invited Address presented at the Association for Behavior Analysis, Nashville, Tennessee.

Phelps, B.J. & Cheney, C.D. (1989). Operant and Respondent Interaction in the Development of Behavioral Tolerance to Ethanol in Pigeons. Poster presented at the Association for Behavior Analysis, Milwaukee, Wisconsin.

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