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# The Differential Effects of Stressors on Aversive, Novel and Appetitive Stimuli in Rats

Wayne J. Bowers

A Thesis

in

The Department

of

Psychology

Presented in Partial Fulfilment of the Requirements

of the Degree of Doctor of Philosophy at

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**ABSTRACT**

The Differential Effects of Stressors on Aversive, Novel and Appetitive Stimuli in Rats

Wayne J. Bowers, Ph.D
Concordia University, 1997


Stressors produce an array of effects on both aversively- and appetitively-motivated behaviors. Because aversive stimuli motivate behaviors in aversively-motivated tasks, assessing stressors effects in these tasks requires re-exposure to aversive stimuli. This is not the case in appetitively-motivated tasks. Based on research that stressors can potentiate responding to subsequent aversive stimuli, the current studies assessed the hypothesis that aversively-motivated behaviors are more sensitive to the effects of stressors than appetitively-motivated behaviors. The studies reported here compared the effects of footshock and restraint in several behavioral procedures that measure responses to aversive and appetitive stimuli. Because of evidence that novel stimuli may also be aversive, the impact of stressors on responding to novel stimuli were also evaluated.

CTA studies indicated that footshock enhanced amphetamine CTA (aversive response) and saccharin neophobia (novelty) but not saccharin consumption in saline-injected rats (appetitive response). Runway studies showed that footshock enhanced the response to reward reduction (aversive response) but had no impact on runway responding when reward magnitude was unchanged or increased (appetitive response).

Two studies examined the effect of restraint on drug self-administration. Restraint did not influence the acquisition or maintenance of cocaine self-administration, although restraint potentiated cocaine-induced locomotion. Restraint increased ethanol intake on the first post-restraint test only in animals deprived of ethanol on restraint days. Footshock decreased novelty-induced locomotion but only in the initial 5 min of the open-field test. Results of these studies indicate that stressors can alter responses to aversive and novel stimuli without altering responses to appetitive stimuli. Finally, to examine whether stressors preferentially enhance reactivity to aversive and novel stimuli, we compared two rat strain that differ in reactivity to aversive stimuli. The light/dark emergence test confirmed that Sprague-Dawley rats are more "anxious" than Long-Evans rats. The more reactive Sprague-Dawley rats exhibited a behavioral profile similar to that seen in stressed Long-Evans rats in the earlier studies. These studies support the hypothesis that exposure to stressors preferentially enhance the response to both aversive and novel stimuli without altering responses to appetitive stimuli.

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# INTRODUCTION

A considerable amount of work has been conducted to assess the relationship between stressful events and subsequent behavior and physiology in both humans and sub-human animals. In humans, stressful life events have been linked to a variety of physical and psychological disorders including depression (Anisman & Zacharko, 1992), schizophrenia (Jacobs, Prusoff & Paykel, 1974), heart disease (Fontana, Kerns, Rosenberg & Colonese, 1989), hypertension (Henry, 1988), and substance abuse (Alexander & Hadaway, 1982; O'Doherty, 1991). In animals, exposure to stressors produce a variety of effects including motoric (Anisman, Remington & Sklar, 1979; Glazer, Weiss, Pohorecky & Miller, 1975), sensory (Amit & Galina, 1988; Bodnar, 1986; Davis, Hitchcock & Rosen, 1989; Terman, Shavit, Lewis, Cannon & Liebeskind, 1984), attentional (Lee & Maier, 1988; Minor, 1984), cognitive (Jackson, 1980; Maier & Seligman, 1976; Rosellini, DeCola & Shapiro, 1982) and motivational (Papp, Muscat & Willner, 1993; Sonoda, Okayasu & Hirai, 1991; Zacharko & Anisman, 1991; Zacharko, Bowers, Kokkinidis & Anisman, 1983) and have been reported in both appetitively- and aversively-motivated tasks. There have, however, been few attempts to directly compare the impact of stressors between appetitively- and aversively-motivated behaviors despite the fact that there are fundamental differences in the nature of these paradigms. For instance, aversively-motivated tasks require

animals to escape or avoid a particular stimulus (the aversive stimulus) while appetitively-motivated behaviors require animals to approach or consume an appetitive stimulus. While it is possible to develop behavioral test procedures that equate task physical requirements between these two types of test paradigms, it is not possible to equate the specific feature that differentiates these test procedures - the affective nature of the motivational stimulus. This, of course, arises since the affective nature of the stimulus defines appetitive and aversive motivation.

One of the difficulties in characterizing the impact of stressors on behavior is that there is a fundamental difference in the nature of appetitively- and aversively-motivated behavioral tasks. Aversively-motivated tasks, by necessity, require the use of aversive stimuli that animals will work to avoid or escape. Because the stimuli that motivate behavior in these paradigms are stressful, assessing the impact of exposure to stressors on these necessitates re-exposure to aversive stimuli. As such, these procedures are inherently stressor re-exposure tasks. In contrast, testing the effects of exposure to stressors on appetitively-motivated behaviors does not require re-exposure to aversive or stressful stimuli since the motivating stimuli are appetitive rather than aversive. This fundamental difference in the nature of appetitively- and aversively-motivated behaviors leaves open the question of the role of the motivating stimuli in modulating the effects of stressors. If, for instance, prior exposure to a stressor alters responsiveness to a subsequent stressor, then this may play a role in the effects of stressors in aversively-motivated behaviors. It would not be expected to play any role in the effects of stressors on appetitively-motivated behaviors since such re-exposure

would not occur. As will be shown, there is evidence that exposure to stressors can alter the response to a subsequently-presented aversive stimulus. Indeed, enhanced responsiveness to aversive stimuli has been shown at both the behavioral level as well as the neurochemical level. Given this, there is reason to suspect that exposure to stressors may differentially influence responding in appetitively- and aversively-motivated tasks and that stressor effects vary as a function of the affective value of the motivating stimulus (i.e., appetitive or aversive stimuli). The converse of the same question is whether the affective value of the motivating stimulus alters the impact of stressors. The purpose of the current work is to address this question by comparing the effects of stressors on appetitively- and aversively-motivated behaviors.

For the current work, appetitive and aversive stimuli are defined within the framework developed by Young (1959) and elaborated by Kornorski (1967). In brief, appetitive stimuli are stimuli that engender approach behavior while aversive stimuli are those that elicit avoidance or escape behavior. In addition, both of these classes of stimuli are capable of producing conditioned forms of approach and avoidance behavior. For instance, animals will learn to escape from a neutral stimulus (such as a tone) that has been paired with shock (Masterson & Crawford, 1982; McAllister & McAllister, 1991; Mineka, 1979). Thus, by pairing the neutral stimulus with an aversive stimulus, the previously neutral stimulus (the conditioned stimulus: CS) begins to take on the aversive qualities of the unconditioned aversive stimulus (UCS). With sufficient conditioning, the CS will elicit avoidance and escape behavior and therefore can be classified as an aversive stimulus. Comparable conditioned approach

responses can be produced by pairing appetitive stimuli with neutral stimuli. Thus, neutral stimuli can become either appetitive or aversive stimuli via Pavlovian conditioning processes. For the current work, the classification of stimuli as appetitive is therefore defined by the ability of the stimulus (whether unconditioned or conditioned forms) to engender approach behavior. Aversive stimuli (whether unconditioned and conditioned forms) are defined as those that are capable of eliciting escape or avoidance responding.

Defining stressors is a difficult task. Indeed, although there have been many attempts to provide definitions of stressors, there is no general agreement on what criteria must be satisfied. Many researchers appear to define stressors by the ability of stimuli to produce hormonal or biochemical responses such as increased adrenocorticotropic hormone (ACTH), norepinephrine (NE), dopamine (DA), etc. Difficulties associated with this approach arise because many stimuli that produce comparable alterations in these chemical measures have no obvious aversive qualities. For instance, both footshock and reinforcing drugs are capable of altering dopamine activity in a variety of brain structures but, on a behavioral level, these treatments have quite different effects (McCullough & Salomone, 1992). On a more general level, there is a more serious problem with explaining the impact of stressors on the basis of the very indices that define stressors. For instance, it is not reasonable to define stressors on the basis of their ability to alter ACTH levels and then propose ACTH as the biochemical mechanism subserving the effects of stressors. Because of these problems, the definition of stressors for the current work employs a different approach.

Stressors are defined as aversive stimuli. Thus, stressors include both unconditioned aversive stimuli as well as conditioned aversive stimuli. Moreover, we specifically exclude appetitive stimuli as stressors. Because appetitive and aversive stimuli have been defined in terms of their effects on behavior, stressors are also defined in behavioral terms. While this approach does not exclude hormonal or biochemical indices as validating tools, it does explicitly exclude these measures as acceptable means of defining a stimulus as a stressor.

In order to provide some framework for the comparison of the effects of stressors on appetitively- versus aversively-motivated behaviors, a brief overview of research on the effects of exposure to stressors on appetitively- and aversively-motivated behavioral tasks is presented below. Given the extensive amount of published research, this overview is not intended to be exhaustive; rather it attempts to provide a general description of the type of consequences stressors have on appetitively- and aversively-motivated behaviors. While this research is presented within an appetitive/aversive dichotomy, there are behavioral test procedures which do not clearly fall into either of these general classes or could be reasonably classified in either class (e.g., neophobia and neophilia). For instance, the consumption of preferred solutions such as saccharin would normally be viewed as a measure of the response to an appetitive stimulus (as indexed by preference tests and data indicating that saccharin can serve as a positive reinforcer (Collier, 1962; Smith & Capretta, 1956). However, the initial consumption of such a solution reflects both the motivational or affective nature of the stimulus as well as the novelty of the stimulus, since animals typically exhibit a neophobic

reaction to novel tastes (Barnett, 1958). Indeed, as will be detailed below, there is evidence that novelty itself may be an aversive stimulus. Under such circumstances, exposure to a stressor before initial saccharin consumption would affect both the neophobic response and the appetitive response to saccharin. When exposure to a stressor occurs after initial saccharin consumption, subsequent saccharin consumption would reflect primarily the effects of the stressor on the appetitive response in the absence of (or, at least, to a lesser degree) the neophobic response. The same argument would hold for other measures where stimulus novelty is involved (e.g., novelty-induced locomotion).

The overview presented below describes the effects of stressors on responding to these three general classes of stimuli: aversive, appetitive and novel.

**Stress and Aversive Stimuli**

There are a number of behavioral procedures that have been used to assess the impact of exposure to stressors on behavioral responses in aversively-motivated paradigms (Anisman, 1975; Anisman & Zacharko, 1990; Minor, Dess & Overmier, 1991; Minor, Trauner, Lee & Dess, 1990; Salamone, 1994). The common feature of these tests is that aversive stimuli are used to motivate the measured behavior(s) and the behavioral response under consideration is either escape from or avoidance of the aversive stimuli.

One of the most frequently used aversively-motivated tasks is shuttle-box escape responding where animals must learn to escape or avoid shock by shuttling between a

shocked and non-shocked chamber (Klein & Mowrer, 1989; Maier, 1989; Minor, Dess & Overmier, 1991). Shock-motivated escape performance has also been assessed in three-chamber Y-mazes in attempts to dissociate the motoric effects of shock from choice accuracy (Anisman, Hamilton & Zacharko, 1984; Maier, 1989; Minor, 1984; Minor & Lolordo, 1984). A number of procedural variants of shock-escape tasks have also been used. Such variants include modifying escape response requirements (e.g., reinforcement schedules, task difficulty) (Anisman, deCatanzaro & Remington, 1978; Anisman, Remington & Sklar, 1979; Maier, Albin & Testa, 1973; Maier & Seligman, 1976; Weiss & Glazer, 1975) and modifying task cues by providing relevant and irrelevant response cues (Baker, 1976; Minor, 1984; Minor, Pellymounter & Maier, 1988; Minor, Dess & Overmier, 1991; Minor & Lolordo, 1984). Regardless of the variants used, these tasks require animals to escape or avoid aversive shock.

Animals previously exposed to inescapable shock exhibit deficits in learning to escape from shock (Anisman, deCatanzaro & Remington, 1978; Anisman, Remington & Sklar, 1979; Glazer, Weiss, Pohorecky & Miller, 1975; Minor, 1984; Maier, 1989; Maier & Seligman, 1976; Seligman & Maier, 1967; Lee & Maier, 1988). For instance, escape deficits have been reported in the shuttle box (Anisman, Remington & Sklar, 1979; Glazer, Weiss, Pohorecky & Miller, 1975; Maier & Seligman, 1976), Y-maze (Anisman, Hamilton & Zacharko, 1984; Maier & Minor, 1993), and bar-press escape tasks (Maier & Seligman, 1976; Seligman & Beagley, 1975). It is now known that inescapable shock produces a variety of disturbances including associative (Jackson, 1980; Minor & Lolordo, 1984; Rosellini, DeCola & Shapiro, 1982), motoric (Anisman,

deCatanzaro & Remington, 1978; Anisman, Remington & Sklar, 1979; Weiss & Glazer, 1975; Weiss, Bailey, Pohorecky, Korzeniowski & Grillione, 1980), motivational (Anisman & Zacharko, 1992; Papp, Willner & Muscat, 1993; Willner, Muscat & Papp, 1992; Zacharko & Anisman, 1991; Zacharko, Bowers, Kokkinidis & Anisman, 1983), attentional (Lee & Maier, 1988; Maier, 1989; Minor, 1984; Minor, Pellymounter & Maier, 1988), and analgesic (Amit & Galina, 1988; Maier, 1986; Maier et al.1980; Porro & Carli, 1988; Terman, Shavit, Lewis, Cannon & Liebeskind, 1984). Because of the diversity of the mechanisms that influence escape deficits, it is difficult to determine from these behavioral procedures whether the prior stress of inescapable shock influences the response to the aversive stimuli (in this case, shock) used in the test situation. Nevertheless, there is some evidence from this literature that this may be the case.

It has been suggested that escape deficits following inescapable shock may be due to alterations in the ability of animals to initiate and maintain motor responding (Anisman, Remington & Sklar, 1979; Weiss & Glazer, 1975). Evidence for this comes from studies that analyze the pattern of motor behavior during the course of escape responding. In normal animals (i.e., animals not previously exposed to inescapable shock), the onset of shock in the shuttle escape task typically produces an initial increase in motor activity which is followed by motor suppression if the animals cannot escape from the shock (Anisman, Remington & Sklar, 1979). In animals previously exposed to inescapable shock, the latency to onset of the motor suppression is reduced (Anisman, Remington & Sklar, 1979). Because, shuttle escape deficits are

typically not evident if there is no delay between escape responding and shock offset, these data support the contention that the inability to maintain motor responding during shock can produce escape deficits (Glazer, Weiss, Pohorecky & Miller, 1975; Weiss & Glazer, 1975). For current purposes, these data also support the suggestion that the experience with inescapable shock reduces the delay in the onset of the unconditioned motor suppression produced by shock in the escape task itself.

It has also been suggested that escape deficits may be mediated by stress-induced alterations in NE (Anisman, Kokkinidis & Sklar, 1985; Anisman & Zacharko, 1988; Cassens, 1980). Exposure to inescapable shock has been shown to alter NE levels in a number of brain regions (Adell, Trullas & Gelpi, 1988; Cassens, 1980; Nestler, 1992; Rossetti, Portas, Pani, Carboni & Gessa, 1990; Weiss, Bailey, Pohorecky, Korzeniowski & Grillione, 1980; Weiss, Glazer, Pohorecky, Brick & Miller, 1975) and pharmacological manipulations that produce similar alterations in NE also induce escape deficits (Anisman, Remington & Sklar, 1979; Glazer, Weiss, Pohorecky & Miller, 1975; Weiss, Glazer, Pohorecky, Brick & Miller, 1975). More importantly, it has been shown that prior exposure to inescapable shock reduces the amount of shock required to produce depletions in NE (Anisman, Remington & Sklar, 1979). For instance, while 10 inescapable shocks typically do not alter NE levels in the hypothalamus of mice, this shock treatment does produce depletions in NE in mice that had been exposed to 60 inescapable shocks 24 hr earlier (Anisman, Remington & Sklar, 1979). It should be emphasized that NE depletions in hypothalamus are evident immediately after 60 inescapable shocks but not 24 hr later. Thus, while 10 shocks are

ineffective in depleting NE levels, the prior experience with 60 shocks sensitizes the NE response to the normally ineffective 10 shocks. It has also been shown that repeated exposure to cold stress enhances the increase in hippocampal NE produced by footshock (Nisenbaum, Zigmond, Sved & Abercrombie, 1991) Similarly, in mice with no prior stressor treatment restraint stress does not alter NE levels; however, restraint does produce NE depletions when mice had received footshock 24 hr earlier (Irwin, Bowers, Zacharko & Anisman, 1982). These studies indicate that the NE response to a normally ineffective stressor can be enhanced by prior exposure to a stressor that alters NE levels (i.e., 60 shocks) and suggest that the experience with one stressor can enhance the response to a subsequent stressor.

Another factor thought to play a role in stressor-induced escape deficits is a reduction in pain sensitivity. Animals exposed to inescapable shock as well as other stressors display a reduction in pain sensitivity (Amir, 1986; Bodnar, 1986; Chance, 1979; Faneslow, 1991; Faneslow, 1985; Giradot & Holloway, 1984; Grau, Hyson, Maier, Madden & Barchas, 1981; MacLennan et al.1982; Maier, 1986; Miczek, Thompson & Schuster, 1982; Puglisi-Allegra & Oliverio, 1983). Prior exposure to inescapable shock reduces the amount of subsequent shock required to induce analgesia (Jackson, Maier & Coon, 1979; Maier, 1986). Since re-exposure to a small number of shocks is capable of re-inducing analgesia, such an analgesic response would be expected to reduce the painfulness of shock in the escape test situation and, presumably, reduce the motivation to escape. This suggests that prior stressor exposure increases subsequent responsiveness to shock as indicated by the decrease in number

of shocks required to produce analgesia. Moreover, the analgesia induced by exposure to stressors is thought to be mediated by an active inhibition of pain sensitivity by fear mechanisms (Faneslow, 1991; Faneslow, 1986). According to this account, exposure to stressors increase fear and this increased fear attenuates the perception of pain when animals are subsequently exposed to painful stimuli in the analgesia test situation.

Rats and mice will readily learn a response to escape from water and a number of studies have assessed the impact of exposure to stressors on swim escape behavior (Cancela, Rossi & Molina, 1991; Kant, 1993; Lee & Maier, 1988; Maier, 1989; Prince & Anisman, 1984; Warren, Castro, Rudy & Maier, 1991). The effect of shock has also been assessed in Y-mazes and T-mazes that are submerged in water. Such swim escape tasks are comparable to shock escape tasks except that animals must escape from the water instead of shock. Exposure to inescapable shock disrupts subsequent swim escape performance of rats in both a Y-maze or T-maze, primarily by increasing errors in choosing the correct arm in the choice task (see Maier, 1989 for a review).

It appears that the increase in choice errors in the Y-maze or T-maze swim task are due to stressor-induced alterations in attentional mechanisms (Lee & Maier, 1988; Maier, 1989). For instance, inescapable shock disrupts choice accuracy when the correct choice is based on proprioceptive factors (i.e., right or left); however, inescapable shock facilitates choice behavior when the correct choice in based upon external visual cues (Lee & Maier, 1988; Maier, 1989). These data suggest that inescapable shock influences choice accuracy in swim escape tasks by directing the subjects attention away from self-produced cues (i.e., proprioceptive cues) and toward

external cues (Lee & Maier, 1988; Maier, 1989). Similar disturbances in attentional mechanisms have also been found in a shock-motivated Y-maze choice task (Maier, 1989; Minor, 1984; Minor, Pellymounter & Maier, 1988) suggesting some generality of shock-induced attentional disturbances. There has also been some suggestion that inescapable shock elicits stimulus perseveration in water escape tests (Anisman & Zacharko, 1988). For instance, mice will normally spend most of the time in the lighted area of a water tank and this preference for the lighted area is increased by prior exposure to inescapable shock (Anisman & Zacharko, 1988). Such results have been interpreted to support the position that stressors disrupt escape behavior by enhancing attention and responsiveness to specific environmental stimuli rather than by disrupting the ability to differentiate relevant and irrelevant environmental cues (Anisman, Hamilton & Zacharko, 1984; Anisman, Zalcman, Schanks & Zacharko, 1991).

Other data indicate that exposure to footshock alters swimming patterns in the Porsolt swim test. Briefly, this task consists of placing rats or mice in a tank of water from which escape is impossible. (Technically, this is a swim escape task although only escape attempts can be measured since escape itself is precluded.) Both escapable and inescapable shock increase active escape attempts (i.e., active swimming) immediately following shock exposure (Prince & Anisman, 1984). However, inescapable shock decreases active swimming and increases passive floating or immobility 24 hr after exposure to shock (Prince & Anisman, 1984). These latter

results are similar to the reduced delay in onset of shock-induced motor suppression in the shuttle escape test (Maier & Seligman, 1976).

The effects of prior shock have also been evaluated in the Morris water maze - a procedure designed to assess spatial navigation. This procedure consists of placing animals in a large tank of water and permitting the animal to swim to a platform that is barely submerged in the water tank (i.e., the escape platform is not visible). Typically animals quickly learn to escape from the water by locating the submerged platform using spatial cues such as room features (Morris, 1984; Morris, 1981; McNamara & Skeleton, 1993). Inescapable shock exerts little impact on the ability of animals to learn to escape water in the Morris water maze (Warren, Castro, Rudy & Maier, 1991). Though there are few studies available, these results suggest that footshock stress does not alter the ability of animals to use spatial cues to escape from water.

Conditioned taste aversions (CTA) provide an index of the avoidance of a neutral or preferred substance that has been paired with a drug (Hunt & Amit, 1986; Gamzu, 1977; Goudie, 1979; Grant, 1987; Riley & Tuck, 1994) and have been demonstrated with a wide range of taste stimuli and a large number of drugs (Goudie, Stolerman, Demellweek & D'Mello, 1982; Grant, 1987; Hunt & Amit, 1986; Riley & Tuck, 1994). Although exposure to stressors have been shown to alter CTA, results have been inconsistent. Both rotation-induced and apomorphine-induced CTA are enhanced by prior exposure to footshock (Lasiter & Braun, 1981) while morphine-induced CTA does not appear to be affected by either shock or swim stressors (Bourne, Calton,

Gustavson & Schachtman, 1992; Revusky & Reilly, 1989). In contrast, LiCl-induced CTA seems to be attenuated by footshock and swim stressors (Bourne, Calton, Gustavson & Schachtman, 1992; Revusky & Reilly, 1989). These data suggest that the effects of stressors on CTA may be dependent upon the nature of the drug employed in CTA testing. This presumes that different classes of drugs produce taste aversions by different physiological mechanisms and there is some evidence to substantiate this position (Goudie, Stolerman, Demellweek & D'Mello, 1982; Grant, 1987; Hunt & Amit, 1986).

The acoustic startle response has also been employed as a measure of sensory reactivity and anxiety (Brown, Kalish & Farber, 1951; Davis, 1989; Davis, 1992). The unconditioned response to acoustic stimuli is enhanced by prior exposure to footshock (Davis, 1989; Hitchcock, Sananes & Davis, 1989) and is potentiated by presentation of cues associated with shock (Davis, 1992; Davis, Hitchcock & Rosen, 1989). The enhanced startle response to acoustic stimuli produced by such conditioned cues is thought to reflect an increase in conditioned fear (Davis, 1992; Davis, Hitchcock & Rosen, 1989) and it is this increase in conditioned fear that potentiates the startle response (Davis, 1992). Thus, prior exposure to footshock stress as well as cues associated with shock may increase sensory reactivity to noise stimuli by increasing fear. As was the case for stress-induced analgesia, it appears that the increased reactivity to acoustic stimuli may be mediated by a stress-induced increase in fear (Davis, 1992; Faneslow, 1986).

The occurrence of non-reward where rewards are expected (reward omission) is thought to be aversive. Indeed, non-reward appears to share a number of characteristics with stressors. First, animals will work to escape from environments where reward was previously delivered (unconditioned escape) (Daly, 1969a; Daly, 1969b; Daly, 1974; Rosellini & Seligman, 1975). Second, stimuli paired with non-reward that occurs during extinction testing or the during the non-rewarded component of a partial reinforcement schedule will support escape behavior (conditioned escape) (Daly, 1969; Daly, 1974; Daly & McCroskery, 1973; Wagner, 1959). Third, non-reward produces stress-like increases in ACTH and corticosterone (Davis, Memmott, Macfadden & Levine, 1976; Earley & Leonard, 1979; Stanford & Salmon, 1989). Accordingly, studies assessing the impact of exposure to stressors on the behavioral response to reward omission may be viewed as aversively-motivated tasks.

A number of studies have shown that exposure to inescapable shock increases the persistence of responding in the absence of reinforcers (i.e., during extinction) in the straight runway (Chen & Amsel, 1977; Chen & Amsel, 1982; Nation & Boyagian, 1981; Rosellini & Seligman, 1975; Wong, 1971). Response persistence during extinction testing has been reported when inescapable shock has been applied either before (Chen & Amsel, 1977; Chen & Amsel, 1982; Nation & Boyagian, 1981; Wong, 1971) or during runway training (Chen & Amsel, 1977; Rosellini & Seligman, 1975). The shock-induced increase in resistance to extinction appears to be independent of the number of shock sessions since increased resistance to extinction is evident after a single session of 60 shocks (Nation & Boyagian, 1981) as well as after 6 days of 72

shocks per day (Chen & Amsel, 1977). However, the duration of the shock (i.e., the length of each shock) seems to influence the impact of shock on resistance to extinction in the runway. Nation & Boyagian (1981), for example, have shown that while either 60 or 300 shocks of 3 sec duration increased resistance to extinction, 60 shocks of 15 sec duration decreased resistance to extinction. They suggest that the shock-induced increase in resistance to extinction may be mediated by the transfer of shock-produced unconditioned responses from the shock situation to the extinction situation. Accordingly, since short-duration shock produces motor activation (Anisman, deCatanzaro & Remington, 1978; Anisman, Remington & Sklar, 1979), the transfer of this response to the extinction situation would result in increased activity and thus increased resistance to extinction. Conversely, the transfer of freezing in the animals exposed to long duration shock would result in reduced activity in the runway and therefore decreased resistance to extinction. (A more detailed description of mechanisms involved in transfer of persistence is available in Amsel, 1992).)

Exposure to shock also decreases the number of retraces (i.e., running away from the goal box) during extinction testing (Chen & Amsel, 1977), and retards the acquisition of a hurdle jump response to escape from the non-rewarded goal box (Rosellini & Seligman, 1975). Since these latter two measures are thought to reflect an unconditioned aversive response to reward omission (Amsel, 1992; Daly, 1969; Daly, 1991), they suggest that exposure to shock attenuates the response to aversive non-reward (and therefore the motivation to escape the non-rewarded goal box).

**Stress and Novel Stimuli**

There is some indication that novel stimuli have at least some aversive component. The biochemical responses to novel stimuli are similar to those produced by stressors such as shock, restraint, immobilization, and swim. For instance, exposure to novel environments produce increases in plasma corticosterone (Anderson, Kant & De Souza, 1993; Bassett, Cairncross & King, 1973; Hennessy, 1991; Kant, Eggleston, Landman-Roberts, Kenion & Driver, 1985; Maccari et al.1991; Pfister, 1979), ACTH (Handa et al. 1993), cortical NE (Handa et al. 1993), and cortical dopamine (Bertolucci-D'Angio, Serrano, Driscoll & Scatton, 1990; Handa et al.1993; Tassin, Herve, Blanc & Glowinski, 1980). Novelty also increases plasma cortisol levels in monkeys (Coe, Franklin, Smith & Levine, 1982). Indeed, many researchers consider novelty as a stressor (Barrington, Jarvis, Redman & Armstrong, 1993; Brodish & Odio, 1989; Dunn, 1988; Flaherty & Rowan, 1989; Handa et al.1993; Pfister, 1979; Pfister & Muir, 1992; Piazza et al.1991; Rouge-Pont, Piazza, Kharouby, LeMoal & Simon, 1993; Stanton, Gutierrez & Levine, 1988; Stanton & Levine, 1990). Because of the similarities between the responses to novelty and stressors, novel stimuli should not be treated as neutral stimuli.

One of the difficulties in assessing the effects of stressor on the response to novel stimuli is that the initial response to most stimuli reflects the combined influence of novelty and the affective value of the selected stimulus (Berlyne, 1963; Williams, Gray, Snape & Holt, 1989; Kelley, 1993; Russell & Williams, 1973; Valle, 1971; File, 1985; Bronson, 1968). Since the response to the affective value of the stimulus is

confounded with the response to the novelty of the stimulus, measures of the initial response to a novel stimulus cannot be attributed solely to the affective value of the stimulus. Alterations in the response to novel stimuli following exposure to stressors may reflect changes in the response to either the novelty or the affective valence of the stimulus or both. Moreover, because the response to the stimulus following the initial encounter (i.e., when it is novel) is influenced to a lesser degree by its novelty, assessing the impact of treatments, like stressors, on the response to novel stimuli requires the measurement of treatment effects both when the stimulus is novel and following habituation to it.

There are a number of means that can be used to tease these apart. For instance, pre-exposure to the novel stimulus prior to stressor treatment should minimize the novelty of the stimulus (i.e., the orientation reflex should habituate) and therefore minimize the impact of the stressors on the response to novelty. The influence of stressors can then be determined from a comparison between subjects pre-exposed to the novel stimulus and subjects not pre-exposed to it. Similarly, the response to novelty can be assessed by analyzing the time course of the response to the novel stimulus within subjects since novelty is expected to dissipate as a direct function of exposure to the stimulus (Bronstein, Neiman, Wolkoff & Levine, 1974; Gray, 1987; King & Appelbaum, 1973). The impact of treatments on the response to novelty would be expected to alter the time course of the response to the novel stimulus. While the particular response will vary with the specific test situation (e.g., open-field,

novel object exploration, taste neophobia), the essential measures must provide a means of comparing the response both before and after the novelty has dissipated.

The effects of stressors on the response to novel stimuli have been assessed in a variety of tasks including the tasks that assess the response to novel environments and novel tastes. Although these test procedures are often used to evaluate exploratory tendencies, they have also been employed to assess fearfulness and anxiety and are thought to provide information on how animals obtain information about their environment (Renner & Rosenzweig, 1986).

Most studies that assess the impact of exposure to stressors on open-field behavior measure open-field locomotion over either a short time period (1-5 min) or over long time period (e.g., 2-3 hours). Since a single prolonged or repeated short exposures to novel environments such as the open-field would be expected to result in habituation to the novel aspects of the environment (Archer, 1972; Beninger, 1984; Berlyne, 1966; Bronstein, Neiman, Wolkoff & Levine, 1974; Britton, Ksir, Britton, Young & Koob, 1984; Carr, Overall, White & Brown, 1959; Feigley, Parsons, Hamilton & Spear, 1972; Stein, 1966; Walsh & Cummins, 1976), those studies that measure total locomotion over a single prolonged exposure to the novel open-field provide little information on the response to novelty. Because of this, studies employing short open-field test periods are better suited to assess the response to novelty than long test periods. Fortunately, most studies have employed brief test periods (1 to 10 min). For this reason, the studies presented below include only those that have employed short open-field test periods.

A single exposure to a number of stressors has been shown to alter locomotion in the open-field. One exposure to either shock or restraint decreases locomotion in a novel open-field (Carli, Prontera & Samanin, 1989; Campbell & Candland, 1961; Molina, Wagner & Spear, 1994; van Dijken, Tilders, Olivier & Mos, 1992; van Dijken, van der Heyden, Mos & Tilders, 1992; Weyers, Bower & Vogel, 1989). Although the interval between stressor exposure and locomotion testing is usually 24-48 hr, shock-induced reductions in novelty-induced locomotion have been reported immediately after shock and up to 28 days after shock (Lemoine, Armando, Brun, Segura & Barontini, 1990; van Dijken, Mos, van der Heyden & Tilders, 1992; van Dijken, Tilders, Olivier & Mos, 1992). Thus, shock-induced alterations in the response to a novel open-field appear to be quite persistent. In addition, it appears that few shocks are required to produce a reduction in open-field locomotion since such reduction have been reported following as few as 5 shocks (Stam, 1996). There are data indicating that less severe stressors such as noise stress (95 dB noise) increase rather than decrease open-field locomotion (Biagini et al.1993; Katz & Baldrighi, 1982; Katz, Roth & Carroll, 1981; Katz, Roth & Schmaltz, 1981; Roth & Katz, 1981). There are no data available to determine whether the increases in novelty-induced locomotion following noise stress are as persistent as the reductions seen following acute shock.

Exposure to repeated or chronic stressors also alters novelty-induced locomotion. Repeated shock or a regimen of variable stressors (e.g., a combination of shock, restraint, changing housing, noise, food deprivation, water deprivation, etc.) also

decrease locomotion in a novel open-field (Biagini et al.1993; Katz, Roth & Carroll, 1981; Levine, Madden, Conner, Moskal & Anderson, 1973). Moreover, exposure to chronic variable stress eliminates the increase in novelty-induced locomotion produced by acute noise stress (Katz, Roth & Carroll, 1981; Katz, Roth & Schmaltz, 1981). It is not known whether the ability of chronic stress to eliminate the impact of acute noise stress is due to a simple summation of stressor effects or whether chronic stress potentiates the effects of noise stress. It is interesting to note, however, that exposure to footshock has been shown to potentiate the ability of changing background noise to decrease locomotion in a novel open-field (van Dijken, Mos, van der Heyden & Tilders, 1992; van Dijken, Tilders, Olivier & Mos, 1992; van Dijken, van der Heyden, Mos & Tilders, 1992).

The impact of exposure to stressors on exploration has also been evaluated in a number of mazes, including the elevated-plus maze, the holeboard and the radial arm maze. Exposure to a variety of stressors alters the behavioral response of animals in the elevated-plus maze. This maze typically consists of both closed and open arms and normal animals usually explore both open and closed arms. The unprotected open arms, however, are thought to be more fear-inducing or anxiety-provoking than the protected closed arms (Montgomery, 1955; Pellow, Chopin, File & Briley, 1985). The ratio of time spent in the open arms relative to the closed arm provides an index of anxiety which has been validated with a number of anti-anxiety drugs (Lister, 1988; Pellow, Chopin, File & Briley, 1985). Exposure to a variety of stressors including isolation (Jankowska, Pucilowski & Kostowski, 1991), footshock (Steenbergen,

Farabollini, Heinsbroek & Van de Poll, 1991) forced swim (Britton, McLeod, Koob & Hauger, 1992) and social defeat (Rodgers & Cole, 1993) decrease the time spent in open arms relative to the closed arms indicating that stressed animals are more anxious than non-stressed animals.

Exposure to stressors also alters behavior in the holeboard. The holeboard has been proposed as a reliable method of assessing fear and anxiety in animals (File, 1985; Kelley, 1993). This apparatus consists of an open-field type of chamber with holes placed either in the floor or on the walls. Objects may be placed inside the holes to measure the response to novel objects. Typically ambulation, head dips into the holes and the duration of the head dips are measured. A single exposure to inescapable shock has been reported to decrease head dips (Fracchia, Jatuff & Alvarez, 1992; Steenbergen, Farabollini, Heinsbroek & Van de Poll, 1991) although a number of other reports have found that neither acute shock nor acute noise stress have any impact on holeboard behavior (Armario, Gil, Marti, Pol & Balasch, 1991; Garcia-Marquez & Armario, 1987). Interestingly, while acute restraint is ineffective, acute immobilization stress decreases ambulation, rearing and head dips in the holeboard (Armario, Gil, Marti, Pol & Balasch, 1991; Garcia-Marquez & Armario, 1987; Gil, Marti & Armario, 1992). This is a curious result given the similarity between restraint and immobilization. Immobilization usually refers to a form of restraint in which movement is almost completely precluded (e.g., limbs are taped to a board or table) and restraint typically permits more movement within a severely constrained area (e.g., a snugly-fitted tube). Although there appears to be

inconsistency in the use of the terms restraint and immobilization in the literature, generally, immobilization can be viewed as a somewhat more severe form of restraint. Given this, the difference in the impact of restraint and immobilization on holeboard behavior may be due to differences in stressor intensity.

Chronic or repeated exposure to stressors appear to exert more consistent effects on holeboard behavior. Repeated exposure to either shock, restraint or immobilization decrease ambulation, head dips and rearing (Garcia-Marquez & Armario, 1987a; Garcia-Marquez & Armario, 1987b; Gil, Marti & Armario, 1992). In addition, chronic variable stressor consistently decrease ambulation, head dips, and rearing in the holeboard (Armario, Restrepo, Castellanos & Balasch, 1985; Fracchia, Jatuff & Alvarez, 1992; Garcia-Marquez & Armario, 1987).

A similar procedure that can be viewed as a variant of the holeboard task is the interaction of animals with novel objects in either a novel or familiar environment. Exposure to a variety of stressors such as restraint, shock, tailpinch and white noise have all been reported to reduce the time animals spend in contact with novel objects (Arnsten, Berridge & Segal, 1985; Berridge & Dunn, 1986; Berridge & Dunn, 1987; Berridge & Dunn, 1989; Carli, Prontera & Samanin, 1989; Rosellini & Widman, 1989). In addition, while the number and duration of contacts with novel objects habituate over repeated testing (i.e., decreases) in normal animals, exposure to footshock attenuates the rate of habituation to novel objects (Rosellini & Widman, 1989). Footshock also decreases the diversity of novel object investigation within

sessions (Rosellini & Widman, 1989) suggesting an impairment in the processing of stimulus novelty.

The radial arm maze has also been employed to examine exploratory patterns in animals. This apparatus consists of a central hub with 8 to 12 narrow alleys (arms) connected to the hub. Animals are placed in the center of the maze and permitted to explore the maze and the pattern of arm entries is recorded. Normally, animals exhibit spontaneous alternation between arms as well as revisits to previously visited arms (perseveration) (Bruto & Anisman, 1983; Bruto, Anisman & Kokkinidis, 1980). Footshock disrupts the acquisition of spatial information primarily by increasing the number of errors (revisits to previously baited arm) (Shors & Dryver, 1992) and increasing response perseveration where all arms are unbaited (Bruto & Anisman, 1983). It appears that shock exerts its effects by reducing exploratory activity on the initial training days and by increasing response perseveration on later training days (Shors & Dryver, 1992). However, the acquisition of radial arm performance cannot be adequately described by either the number of reinforced arm entries or the number of errors. For instance, an animal that makes few arm entries will have few errors. Moreover, as the number of arms visited increases, the probability of visiting a previously visited arm and therefore the chances of making an error also increases. Since entries into a previously visited arm is typically measured as an error, error measures must be adjusted to account for this increased error probability. When such adjustments are incorporated into an acquisition index, the rate of learning in the radial arm maze does not differ between shocked and non-shocked animals (Shors &

Dryver, 1992). Thus, shock alters radial arm performance by altering exploration and response perseveration but not by altering the ability to learn the maze.

Just as stressors can influence the response of animals to novel environments, it can also modify the response to novel taste stimuli. For instance, footshock increases the avoidance of novel quinine solutions (Dess, 1993), as well as novel saccharin solutions (Dess, 1993; van Dijken, Mos, van der Heyden & Tilders, 1992). In the case of saccharin, the decrease in intake is transient (Dess, 1992; Dess, 1993; van Dijken, Mos, van der Heyden & Tilders, 1992) suggesting that novelty is the pertinent feature. The impact of shock on saccharin intake, however, appears to depend upon shock parameters. For instance, a brief session of footshock (5 one sec shocks over 5 min) decreases the intake of novel saccharin 24 hr after shock but not immediately after shock (van Dijken, Mos, van der Heyden & Tilders, 1992). In contrast, more severe shock (100 five sec shocks) produces an immediate decrease in saccharin intake regardless of the novelty of the saccharin solution (Dess, 1992; Dess, 1993). Exposure to stressors appear to have a different impact on the consumption of novel sucrose. Sucrose intake is transiently increased following exposure to stressors (Dess, 1992) but is subsequently decreased (Dess, 1993; Willner, Golembiowska, Klimek & Muscat, 1991). Because saccharin may have aversive qualities in addition to its appetitive properties, the differential effect of stressors on sucrose versus saccharin or quinine may be related to inherent aversive properties of both quinine and saccharin, a property that is absent in sucrose (Dess, 1993). The stressor-induced avoidance of novel saccharin or quinine may reflect the impact of stressors on the combined

novelty and aversiveness of these solutions (Dess, 1993). While it has been argued that stressors decrease saccharin intake by enhancing the response to an inherent aversive feature of saccharin rather than by enhancing novelty (Dess, 1993; Dess, 1992), data indicating that brief exposure to shock (i.e., 5 shocks) decreases saccharin intake only when it is novel (van Dijken, Mos, van der Heyden & Tilders, 1992) suggests that stressors may alter the response to novel saccharin depending upon the stressor regimen.

Exposure to shock also appears to alter the amount of time animals spend in preferred environments. For instance, when animals are given a choice between a familiar and unfamiliar compartment of a two-compartment chamber they usually show a preference for the unfamiliar chamber (McAllister, McAllister & Zellner, 1966). Exposure to stressors alters the pattern of investigating novel stimuli and increases the avoidance of novel stimuli (Baron, 1963; Mitchell, Osborne & O'Boyle, 1985; Sheldon, 1968; Williams, 1972). In choice tests, exposure to shock increases preference for familiar environments. For example, rats that had been previously exposed to one arm of a Y-maze normally choose the alternate unfamiliar arm in a subsequent choice test while rats exposed to shock choose the familiar arm (Sheldon, 1968). Moreover, in rats previously tested for arm preference in a Y-maze, exposure to shock increases preference for the preferred arm when compared to non-shocked rats (Williams, 1972). These latter results may be viewed as indicating that shock decreases the preference for an initially non-preferred environment. In addition, the shock-induced increase in preference for familiar stimuli appears to be independent of

shock contingencies since mice exhibit an increase in preference for the preferred arm of the T-maze regardless of whether they are shocked for perseverating or alternating (Mitchell, Osborne & O'Boyle, 1985).

Stressors appear to produce effects on novelty that are evident when measured by responses to both novel environments and novel tastes. Data obtained from the elevated-plus maze and the holeboard indicate that stressed animals are more anxious than non-stressed animals. Other data showing that anti-anxiety drugs can eliminate the impact of footshock on locomotion in a novel open-field suggest that open-field behaviors may also measure anxiety and fearfulness (van Dijken, Mos, van der Heyden & Tilders, 1992; van Dijken, Tilders, Olivier & Mos, 1992). The consistency of stressor effects on responding to novel stimuli therefore appears to indicate that exposure to stressors enhance the anxiogenic or aversive qualities of novel stimuli.

It also seems that, in addition to stressors enhancing the response to novelty, novelty can potentiate the impact of stressors. For instance, conditioned suppression of fluid consumption induced by pairing inescapable shock with odours is enhanced by testing the conditioned suppression in a novel environment (Minor, Dess & Overmier, 1991). Moreover, the disruptive effects of shock on open-field ambulation is enhanced by testing animals in a novel open-field rather than a familiar open-field (Baron, 1963).

**Stress and Appetitive Behaviors**

Two theoretical positions suggest that exposure to stressors can alter the response to appetitive stimuli. Learned helplessness theory postulates that one of the consequences of exposure to uncontrollable stressors is a motivational deficit (Maier, 1989; Maier & Seligman, 1976) characterized by a blunting of the reinforcing value of appetitive stimuli. Thus, based upon learned helplessness theory, exposure to stressors should reduce responding for appetitive reinforcers.

The second theoretical framework predicts that exposure to stressors will increase rather than decrease responding for appetitive reinforcers. This is based upon the well documented cross-sensitization between stressors and self-administered drugs (Antelman, Eichler, Black & Kocan, 1980; Kalivas, Richardson-Carlson & Van Orden, 1986; Kalivas & Stewart, 1991). Briefly, cross-sensitization is the process by which exposure to a stressor enhances the response to a subsequent drug treatment. That drugs such as amphetamine and cocaine also enhance the response to subsequent stressors indicates that cross-sensitization is a symmetrical process. Cross-sensitization has been demonstrated for a number of drugs that animals will self-administer such as amphetamine (Antelman, Eichler, Black & Kocan, 1980; Deroche et al.1992; Hahn, Zacharko & Anisman, 1986; Herman, Stinus & LeMoal, 1984; Leyton & Stewart, 1990; Robinson & Becker, 1986), cocaine (Hooks, Jones, Liem & Justice, 1992; Kalivas & Duffy, 1989; MacLennan & Maier, 1983; Post, Weiss, Fontana & Pert, 1992; Sorg, 1992), morphine (Abrahamsen, Stock, Caldarone & Rosellini, 1993; Deroche et al.1992; Leyton & Stewart, 1990), D-Ala2-Met5-enkaphalinamide (DALA),

(Kalivas, Richardson-Carlson & Van Orden, 1986), apomorphine (Cabib & Puglisi-Allegra, 1991), and enkephalin (Kalivas, Richardson-Carlson & Van Orden, 1986). Because cross-sensitization develops between these drugs and stressors, one would expect that in tasks where these drugs are used as appetitive reinforcers, exposure to stressors will enhance the behavioral response to these reinforcers as a result of this cross-sensitization. Indeed, it has been reported that stimulant-induced locomotion does predict the rate of acquisition of drug self-administration for both amphetamine and cocaine (Haney, Maccari, LeMoal, Simon & Piazza, 1995; Jodogne, Marinelli, LeMoal & Piazza, 1994; Piazza, Deminiere, LeMoal & Simon, 1989; Piazza, Deminiere, LeMoal & Simon, 1990).

As will be seen, results of studies evaluating the effects of stressors on appetitively-motivated behaviors provide support for both of theoretical positions. While the factors that determine whether stressors increase or decrease responding for appetitive reinforcers have not been elucidated, there is little doubt that stressors can alter responding for appetitive reinforcers. Appetitively-motivated behaviors that have been employed include intracranial self-stimulation (ICSS), drug self-administration, place preference conditioning, consumption of food and highly palatable solutions and food reinforced operant behaviors.

Animals with electrodes implanted in specific brain structures will readily learn an operant response to electrically stimulate those brain structures (Gallistel, Shizgal & Yeomens, 1981; Milner, 1991; Olds & Milner, 1954; Wise, 1989). Because the direct electrical stimulation of brain structures is thought to be a powerful reinforcer (Milner,

1991; Olds & Milner, 1954; White & Milner, 1992; Wise, 1989) and ICSS has been extensively characterized, this provides a particularly useful means to assess the impact of stressors on reinforcement mechanisms (Moreau, Jenck, Martin & Haefely, 1992; Zacharko & Anisman, 1991; Zacharko, Bowers, Kokkinidis & Anisman, 1983).

Exposure to acute uncontrollable footshock has been reported to reduce the rate of ICSS in both mice (Bowers, Zacharko & Anisman, 1987; Kasian, Zacharko & Anisman, 1987; Zacharko, Bowers & Anisman, 1984; Zacharko, Bowers, Kokkinidis & Anisman, 1983) and rats (McCutcheon, Rosellini & Bandel, 1991). In addition, footshock reduces response rates for ICSS across a range of current intensities (Bowers, Zacharko & Anisman, 1987) and increases current thresholds required to maintain responding in rats (McCutcheon, Rosellini & Bandel, 1991). It also appears that footshock-induced reductions in ICSS are anatomically specific. For instance, uncontrollable footshock reduces responding for ICSS elicited from electrodes placed in the medial forebrain bundle (Zacharko, Bowers, Kokkinidis & Anisman, 1983), nucleus accumbens (Zacharko, Bowers & Anisman, 1984; Zacharko, Bowers, Kelly & Anisman, 1984; Zacharko, Bowers, Kokkinidis & Anisman, 1983) frontal cortex (Zacharko, 1990) and ventral tegmental area (Bowers, Zacharko & Anisman, 1987; Kamata, Yoshida & Kameyama, 1986; Kasian, Zacharko & Anisman, 1987). Footshock does not appear to alter ICSS elicited from the substantia nigra (Bowers, Zacharko & Anisman, 1987; Zacharko, Bowers, Kokkinidis & Anisman, 1983). This anatomical specificity suggests that the shock-induced decreases in ICSS responding are unrelated to nonspecific stressor effects such as motoric disturbances.

Similar to behavioral disturbances in shuttle escape tasks, shock controllability also plays an important role in the appearance of stressor-induced alterations in ICSS (Bowers, Zacharko & Anisman, 1987; Zacharko, Bowers, Kokkinidis & Anisman, 1983). While controllable shock does not alter ICSS, exposure to uncontrollable footshock decreases ICSS responding (Bowers, Zacharko & Anisman, 1987; Zacharko, Bowers, Kelly & Anisman, 1984; Zacharko, Bowers, Kokkinidis & Anisman, 1983; Zacharko, Lalonde, Kasian & Anisman, 1987). Stressor chronicity also influences the impact of stressors on responding for ICSS. Unlike acute footshock, exposure to chronic footshock does not appear to alter responding for ICSS (Zacharko, Bowers & Anisman, 1984). Similarly, chronic mild stress increases thresholds for ICSS from the ventral tegmental area (VTA) in rats (Moreau, Jenck, Martin & Haefely, 1992). However, chronic mild stress consists of exposure to a series of different mild stressors over a 3-7 week period (Willner, Muscat & Papp, 1992) and appears to produce many of the behavioral and biochemical effects of acute footshock stress (Willner, Muscat & Papp, 1992; Willner, Muscat & Papp, 1992). For instance, both acute footshock and chronic variable stress produce shuttle escape deficits (Murua, Gomez, Andrea & Molina, 1991), decrease intake of palatable diets (Griffiths, Shanks & Anisman, 1992; Sampson, Muscat, Phillips & Willner, 1992), and increase dopamine turnover (Dunn, 1988; Stamford et al.1991; Willner, Golembiowska, Klimek & Muscat, 1991). Given the comparable effects between the effects of acute shock and chronic mild stress, it may be prudent to view chronic mild stress as comparable to acute exposure to more severe stressors such as shock. Unfortunately, this issue

remains unresolved as there have been no studies that have directly compared the effects of exposure to chronic mild stressors with acute exposure to more severe stressors such as shock.

There have also been reports of increased responding for ICSS following exposure to shock. For instance, 50 footshocks immediately before each ICSS test increases responding elicited from electrodes placed in the lateral hypothalamus (MacDougall & Bevan, 1968). Similarly, responding for ICSS from the medial forebrain bundle is increased following repeated exposure to tailpinch (Katz & Roth, 1979). More recently, McGregor, Balleine & Atrens (1989) have reported that ICSS elicited from the medial prefrontal cortex was increased following exposure to one session of 60 footshocks.

The discrepancy between studies reporting increased and decreased responding for ICSS following exposure to stressors may be related to the stressor treatment. Studies reporting stressor-induced decreases ICSS responding have employed stressor parameters that are known to be effective in producing performance deficits in aversively-motivated paradigms such as the shuttle escape task (Bowers, Zacharko & Anisman, 1987; Moreau, Jenck, Martin & Haefely, 1992; Zacharko, Bowers, Kokkinidis & Anisman, 1983; Zacharko, Lalonde, Kasian & Anisman, 1987). In contrast, studies reporting increases in ICSS responding have employed shock regimens that are usually insufficient to produce behavioral deficits in aversively-motivated paradigms (Anisman, 1982; Anisman, Kokkinidis & Sklar, 1985; Anisman & Zacharko, 1990; Maier & Seligman, 1976). For instance, while exposure to 50 or

60 footshocks increases ICSS responding in rats (MacDougall & Bevan, 1968; McGregor, Balleine & Atrens, 1989), these stressor treatments are generally ineffective in producing shuttle escape deficits. Similarly, tailpinch increases responding for ICSS (Katz & Roth, 1979) but has not been reported to influence shuttle escape responding. Moreover, while stressor controllability plays a critical role in shock-induced depressions in ICSS responding as well as shuttle escape performance, increased ICSS responding is evident following both controllable and uncontrollable footshock (McGregor, Balleine & Atrens, 1989). Since there was no difference between uncontrollable and controllable shock, it is possible that the shock treatment was not sufficiently severe to produce decreases in ICSS responding. Although further direct comparison are necessary, it appears that milder stressor treatment may increase ICSS responding while more severe treatments decrease ICSS responding.

Drug self-administration also appears to be sensitive to the effects of exposure to stressors. Two basic procedures have been employed: oral consumption of drugs or intravenous drug self-administration. In addition, a variety of stressors have been employed including shock, restraint, hot plate, tailpinch and psychological stress (exposure to the smell and sounds of animals undergoing footshock).

The effects of stressors on ethanol (ETOH) consumption has received considerable attention, primarily because of theoretical formulations suggesting that ethanol is consumed for its anxiety reducing properties (Cappell, 1972; Conger, 1951; Hodgson, Stockwell & Rankin, 1979; Kalant, 1990). Although this premise remains

controversial, there is little doubt that exposure to stressors can increase ETOH consumption. For instance, shock (Anisman & Waller, 1974; Bond, 1978; Mills, Bean & Hutcheson, 1977; Volpicelli & Ulm, 1990; Volpicelli, Ulm & Hopson, 1990), restraint (Krishnan, Nash & Maickel, 1991; Rockman, Hall & Glavin, 1986; Rockman, Hall, Hong & Glavin, 1987), social separation (Kraemer & McKinney, 1985), immobilization (Nash & Maickel, 1985), isolation housing (Higley, Hasert & Linniola, 1991; Kraemer & McKinney, 1985), and changes in housing conditions (Hannon & Donlon-Bantz, 1976; Schenk, Gorman & Amit, 1990; Weisinger, Denton & Osborne, 1989) have all been reported to increase ETOH consumption. It appears that a number of factors play a role in stressor-induced increases in ETOH intake. Most studies have employed repeated exposures to stressors and the effects of stressor on ETOH consumption generally occur after the completion of the stressor regimen (Pohorecky, 1990). Daily exposure to footshock increases ETOH intake on stress days (Anisman & Waller, 1974; Bond, 1978; Myers & Cicero, 1969; Volpicelli, Ulm & Hopson, 1990). However, shock-induced increases in ETOH intake are evident only if there is a no-shock period on each stress day. For instance, exposure to footshock for 6 or 12 hr per day increase ETOH intake during the no shock period (Anisman & Waller, 1974). However, if a shock-free period is not present on stress days, there is no increase in ETOH intake (Myers & Holman, 1967). When animals are shocked in a different chamber than their home cages, ETOH consumption is increased in the home cages but not in the shock chamber (Caplan & Puglisi, 1986). In animals exposed to shock for the first 12 min of a 1 hr ETOH consumption test, shock increases ETOH intake

in the 30 min period following the shock period but not during the shock period itself (Mills, Bean & Hutcheson, 1977). In the case of restraint or immobilization stress, ETOH intake is also increased primarily in the post-stress period (Nash & Maickel, 1985; Nash & Maickel, 1988; Rockman, Hall & Glavin, 1986) although increases and decreases on restraint days have also been reported (Krishnan, Nash & Maickel, 1991; Rockman, Hall & Glavin, 1986; Rockman, Hall, Hong & Glavin, 1987). It therefore appears that when stress-induced increases in ETOH intake are observed, these increases will be evident primarily in the post-stress period. It should be noted that a number of studies have been unable to detect any stress-induced increases in ETOH intake (Fidler & Lolordo, 1996; Koeter & van den Brink, 1992; Ng Cheong Ton, Brown, Michalakeas & Amit, 1983).

A second factor that significantly influences the impact of stressors on ETOH intake is baseline ETOH consumption. For example, among animals that do not prefer ETOH (preference is measured relative to water) shock increases ETOH intake while in animals that prefer ETOH, shock decreases ETOH intake (Bond, 1978; Volpicelli, Ulm & Hopson, 1990). Similarly, immobilization increases ETOH intake in animals that normally consume little ETOH but decreases ETOH intake in animals that normally consume large amounts of ETOH (Rockman, Hall & Glavin, 1986; Rockman, Hall, Hong & Glavin, 1987).

More recently, a number of studies have examined the effects of stressors on the intake of other self-administered drugs. Repeated exposure to either brief shock or to restraint increase the oral consumption of morphine (Shaham, 1993; Shaham, Alvares,

Nespor & Grunberg, 1992) and fentanyl (Shaham, 1993; Shaham, Klein, Alvares & Grunberg, 1993). In addition, operant responding for fentanyl is increased by exposure to footshock (Shaham, Klein, Alvares & Grunberg, 1993). Shock also increases responding for intravenous heroin (Shaham & Stewart, 1994), morphine (Beck & O'Brien, 1980), cocaine (Goeders & Guerin, 1994) and intraventricular morphine (Dib, 1985; Dib & Duclaux, 1982). Other stressors have also been reported to increase drug self-administration. Isolation stress has been reported to increase (Boyle, Gill, Smith & Amit, 1991) and decrease (Phillips et al.1994) self-administration responding for cocaine and to produce a nonsignificant increase in amphetamine self-administration (Schenk, Robinson & Amit, 1988). Repeated prenatal restraint has also been reported to increase amphetamine self-administration (Deminiere et al.1992). In addition, repeated exposure to brief tail-pinch or unstable housing conditions (switching cage mates) facilitates the acquisition of amphetamine self-administration but does not appear to influence the asymptotic rate of responding for amphetamine (Piazza, Deminiere, LeMoal & Simon, 1989; Piazza, Deminiere, LeMoal & Simon, 1990). More recently, it has been reported that repeated social conflict (i.e., aggressive encounters) also enhance the acquisition of cocaine self-administration (Haney, Maccari, LeMoal, Simon & Piazza, 1995). There is one report that psychological stress (exposure to animals undergoing footshock) increases the acquisition of cocaine self-administration (Ramsey & van Ree, 1993); however, the same report also found that exposure to either a hotplate or 15 min of footshock does not alter acquisition rate for cocaine self-administration. A close review of the results of this study indicates

that the facilitation in acquisition produced by psychological stress may actually be an artifact of unusually low response rates among non-stressed control animals. Indeed response rates among psychologically stressed rats appear to be comparable to response rates among non-stressed control animals in the hot plate and footshock studies (Ramsey & van Ree, 1993). Thus, the evidence that psychological stress alters cocaine self-administration is unconvincing.

The precise meaning of changes in drug consumption or operant response rates in drug self-administration tasks is not clear, however. Treatments that increase drug self-administration responding may be interpreted to indicate either increased or decreased reinforcement value of the drug stimulus. Similarly, treatments that decrease self-administration responding may also be interpreted to indicate either increased or decreased reinforcing value of the drug stimulus. To circumvent these interpretive difficulties a number of alternative procedures have been employed including progressive ratio schedules of drug self-administration and response reinstatement procedures. In progressive ratio tests, the number of responses required to receive a drug injection is incremented following each reinforced response (i.e., the fixed ratio (FR) reinforcement schedule is incremented). Because the dependent measure is the highest fixed ratio completed (i.e., the breakpoint) within a specified period of time and not the response rate, this procedure is thought to provide an index of the relative efficacy of drug reinforcers and obviates the difficulties in interpreting response rate measures (Hodos, 1961; Roberts, 1989; Roberts, Loh & Vickers, 1989). Only one reported study has assessed the impact of stressors on drug self-administration on a

progressive ratio schedule (Shaham & Stewart, 1994). Exposure to 10 min footshock immediately prior to each self-administration session increases the breakpoint for heroin self-administration (Shaham & Stewart, 1994). If the breakpoint provides an index of the relative reinforcing efficacy of heroin, these results provide strong evidence that footshock increases the reinforcing value of heroin.

Exposure to footshock also reinstates both cocaine and heroin reinforced responding (Erb, Shaham & Stewart, 1996; Shaham & Stewart, 1995). This procedure involves training animals to self-administer heroin, exposing them to extinction conditions (i.e., responses are no longer reinforced by heroin injections) and finally, exposing them to either noncontingent heroin injections or footshock and testing for the occurrence of self-administration responding (response reinstatement). Because footshock produces response reinstatement similar to that produced by noncontingent heroin, it has been suggested that shock may activate brain systems similar to those involved in the reinforcing effects of incentive stimuli (Shaham & Stewart, 1995) although more recent evidence indicates that reinstatement produced by shock and heroin can de differentiated on neurochemical bases (Shaham & Stewart, 1996).

To date, the impact of stressors other than footshock on progressive ratio or reinstatement responding have not been evaluated. Nevertheless, the data available from progressive ratio and reinstatement studies provide evidence that footshock can increase the reinforcing value of heroin. Whether stressors produce comparable effects on other self-administered drugs remains to be determined.

A number of studies have assessed the impact of exposure to stressors on place preference conditioning - a procedure thought to measure Pavlovian conditioned appetitive behavior (Beninger, 1989; Carr & White, 1986; Mucha & Iversen, 1984). Chronic mild stress attenuates or eliminates place preference conditioned with amphetamine (Papp, Muscat & Willner, 1993; Papp, Willner & Muscat, 1991) morphine (Papp, Lappas, Muscat & Willner, 1992), quinpirole (Papp, Muscat & Willner, 1993), and sucrose (Papp, Willner & Muscat, 1991; Papp, Willner & Muscat, 1993). Isolation housing has been reported to increase the dose of heroin required to produce place preference (Schenk, Ellison, Hunt & Amit, 1985) and can eliminate heroin-induced place preference (Schenk et al.1986) but does not appear to influence amphetamine-induced place preference (Schenk et al.1986). While these data appear to indicate that stressors can reduce conditioned responding to a number of appetitive stimuli, the small number of studies available preclude any firm conclusions.

The impact of stressors on the consumption of other non-drug reinforcers has also received attention. Typically, these studies assess the impact of stressors on the intake of a palatable substance such as a sweetened diet. Normally, no specific operant response is required and oral consumption of the test substance is measured over a period of days or weeks. Exposure to acute uncontrollable footshock decreases the consumption of food and saccharin (Desan, Silbert & Maier, 1988; Dess, 1992; Katz, 1982; van Dijken, Mos, van der Heyden & Tilders, 1992; Wagner, Hall & Cote, 1977). Inescapable footshock also decreases consumption of a palatable food mixture in mice while escapable shock has little impact (Griffiths, Shanks & Anisman, 1992).

Moreover, the decreased consumption produced by acute footshock is enhanced by prior exposure to repeated footshock or a chronic regimen of variable stressors (Griffiths, Shanks & Anisman, 1992). The reduced consumption of palatable diets is consistent with the effects of exposure to chronic variable stress on sucrose consumption (Nowak, Papp & Paul, 1995; Papp, Klimek & Willner, 1994; Stamford et al.1991; Sampson, Muscat, Phillips & Willner, 1992; Willner, Golembiowska, Klimek & Muscat, 1991) and the decrease in consumption of unadulterated food following repeated restraint (Gorka & Adamik, 1993; Marti, Marti & Armario, 1994; Wagner, Hall & Cote, 1977).

The interpretation of these results is not straightforward, however, since inescapable shock has also been shown to increase sucrose consumption (Dess, 1992). Moreover, as pointed out by Dess (1993), the temporal pattern of alterations in consumption of palatable substances varies as a function of the specific test substance. Stressor-induced reductions in saccharin intake occur immediately following stressor treatment and are transient (Dess, 1992; Dess, 1993) while reductions in sucrose intake are usually delayed and sustained (Dess, 1993; Willner, Golembiowska, Klimek & Muscat, 1991). Differences in the temporal pattern of decreases in saccharin and sucrose intake following exposure to stressors may be related to inherent differences in the reinforcing properties of these substances. Dess (1993) has suggested that there is an inherent aversive component to the taste of saccharin that is not present in sucrose and that shock decreases saccharin intake by enhancing this aversive property rather than by decreasing the reinforcing value of saccharin. In the case of sucrose, the

stress-induced decrease in sucrose consumption may be mediated by a stress-induced reduction in the rewarding value of sucrose possibly mediated by alterations in dopaminergic function (Griffiths, Shanks & Anisman, 1992; Katz, 1982; Willner, Golembiowska, Klimek & Muscat, 1991; Willner, Muscat & Papp, 1992).

A number of studies have examined the impact of stressors on operant responding for food reinforcers (Chen & Amsel, 1977; Nation & Boyagian, 1981; Rosellini, 1978; Rosellini & DeCola, 1981; Rosellini, DeCola, Plonsky, Warren & Stilman, 1984; Rosellini, DeCola & Shapiro, 1982; Warren, Rosellini, Plonsky & DeCola, 1985; Widman, Abrahamsen & Rosellini, 1992). Inescapable shock increases inter-response times in food-reinforced bar press operant tasks (Rosellini, 1978; Widman, Abrahamsen & Rosellini, 1992), decreases correct choices (Rosellini, DeCola & Shapiro, 1982), increases response latencies in discrimination tests (Rosellini, DeCola & Shapiro, 1982) and decreases the number of responses to non-contingent food presentation (Rosellini, DeCola, Plonsky, Warren & Stilman, 1984; Rosellini, DeCola & Shapiro, 1982; Widman, Abrahamsen & Rosellini, 1992). These measures are thought to indicate that stressors disrupt the associative learning of the relationship between responding and reinforcement delivery. They do not, however, provide evidence that shock alters the reinforcing value of food reinforcers.

The effect of shock on food-reinforced responding in the straight runway has also received some attention. In mice, inescapable shock decreases acquisition running speed in the runway relative to mice exposed to escapable shock. (Caspy & Lubow, 1981). Moreover, the decrease in acquisition speed appears to be related to shock

durations as 6 sec shock has a larger impact than 2 sec shock (Caspy & Lubow, 1981). A small number of studies have assessed the impact of shock on runway acquisition in rats. Most studies have reported that exposure to footshock before runway training does not influence runway acquisition speed (Chen & Amsel, 1977; Chen & Amsel, 1982; Rosellini & Seligman, 1975; Wong, 1971) although a transient decrease in runway acquisition speed in the early stage of training has been reported (Anderson, Cole & McVaugh, 1968).

**Summary**

Exposure to stressors can alter responsivenes to aversive stimuli as measured behaviorally and biochemically. For instance, prior exposure to a severe stressor treatment such as 60 footshocks potentiates the motoric effects and NE depletions produced by a normally ineffective shock treatment. Prior stressor exposure also decreases the amount of shock required to produce analgesia. In addition, stressors can potentiate the avoidance of a conditioned aversive stimulus in CTA tests, although the nature of the conditioning drugs appears to be a significant factor. Lastly, stressors appear to increase response perseveration in a number of mazes and increase response persistence in extinction tests. These data suggest that exposure to stressors can enhance responsiveness to subsequent aversive stimuli as well as the pattern of response emission (i.e., perseveration) in a number of situations.

Responding to novel stimuli is increased in a number of test situations by exposure to stressors. For instance, exposure to a variety of stressors increase

responses to novel environments in test situations that have been suggested to measure anxiety. Stressors can also enhance responding to novel tastes. Moreover, there is some indication that the effects of stressors may be potentiated by testing in novel environments. Because these stressor effects abate with prolonged exposure to novel stimuli it is likely that stressors are exerting their effects primarily on the novelty of the test situation. These results, in addition to data showing that novelty shares a number of characteristics with stressors, suggest that novel stimuli may be appropriately viewed as aversive stimuli.

Responding for appetitive stimuli is also altered by exposure to stressors. Both increases and decreases in responding to appetitive stimuli have been reported following stressors. Mild stressors such as tailpinch and brief shock increase responding for appetitive stimuli such as ICSS and drug self-administration while more severe stressors like 60 shocks decrease responding for appetitive reinforcers. Although few direct comparisons are available, the literature suggests that stressor severity may be the critical determinant of whether stressors increase or decrease responding for appetitive reinforcers.

It is interesting to note that both the learned helplessness and the cross-sensitization positions are supported by this research. Learned helplessness theory predicts that exposure to uncontrollable stressors results in an associative deficit such that animals learn that responses and outcomes are independent. This, then engenders a motivational deficits that would be reflected in reduced responding for appetitive reinforcers. The cross-sensitization literature, in contrast, has shown that exposure to

stressors enhance the biochemical and behavioral responses to a variety of self-administered drugs. Although the relationship between self-administration responding for such drugs and the cross-sensitization produced by stressors is not clear, it would be expected that stressors would enhance the response to these drugs in self-administration tests. The research showing increased drug self-administration following exposure to stressors supports this position.

This is an unfortunate state as these positions are, in essence, opposing views: learned helplessness maintains that stressors decrease motivation while the cross-sensitization position suggests that stressor-induced enhancements in dopamine function enhance motivation. Differences in stressors regimens and the specific stressors are likely to be significant factors. Unfortunately, because there is no generally accepted basis on which to rate (or even rank order) the various stressors employed, much less the various stressor regimens, explanations based upon the nature of the stressor are of limited utility.

Based upon the evidence that exposure to stressors enhance the subsequent response to aversive stimuli and that appetitively-motivated behaviors do not involve this inherent re-exposure feature, one would expect that responsiveness to aversive stimuli would be more sensitive to the effects of stressors than would responsiveness to appetitive stimuli. The studies reported below attempted to evaluate this hypothesis by comparing the effects of two commonly used stressors (footshock and restraint) in a number of behavioral procedures that measure responses to aversive and appetitive stimuli. Moreover, based on evidence that novel stimuli share many of the

characteristics of stressors, we also evaluated the impact of these stressors on the behavioral response to a novel taste and a novel environment. If it is appropriate to view novelty as aversive, then exposure to stressor should also alter the response to the novel stimuli.

## EXPERIMENT 1A

Experiment I was designed to assess the impact of footshock stress on saccharin consumption using a CTA procedure. This procedure was selected because it permits the evaluation of a) saccharin intake among saline treated animals which provides a measure of the effect of shock on the consumption of an appetitive reinforcer, and b) an index of the effect of shock on the avoidance of a conditioned aversive stimulus in drug-injected animals. An additionnal advantage of this procedure is that the task requirements (i.e., saccharin consumption) are the same for the appetitive measure and the aversive measure.

Amphetamine was selected as the conditioning drug since amphetamine has been shown to be an effective agent in producing the conditioned avoidance of saccharin (Cappell & LeBlanc, 1977; D'Mello, 1977; Goudie, Thornton & Wheatley, 1975; Wagner, Foltin, Seiden & Schuster, 1981). Moreover, as previously described, the impact of stressors on CTA depends upon the nature of the conditioning agent. Indeed, it has been argued that CTA induced by illness-inducing agents such as LiCl are fundamentally different from CTA induced by drugs that do not produce illness (i.e., self-administered drugs) (Goudie, Stolerman, Demellweek & D'Mello, 1982; Grant, 1987; Hunt & Amit, 1986). Because both apomorphine and amphetamine act primarily on dopaminergic systems, albeit on different receptor mechanisms, (Seeman & Van Tol, 1994) and because shock has been shown to enhance apomorphine CTA (Lasiter & Braun, 1981), it seems likely that footshock will also enhance amphetamine CTA. Stressors are also known to disrupt dopaminergic activity (Abercrombie, Keefe,

DiFreschia & Zigmond, 1989; Anisman & Zacharko, 1988; Antelman et al.1988; Deutch, Tam & Roth, 1985; Dunn, 1988; Herman, Guillonneau, Dantzer, Scatton & Semerdjian-Rouquier, 1982; Imperato, Angelucci, Casolini, Zocchi & Puglisi-Allegra, 1992; Roth, Tam, Ida, Yang & Deutch, 1988) and pharmacological manipulations of dopaminergic function has been shown to play a role in amphetamine CTA (Lorden, Callahan & Dawson, 1980; Roberts & Fibiger, 1975; Wagner, Foltin, Seiden & Schuster, 1981).

This procedure permits us to assess the impact of footshock stress on both appetitive responding for saccharin as well the conditioned avoidance of saccharin. If stressors enhance the response to aversive stimuli to a larger degree than the response to appetitive stimuli, then footshock should increase the conditioned avoidance of saccharin in amphetamine-injected animals but should have little impact on saccharin consumption in saline-injected animals.

**Materials and Method**

*Subjects:* Subjects were 40 male Long-Evans rats individually housed in standard hanging wire cages and acclimatized to the colony room for seven days. Animals were maintained on a 12 hr ON: 12 hr OFF light-dark cycle and permitted free access to Purina Rat Chow and water, except where specified. Subjects weighed between 260 and 390 g on the first day of amphetamine injections. All fluid consumption tests were conducted during the second quarter of the light cycle.

*Apparatus*: Fluid consumption tests were conducted in each animal's home cage by inserting 100 ml plastic centrifuge tubes with ball bearing spouts into the front wall of the cage. Footshock was applied in a separate room containing shock chambers measuring 31 cm by 20 cm by 19 cm with stainless steel sides, a grid floor constructed of stainless steel rods spaced 1.7 cm apart, and a translucent plexiglass top. Shock treatment consisted of 30 minutes of footshock (30 shocks, 1.0 mA, 1.5 sec duration, 60 sec ITI) delivered through the floor rods connected to a shock generator (Grason-Stadler Model 700). No-shock treatment consisted of placing animals in identical chambers in a different room but shock was not applied. Drugs were injected i.p. and consisted of either 0.9 % saline or 2 mg/kg d-amphetamine sulfate. Saccharin solutions (0.1%) were mixed fresh daily in tap water.

*Procedures*: Following at least seven days of acclimatization to the colony room, animals were placed on a restricted water schedule with water available for 20 minutes at the same time each day (± 30 min). Fluid consumption was measured to the nearest ml. Water was presented in the home cages in plastic centrifuge tubes with steel ball bearing spouts. Food was always available. Baseline water intake values were obtained by taking a weighted average of water intake for the last four days of the restricted water access schedule. Twenty-four hr after the sixth day of restricted water (i.e., Pairing Day 1: PD1) rats were matched on the basis of baseline water consumption and assigned to one of two Drug treatment groups (saline or amphetamine). Each Drug treatment group was then subdivided such that half the animals in each drug group were assigned to the Shock treatment group while the

remaining animals were assigned to the No-shock control group. All animals were presented with saccharin for 20 min. Immediately following saccharin presentation, animals were transported to a separate room and exposed to either 30 minutes of unsignalled footshock or no-shock treatment. Immediately following the shock treatment, animals were returned to the colony room, injected with either saline or amphetamine and returned to their home cages. On the next day (Day 8), all animals were given 20 min access to water. On Day 9 (Pairing Day 2: PD2), the treatment given on PD1 was repeated. Water was again presented on Day 10. Extinction trials began on Day 12 (EXT1) and were repeated on alternate days (EXT2, EXT3, EXT4). Extinction testing consisted of a 20 min presentation of saccharin to all animals. Water was presented for 20 min on days between extinction trials.

*Data Analysis*: Only animals consuming at least 10 ml of saccharin on the first exposure to saccharin were included in data analysis. This criterion was selected on the basis of pilot studies indicating that fluid consumption was not stable in animals consuming less that 10 ml of saccharin regardless of stressor or drug treatments. This criterion eliminated three animals from the No-shock group and four animals from the Shock group. Baseline water intake values were computed by taking a weighted average of the last four water days prior to saccharin exposure and analyzed with a 2 x 2 ANOVA to ensure that treatment groups consumed comparable amounts of water prior to drug and shock treatments. Saccharin consumption data were analyzed with a 2 x 2 x 5 repeated measures ANCOVA with Days as the repeated measures factor. The covariate used was the difference between baseline water intake and initial

saccharin consumption. This covariate was selected to ensure that the effects of footshock on amphetamine CTA took into account both baseline water consumption values as well as initial taste neophobia. Following the omnibus *F* test, simple effects analysis was used to probe main effects and interactions. Significance testing was conducted with $\alpha$=.05 in this and all subsequent studies.

**Results**

ANOVA revealed that there were no group differences in baseline water intake (*F*s < 3.0, *p*s > .08). A separate ANOVA on saccharin consumption on PD1 also revealed no group differences (*F*s < 1.0, *p*s > .10). A separate ANOVA on water intake on days between saccharin consumption tests indicated that neither shock nor amphetamine influenced water intake. Thus, water intake was comparable between treatment groups both prior to and following treatments.

Repeated measures ANCOVA performed on saccharin consumption data from PD2 to EXT4 revealed that saccharin-amphetamine pairing reduced saccharin consumption ($F_{1,28} = 45.03$, $p < .001$) but footshock did not influence saccharin consumption ($F_{1,28} = .09$, $p = .741$). Inspection of Figure 1 shows that the suppression in saccharin consumption induced by saccharin-amphetamine pairing varied over test days. This was confirmed by a significant Drug by Days interaction ($F_{4,116} = 5.67$, $p <$ .001). Simple effects analysis of the Drug by Days interaction revealed that amphetamine-injected animals consumed significantly less saccharin than saline-

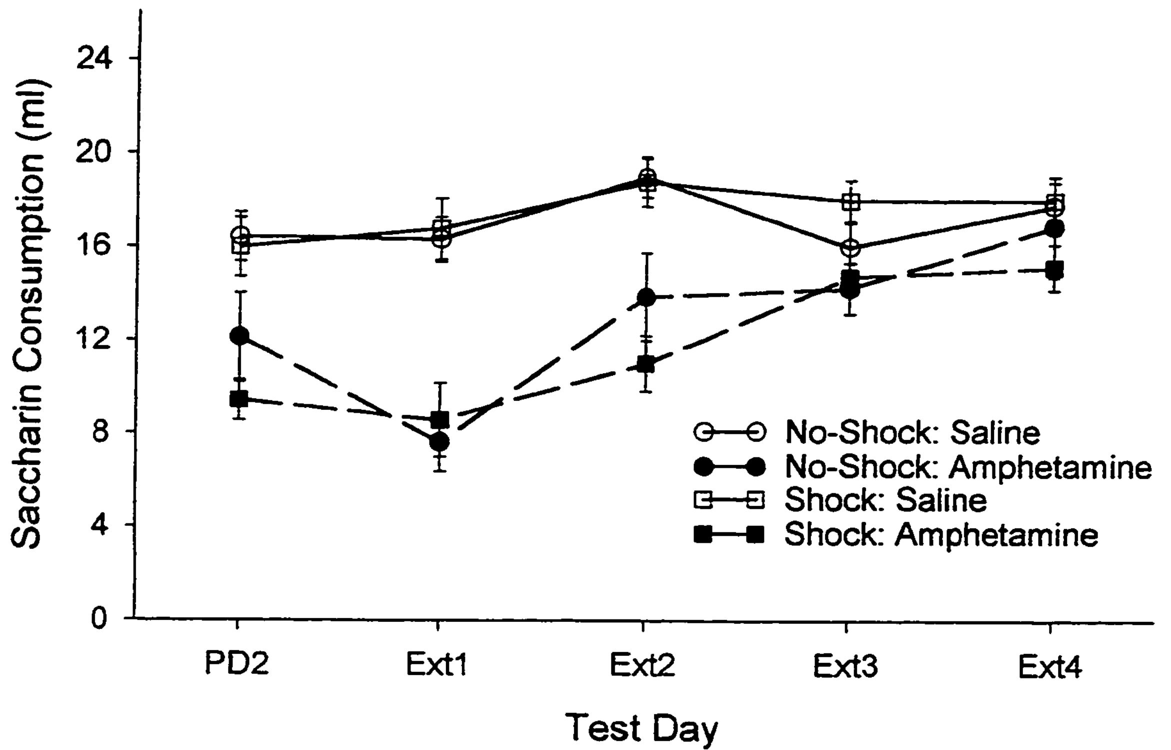


**Figure 1**. Mean saccharin intake (± s.e.m) among animals exposed to either Shock or No-Shock immediately before saccharin-amphetamine pairing. Saccharin was presented on alternate days. (Abbreviations: PD2 - pairing day 2, Ext1 to Ext4 - extinction trial 1 to extinction trial 4).

injected animals from PD2 to EXT3 ($F$s > 5.0, $p$s < .03) but recovered to the level of saline-injected animals on the last extinction trial (EXT4) ($F_{1,28} = 1.69$, $p = .204$). Footshock did not alter the drug-induced suppression of saccharin consumption since the Shock by Drug by Days interaction was not significant ($F_{4,116} = .29$, $p = .887$).

**Discussion**

One saccharin-amphetamine pairing seems to be sufficient to induce a conditioned avoidance of saccharin. Following a second saccharin-amphetamine pairing, saccharin avoidance persists for three extinction trials. Exposure to footshock between saccharin consumption and amphetamine injections does not alter amphetamine CTA. Similarly, water intake on days between saccharin tests was unaffected. It would appear that exposure to footshock immediately prior to amphetamine injections has little impact on either subsequent consumption of saccharin or the amphetamine-conditioned avoidance of saccharin.

Because footshock exerted no effect on the conditioned avoidance of saccharin, these results appear inconsistent with the hypothesis that exposure to shock enhances the response to a conditioned aversive stimulus. However, stressor-induced alterations in avoidance behavior are not always evident immediately following exposure to stressors. For example, inescapable footshock produces deficits in shuttle escape performance in rats 24 to 72 hr after exposure to shock but escape deficits are typically not evident immediately following shock (Anisman, 1975; Anisman, deCatanzaro & Remington, 1978; Prince & Anisman, 1984). It is therefore possible

that footshock can alter amphetamine CTA but only when footshock precedes saccharin-amphetamine pairing by 24 to 72 hr.

## EXPERIMENT 1B

Experiment 1b was conducted to evaluate the impact of exposure to footshock a number of days prior to saccharin-amphetamine pairing on the acquisition and extinction of amphetamine CTA. If the impact of exposure to footshock on avoidance responses requires a delay between shock exposure and the avoidance test, then exposing animals to shock before saccharin-amphetamine pairing should potentiate the amphetamine-conditioned avoidance of saccharin. This study also assessed the impact of footshock on the neophobic response to novel saccharin. If, as has been previously suggested, novelty does reflect a degree of aversiveness, then exposure to shock prior to saccharin should also enhance the neophobic response to novel saccharin.

### Materials and Method

*Subjects*: Subjects were 34 male Long Evans rats, weighing between 280 and 390 g on the first day of amphetamine injections. Housing conditions were identical to those outlined in Experiment 1a. All rats were acclimatized to the colony room for seven days, as in Experiment 1a, before imposing the restricted water schedule for six days.

*Procedures*: Procedures were identical to Experiment 1a with the following exceptions. Following 6 days of restricted water access, animals were matched on the basis of baseline water intake and assigned to Shock treatment or No-shock treatment. Water was provided for 20 min on Days 7 to 10, and animals were exposed to the assigned Shock treatment immediately after the 20 min water presentation on Days 7

and 9. Saccharin-amphetamine pairing was conducted on Days 11 and 13 (PD1 and PD2). On pairing days, saline or amphetamine was injected 30 min after saccharin consumption to ensure comparability of the CS-UCS delay between Experiments 1a and 1b. Drug doses, saccharin concentrations, and shock parameters were identical to Experiment 1a.

*Data Analysis*: As in Experiment 1a, only animals consuming at least 10 ml of saccharin on the first pairing day were included in the data analysis. This eliminated four animals from the No-shock group and 3 animals from the Shock group. Baseline water intake values were computed by taking a weighted average of the last six water days prior to saccharin exposure. A separate repeated measures ANOVA was conducted on baseline water intake and water intake on the two shock days. Saccharin consumption data were analyzed with repeated measures ANCOVA as in Experiment 1a. A separate between-groups ANOVA was conducted on saccharin intake on the first pairing day to assess the impact of footshock on neophobic response to novel saccharin.

**Results**

Repeated measures ANOVA performed on baseline water intake and water intake on shock days indicated that there were no group differences in water intake ($F$s < 1.1, $p$s > .36) prior to CS-UCS pairing. A separate ANOVA on water intake on days between saccharin consumption tests (Days 10, 12, 14, 16 and 18) also indicated that neither shock nor amphetamine influenced water intake ($F$s < 2.0, $p$s > .15). Thus

water intake was comparable between treatment groups both prior to and after exposure to shock. A separate ANOVA on saccharin consumption on PD1 revealed that shocked animals consumed significantly less saccharin than non-shocked animals ($F_{1,23} = 4.63$, $p = .042$) (see Figure 2). Estimates of effect size indicated that Shock treatment accounted for between 14 and 17% of the variance in the intake of novel saccharin ($\omega^2 = .14$ and $R^2 = .17$).

Repeated measures ANCOVA conducted on saccharin consumption PD2 to EXT4 revealed that saccharin-amphetamine pairing reduced saccharin consumption ($F_{1,22} = 35.35$, $p < .001$). Figure 3 shows that the reduction in saccharin intake induced by saccharin-amphetamine pairing varied over test days. This was confirmed by a significant Drug by Days interaction ($F_{4,92} = 3.37$, $p = .013$). Simple effects analysis of the Drug by Days interaction revealed that amphetamine-injected animals consumed significantly less saccharin than saline-injected animals from PD2 to EXT4 ($F$s > 4.00, $p$s $\leq .050$). Thus, saccharin consumption was suppressed following one saccharin-amphetamine pairing, and was reduced for at least four extinction trials following a second saccharin-amphetamine pairing. The amphetamine-induced suppression in saccharin intake, however, was modified by footshock as indicated by a significant Shock by Drug by Days interaction ($F_{4,92} = 3.00$, $p = .023$). As shown in Figure 3, shocked animals exhibited a larger suppression of saccharin consumption following one saccharin-amphetamine pairing (i.e., PD2). Simple-simple effects analysis of the Shock by Drug by Days interaction revealed that shocked animals exhibited a

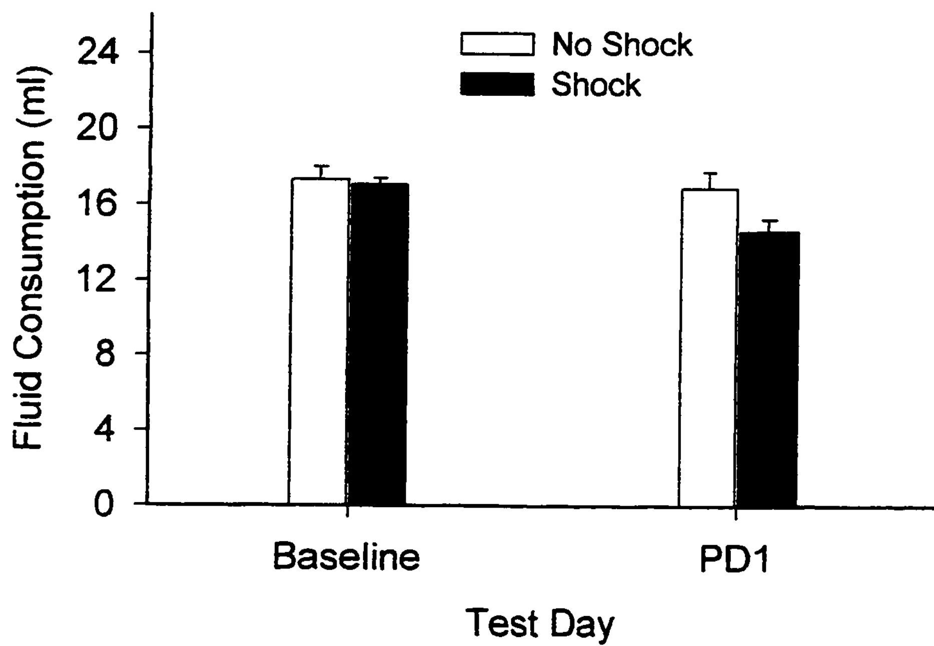


**Figure 2.** Mean fluid intake (± s.e.m) among animals exposed to either Shock or No-Shock 2 and 4 days prior to the first saccharin presentation (PD1) on saccharin neophobia. Baseline refers to water intake prior to initial saccharin presentation.

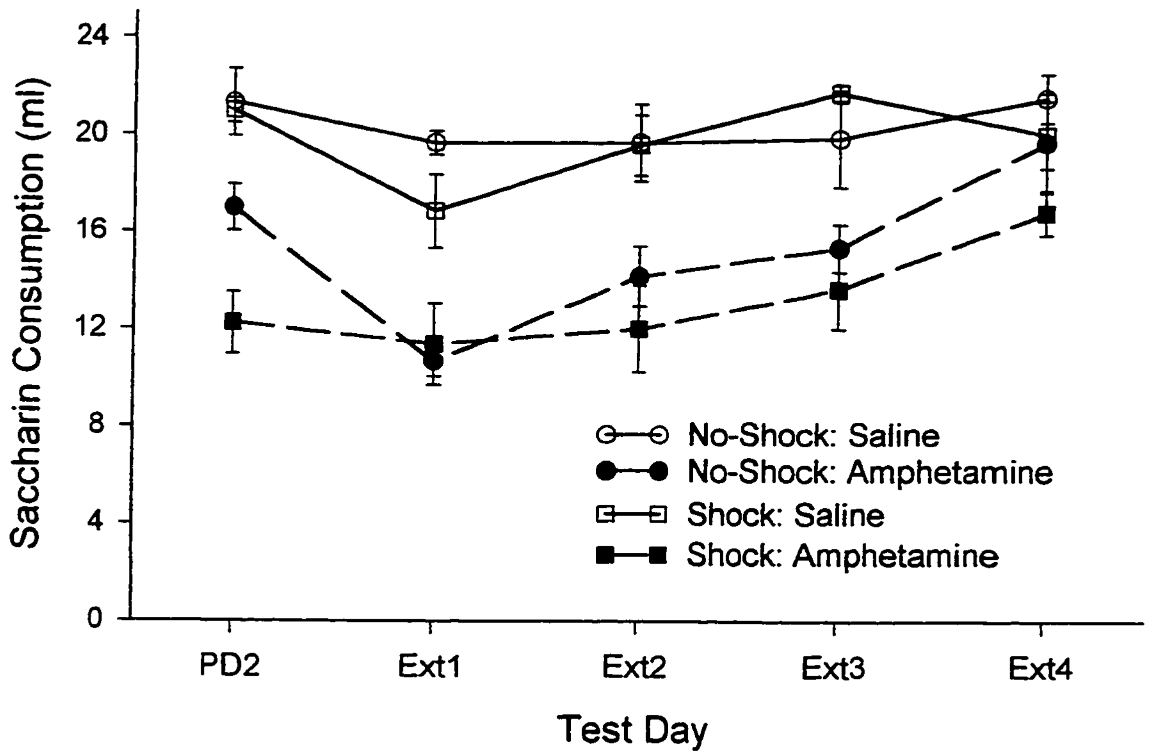


**Figure 3.** Mean saccharin intake (± s.e.m) among animals exposed to either Shock or No-Shock 2 and 4 days before the first saccharin-amphetamine pairing. Saccharin was presented on alternate days. (see Figure 1 for abbreviations).

significantly larger reduction in saccharin intake than non-shocked animals after one CS-UCS conditioning trial (i.e., PD2) ($F_{1,22} = 9.34$, $p = .006$).

There was also some indication that shock alters resistance to extinction of the amphetamine-CTA. Simple-simple effects analysis of drug effects for both non-shocked and shocked animals revealed that saccharin-amphetamine pairing reduced saccharin consumption in both non-shocked and shocked animals on PD2, EXT1 and EXT2 ($F$s > 5.0, $p$s < .025). However, on EXT3 amphetamine-saccharin pairing did not significantly reduce saccharin intake in non-shocked animals ($F_{1,22} = 4.19$, $p = .053$) while shocked animals continued to exhibit suppressed saccharin consumption ($F_{1,22} = 15.98$, $p < .001$). Amphetamine-induced suppression of saccharin intake was no longer evident in either non-shocked ($F_{1,22} = .96$, $p = .339$) or shocked ($F_{1,22} = 3.72$, $p = .067$) animals on EXT4.

**Discussion**

As in Experiment 1a, one saccharin-amphetamine pairing appears to be sufficient to significantly reduce subsequent saccharin intake. Also consistent with Experiment 1a, water intake was not influenced by either exposure to shock or amphetamine. However, exposure to footshock prior to initial saccharin consumption did reduce the consumption of novel saccharin. Since footshock did not alter the intake of saccharin on the second exposure to saccharin, it is unlikely that the shock-induced reduction in consumption of novel saccharin is related to an alteration in the palatability of the saccharin solution. Moreover, because water intake was not affected by footshock, the

shock-elicited reduction in novel saccharin intake is not due to a general suppression in fluid consumption. It is more likely that footshock enhanced the neophobic response to novel saccharin and the shock effect dissipates by the second saccharin test simply because the saccharin solution is no longer novel. That shock does not significantly influence the palatability of saccharin is also consistent with the lack of effect of shock on saccharin intake in Experiment 1a. Recall, that in Experiment 1a the first exposure to shock occurred immediately after the first exposure to saccharin. Thus, while it was not possible to assess the effect of footshock on saccharin neophobia, these data indicate that the response to saccharin is not altered by shock if initial saccharin consumption precedes exposure to shock.

Unlike Experiment 1a, exposure to shock prior to saccharin-amphetamine pairing increased the magnitude of the conditioned avoidance of saccharin after the first CS-UCS pairing. Moreover, shock influenced the extinction of the amphetamine CTA. For instance, while amphetamine CTA was no longer evident in non-shocked animals by EXT3, among shocked animals the conditioned reduction in saccharin intake was still significantly reduced on EXT3. It should be noted, however, that the shock-induced increases in resistance to extinction of the amphetamine CTA are modest at best, particularly since there was no indication in Experiment 1a that footshock altered resistance to extinction. On this basis, it would seem prudent to hold in abeyance any conclusions about the impact of shock on the extinction of amphetamine CTA.

In summary, it appears that exposure to footshock can enhance the conditioned avoidance of saccharin but only when shock precedes saccharin-amphetamine pairing.

It also appears that footshock increases the neophobic response to novel tasting saccharin solution.

## EXPERIMENT 1C

Experiment 1c was conducted to assess the impact of footshock on the neophobic response to a novel environment. If, as the results of Experiment 1b suggest, shock increases the response to novel stimuli, then shocked animals should also exhibit alterations in their response to a novel open-field. To investigate this, animals from Experiments 1a and 1b were tested for novelty-induced locomotion in a novel open-field. The impact of amphetamine injections on novelty-induced locomotion was also evaluated to determine whether prior amphetamine injections (during CTA training) or footshock influenced amphetamine-induced locomotion. If the increase in amphetamine CTA detected in Experiment 1b is due to a shock-induced increase in the sensitivity to amphetamine, then shock should also enhance the stimulatingly effect of amphetamine in the open-field test.

### Materials and Method

*Subjects and Apparatus*: Thirty-seven animals from Experiments 1a and 1b served as subjects. Because some of these subjects were assigned to another study, only half the sample from each of these studies were used. Open-field locomotion was assessed in a novel open-field measuring 1 m by 1 m with two photocell beams on each wall. A locomotor count was registered on counters in a separate room each time a photocell beam was interrupted. The open-field chambers were housed in a separate room and all testing was conducted during the second and third quarters of the light

cycle. Open-field chambers were illuminated by overhead lights. Drug injections consisted of either 0.9% saline or 1.5 mg/kg d-amphetamine sulfate.

*Procedures*: Following the last saccharin test, animals from both CTA studies were returned to a schedule of ad lib food and water for 13 days. Twenty-four hr later, half the animals in each treatment cell from Experiments 1a and 1b (i.e., the drug/shock treatments) were assigned to one of two drug conditions: saline or amphetamine (1.5 mg/kg). The animals were transported to a separate room, injected with either saline or amphetamine and immediately placed in the open-field for a 30 min test. Photocell counts were recorded at 2, 5, 10, 20 and 30 min.

*Data Analysis*: Locomotor counts in the novel open-field were analyzed with a 2 x 2 x 5 repeated measures ANOVA. Between-subjects factors were CTA drug, Shock treatment and Open-field drug. The within-subjects factor was Time in the open-field test. Locomotor counts at each time block were standardized by computing locomotor counts per minute thus accounting for differences in the duration of the time blocks. Multivariate $F$ tests were used to assess all effects involving the repeated measures factor in order to avoid restrictions imposed by the circularity assumption and unequal cell sizes (Kirk, 1982; Stevens, 1986).

**Results**

ANOVA revealed that amphetamine injections immediately prior to open-field testing increased locomotor counts ($F_{1,29}$= 10.93, $p$=.003) and that this varied by time ($F_{4,26}$ = 5.61, $p$ = .002). Simple effects analysis revealed that amphetamine injections

increased locomotor counts at all time blocks (*F*s > 5.0 , *p*s < .03) except at 10 minutes ($F_{1,29}$ = .69, $p$ = .413). As can be seen in Figure 4, shock also influenced locomotion in the novel open-field but this effect varied over Time blocks ($F_{4,26}$ = 30.59, $p$ < .001). Analysis of simple effects indicated that shock decreases locomotion only at 2 and 5 minutes (*F*s = 60.36 and 5.87, *p*s < .03, respectively) but not thereafter (*F*s < 2.7, *p*s > .10). Exposure to shock did not alter the effect of amphetamine on locomotion ($F_{4,26}$ = 2.61, $p$ = .058). More surprising, was that the ANOVA revealed that the drug injections used in CTA training also influenced the temporal pattern of locomotion ($F_{4,26}$ = 5.61, $p$ = .002) but did not influence the impact of either shock ($F_{4,26}$ = 2.54, $p$ = .063) or amphetamine-induced locomotion ($F_{4,26}$ = .48, $p$ = .750). Simple effects analysis indicated that locomotion at the 5-minute time block was reduced in animals that had received amphetamine during CTA training ($F_{1,29}$ = 6.50, $p$ = .016). A closer look at group means indicated that the reduced locomotion at 5 minutes in animals that had received amphetamine during CTA training was evident primarily in the shocked animals. Given that shock alone reduced locomotion at the 5-minute time block, the reduction in locomotion produced by amphetamine injected during CTA training should be considered questionable at best.

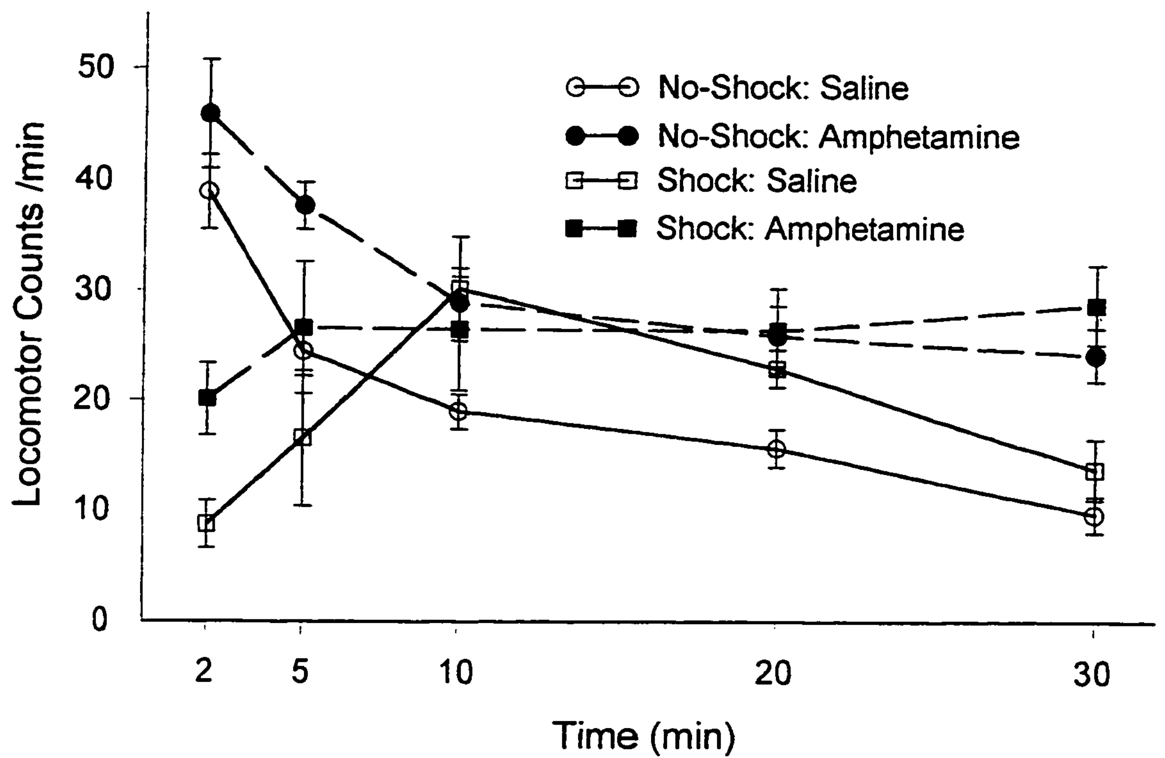


**Figure 4.** Mean locomotor counts/min (± s.e.m ) in a novel open-field among animals exposed to either Shock or No-Shock 28 days earlier. Animals were injected with either saline or amphetamine (1.5 mg/kg) immediately before the open-field test.

**Discussion**

The pattern of locomotion in the 30 minute novel open-field test indicates that among non-shocked animals locomotion is greatest when the open-field is the most novel (i.e., during the first few minutes) and that locomotor counts decrease monotonically over the 30 minute exposure to the open-field. This pattern of locomotion in a novel environment has been previously reported following repeated brief exposure (≤ 5 min) to a novel environment (Bronstein, Neiman, Wolkoff & Levine, 1974; Dickson, 1974; Gray, Solomon, Dunphy, Carr & Hession, 1976; King & Appelbaum, 1973; Valle, 1971). Thus, it appears that the locomotor response to novelty observed in this study is consistent with previously reported patterns of locomotion.

As expected, amphetamine injections immediately before placement in the novel open-field increased locomotion. However, there was no indication that prior exposure to shock or amphetamine (during CTA training) influenced amphetamine-induced locomotion. These results indicate that with the shock parameters employed here cross-sensitization does not occur between shock and amphetamine. In addition, injections of amphetamine during CTA training does not influence the increased locomotion produced by amphetamine immediately prior to locomotion testing.

The pattern of locomotion in the novel open-field differs considerably between non-shocked and shocked animals. Shocked animals exhibit a substantial reduction in locomotion in the first 5 minutes of the open-field test. These results are consistent with a number of reports showing that shock decreases locomotion in a novel

environment in 5 min open-field tests (van Dijken, Mos, van der Heyden & Tilders, 1992; van Dijken, Tilders, Olivier & Mos, 1992; van Dijken, van der Heyden, Mos & Tilders, 1992; Weyers, Bower & Vogel, 1989). The current study also indicates that the shock-induced reduction in locomotion is restricted to the initial time period in the open-field (i.e., only the first 5 minutes). That amphetamine injections increase locomotion but do not mask this effect attests to the robustness of this shock-induced reduction in locomotion.

The most obvious explanation for the observed reduction in locomotion produced by footshock is that exposure to shock (even 28 days earlier) alters the response of animals to the novelty of the open-field. Under such conditions, one would expect that as animals habituate to the novel environment, the effects of shock would dissipate. The normalization of the locomotor pattern after 5 minutes would thus reflect the decrease in novelty of the open-field over the protracted exposure to this novel environment. It seems unlikely that the shock-induced depression in locomotion is related to alterations in motoric capacity because shocked animals exhibited increased locomotion 10 minutes into the locomotion test.

## EXPERIMENT 2A

The results of Experiment 1 suggest that exposure to footshock enhances only the aversive response to saccharin. For instance, both conditioned taste aversion and taste neophobia were enhanced by prior exposure to footshock. The appetitive response to saccharin, as measured by saccharin intake among saline-injected animals, was not influenced by exposure to footshock. These results suggest that footshock exerts differential effects on responding to appetitive and aversive stimuli and raise the possibility that footshock may produce a more generalized enhancement in responsiveness to aversive stimuli while leaving the response to appetitive stimuli relatively unaffected.

Experiment 2a was conducted to provide a further test of this hypothesis. The reward reduction procedure was selected because it permits the assessment of the effect of shock on responding for food reinforcement (appetitive response) as well as the response to a reduction in reinforcer magnitude (aversive response). Briefly, this consists of training animals to traverse a runway for food reinforcement, exposing them to footshock, and testing runway responding under either the same or a reduced level of reinforcement. The impact of shock on appetitive responding for food reinforcement can be measured in animals where reinforcer magnitude has not been changed. Since reducing reinforcer magnitude is thought to be aversive, the effect of footshock on runway responding among animals where reinforcer magnitude has been reduced provides an index of responsiveness to aversive stimuli. If shock enhances responding to aversive stimuli but has little impact on responding to appetitive stimuli,

then shock should enhance the response to reward reduction but have no impact on runway responding among animals for which reward magnitude is not changed.

**Materials and Method**

*Subjects*: Subjects were 31 male Long-Evans rats (Charles River, St Constant, Que), weighing 265-375 g at the start of the experiment. Animals were individually housed in stainless steel hanging cages and had free access to Purina Rat Chow and water prior to the start of the experiment. They were maintained on a 12 hr ON: 12 hr OFF light-dark cycle. All animals were permitted 1 week to acclimatize to the housing facilities. They were handled daily for the next 5-7 days. All testing was conducted during the light cycle.

*Apparatus*: The experiment was conducted in a straight runway (181 cm by 19 cm by 29 cm) with a start box (30 cm by 19 cm by 29 cm) and a detachable goal box (30 cm by 19 cm by 29 cm) at the end of the runway. Vertically sliding doors separated both the start box and the goal box from the runway. The entire runway was painted grey and illuminated by overhead fluorescent lights. The shock apparatus was exactly as described in Experiment 1a and the open-field chambers were exactly as described in Experiment 1c.

*Procedure:* Runway training began 24 hr after the last day of daily handling and animals were always tested in groups of eight rats. Rats were transported from the housing facilities to the test room in individual plastic carrying containers. The first two days consisted of 10 min habituation trials. Animals were individually carried to

the runway room, weighed, and placed in the start box of the runway. The doors of the start and goal boxes were opened, and the rat was permitted to explore the runway for 10 min. During this time 15 Noyes pellets (Formula A1) were available in a food cup in the goal box. Following this 10 min habituation period, the rat was returned to its carrying container and the next rat in the group was tested. All food was removed from the home cage following the first habituation trial. A second habituation trial was conducted on the next day and runway training began 24 hr later. All animals were given 12 days of runway training consisting of three trials per day. On training days, rats were weighed and placed in the start box of the runway with the door closed. The door was then opened to permit the rat to traverse the runway to the goal box where 15 Noyes pellets were available in a food cup. Once the rat entered the goal box, the goal box door was closed and the rat was confined in the goal box for one minute. The rat was then removed from the goal box, placed in a holding cage and the next rat in the group was tested. Each rat was tested for three trials per day with an inter-trial interval of approximately 10 min. The latency to enter the goal box and the number of pellets consumed were recorded. Following each daily test session, rats were returned to their home cages and given approximately 13 g of rat chow. Where required, supplemental chow was provided to ensure that animals maintained 85 to 95 % of normal body weight.

Twenty-four hr after the last training trial, animals were matched on the basis of running speed and assigned to either No-shock or Shock treatment. Animals assigned to the shock condition were transported to a separate room and exposed to 30 min of

footshock (1.0 mA, 1.5 sec duration, 60 sec ITI) while non-shocked rats were transported to another room and placed in identical shock chambers but no footshock was applied. Following shock treatment, animals were carried to the runway room for testing. Half the animals in each shock treatment group were tested in the runway under the same level of reinforcement as during training days (Unshifted condition). The remaining animals were tested as on training days except the food cup in the goal box contained only 1 Noyes pellet (Shifted condition). Each animal received three trials per day under the appropriate Shift condition. Runway testing continued under the new reinforcer condition for 14 days following shock treatment (42 trials). Animals were exposed to footshock only on the first day of the test phase. Following each test day, animals were returned to their home cages and given supplemental food to ensure adequate weight gains. Body weight, latency to enter the goal box and number of pellets consumed were recorded for each trial.

Immediately following the last runway trial, all animals were returned to a schedule of ad lib food and water. Fourteen days later, half the animals in each shock/shift treatment cell were injected with saline while the remaining animals were injected with 1.5 mg/kg d-amphetamine sulfate. Animals were placed in the open-field chambers for a 30 min test. Locomotor counts were recorded at 2, 5, 10 20 and 30 min.

*Data Analysis:* Deprivation level was computed as the percent of free-feeding body weight (deprivation level= [(body weight/free-feeding body weight]100). Free-feeding body weight was defined as body weight on the first habituation trial. Mean

runway latencies were computed for each day. Mean latencies for blocks of six trials were computed from the mean latency for 2 days of testing. Baseline runway latencies were computed by calculating a weighted average of daily latencies for the last six days of pre-shift training. Coefficients used were .10, .10, .15, .15, .25 and .25. A weighted average was used because this permits the most recent pre-shift daily results to exert a greater weight on the baseline latency than more distant daily scores. To eliminate interpretative difficulties associated with nonadditivity, latencies were transformed with a $\log_{10}$ transformation (Kirk, 1982). This procedure has the added advantage of reducing heterogeneity of variance. All subsequent analyses on latency scores was conducted on the $\log_{10}$ transformed latency scores.

Preliminary diagnostic tests were conducted to assess the circularity assumption (Mauchly's sphericity test) for repeated measures designs (Kirk, 1982; Lewis, 1993; Stevens, 1986). Where this test indicated that the sphericity assumption was not tenable (alpha was set at .01 since this test tends to be excessively sensitive) (Stevens, 1986), multivariate $F$ tests (estimated from Wilks $\lambda$) were used to test within-subjects effects. This approach was selected since these multivariate $F$ tests do not require the circularity assumption (Kirk, 1982; Stevens, 1986) and these multivariate $F$ tests are interpreted in the same manner as univariate $F$ tests. Open-field data were analyzed as described in Experiment 1c.

**Results**

The imposition of the food deprivation schedule produced comparable reductions in body weight among the treatment groups. Figure 5 illustrates deprivation levels for the four treatment groups throughout the 12 days of runway training (pre-shift) and the 14 days of post-shift testing. During runway training, the level of deprivation gradually decreased but there were no differences between treatment groups. This was confirmed by a repeated measures ANOVA on pre-shift deprivation levels that revealed a significant Days effect ($F_{11,17} = 78.12$, $p < .001$) but no significant effects of Reward magnitude ($F$s $< 1.0$, $p$s $> .30$). Figure 5 also shows that during the post-shift period the level of deprivation continued to decrease. However, while deprivation levels among Unshifted groups continued to decrease, deprivation levels were relatively constant throughout post-shift testing. These results were confirmed by a separate repeated measures ANOVA on post-shift deprivation levels. This ANOVA revealed a significant main effect of Shift condition ($F_{1,27}$=4.20, $p$=.050) and a main effect of Days ($F_{13,15}$=27.34, $p$<.001). There were no other main effects or interactions ($F$s<2.1, $p$s>.05). The difference in deprivation levels between Unshifted and Shifted groups probably indicates the impact of the decrease in daily food that resulted from the reward reduction since shifted animals received 3 Noyes pellets per day during the post-shift phase while unshifted animals continued to receive 45 pellets. More importantly, however, deprivation levels among shifted animals were not influenced by the shock treatment.

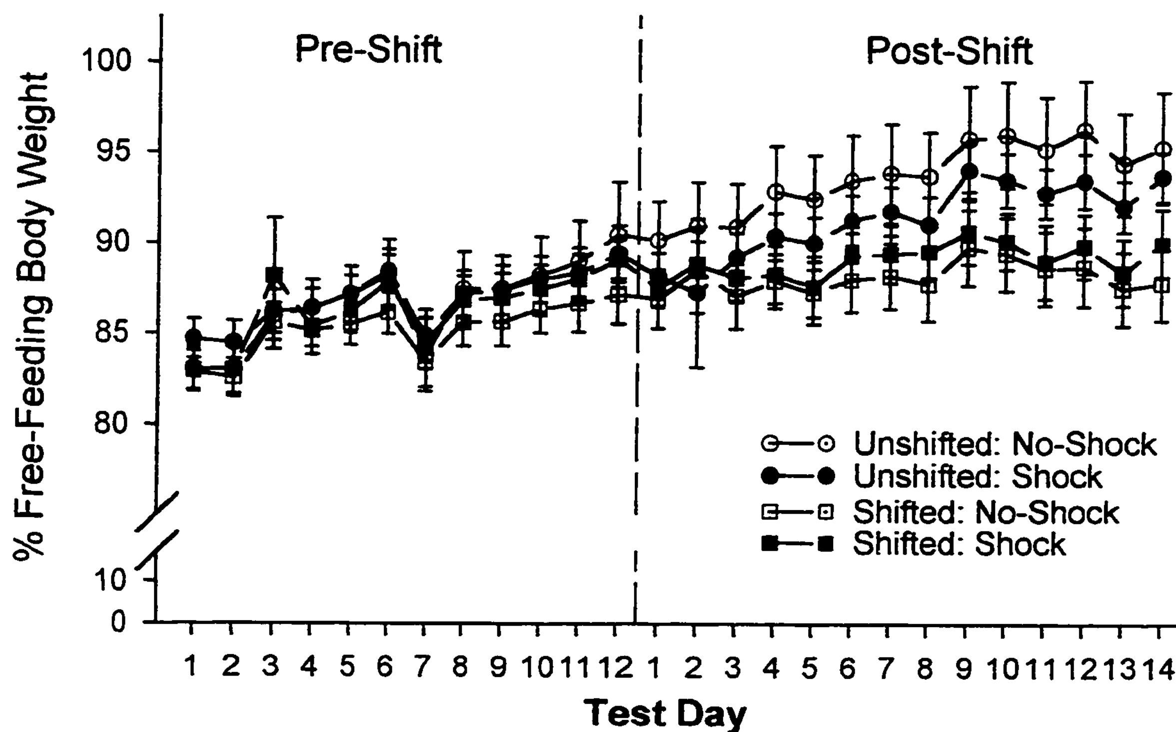


**Figure 5.** Mean deprivation levels (expressed as % free-feeding body weight) (± s.e.m) on each test day among animals trained with 15 pellets in the goal box on each trial and tested with the same (Unshifted) or reduced (Shifted) level of reinforcement in the goal box. Footshock was applied immediately before the first trial where reward magnitude was reduced (Post-Shift Day 1).

All animals learned to traverse the runway to obtain food reinforcement in the goal box. As shown in Figure 6, latencies to enter the goal box decreased over blocks of trials and reached asymptotic levels after 8 days of training (training block 4) and remained constant thereafter. This was confirmed with repeated measures ANOVA which revealed only a significant Blocks effect ($F_{5,23}$= 18.51, $p$ < 001). The lack of any significant effects of either Shift condition or Shock condition indicates there were no differences in treatment groups in baseline acquisition latencies.

A separate repeated measures ANOVA was conducted on post-shift runway latencies. This ANOVA also included the weighted pre-shift baseline latency. As shown in Figure 7, reducing reward magnitude (Shifted group) increased runway latencies ($F_{1,27}$ = 27.53, $p$<.001) and the increase in latencies produced by reward reduction varied over Blocks ($F_{7,21}$= 5.36, $p$ = .001). Simple effects test revealed that latencies were significantly greater in Shifted animals than Unshifted animals from post-shift Block 2 to post-shift Block 6 ($F$s ≥ 4.5, $p$s < .05). There were no differences between the Shifted groups on the weighted baseline latency ($F_{1,27}$ =< 1.0, $p$ = .904) or post-shift Block 7 ($F_{1,27}$ = 3.74, $p$ = .064).

ANOVA also revealed a significant Shift by Shock interaction ($F_{1,27}$ = 6.67, $p$ = .016). As shown in Figure 8, Shock treatment exerted little effect on the increase in latency produced by reward reduction in the first three post-shift trial blocks. However, while runway latencies in non-shocked animals returned to unshifted values by post-shift Block 4, among shocked animals the increase in latencies produced by

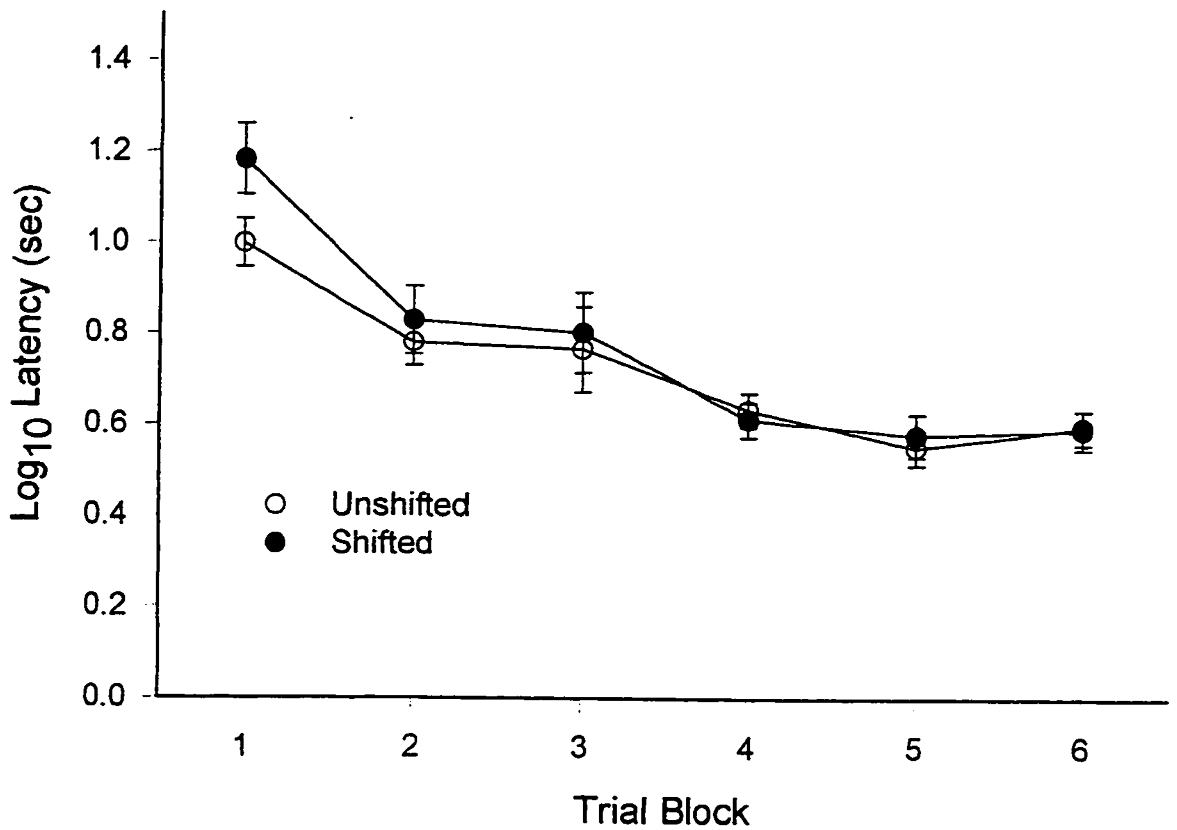


**Figure 6.** Mean runway latencies ($\log_{10}$ transformed) (± s.e.m) during the 12 days of runway acquisition training for animals assigned to the Shifted and Unshifted reward magnitude conditions. All animals were trained with the large level of reinforcement (i.e., 15 pellets). Each training block consists of 2 days of 3 runway trials per day (i.e., 6 runway trials).

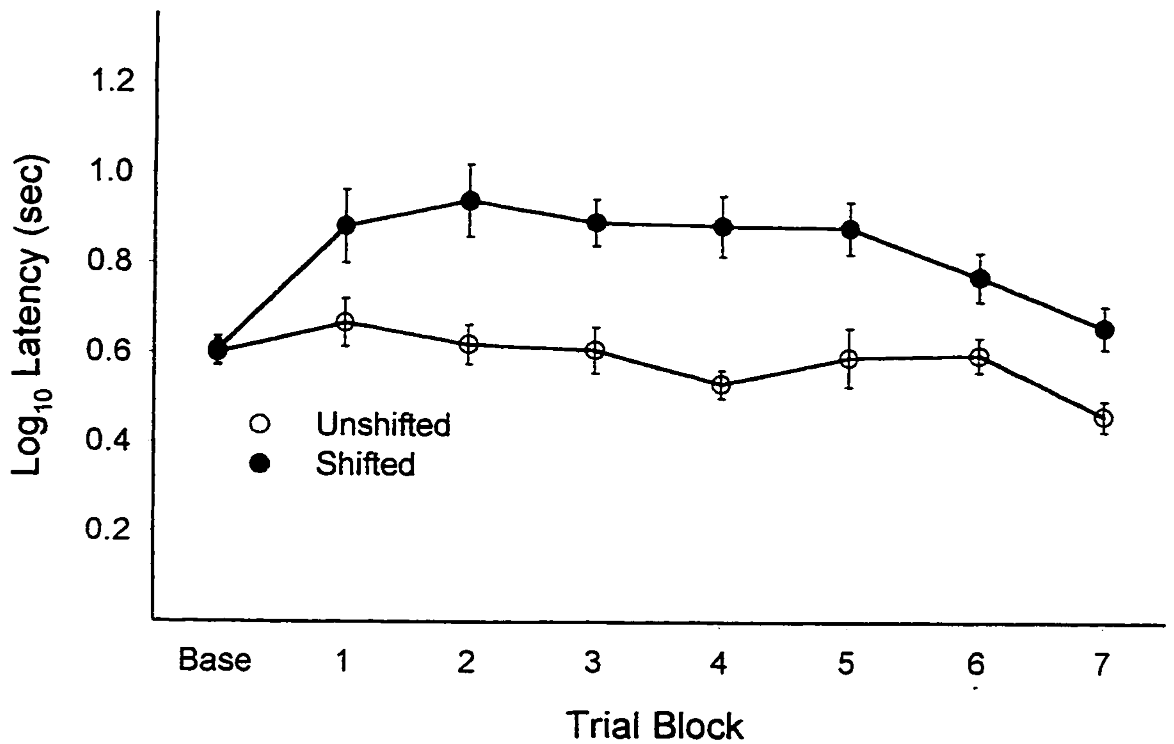


**Figure 7.** Mean runway latencies ($\log_{10}$ transformed) (± s.e.m) in animals trained with a large level of reinforcement and tested with the same (Unshifted) or reduced reinforcement (Shifted). Base refers to latencies averaged over the last 6 days of runway training. Each trial block consists of 6 runway trials.

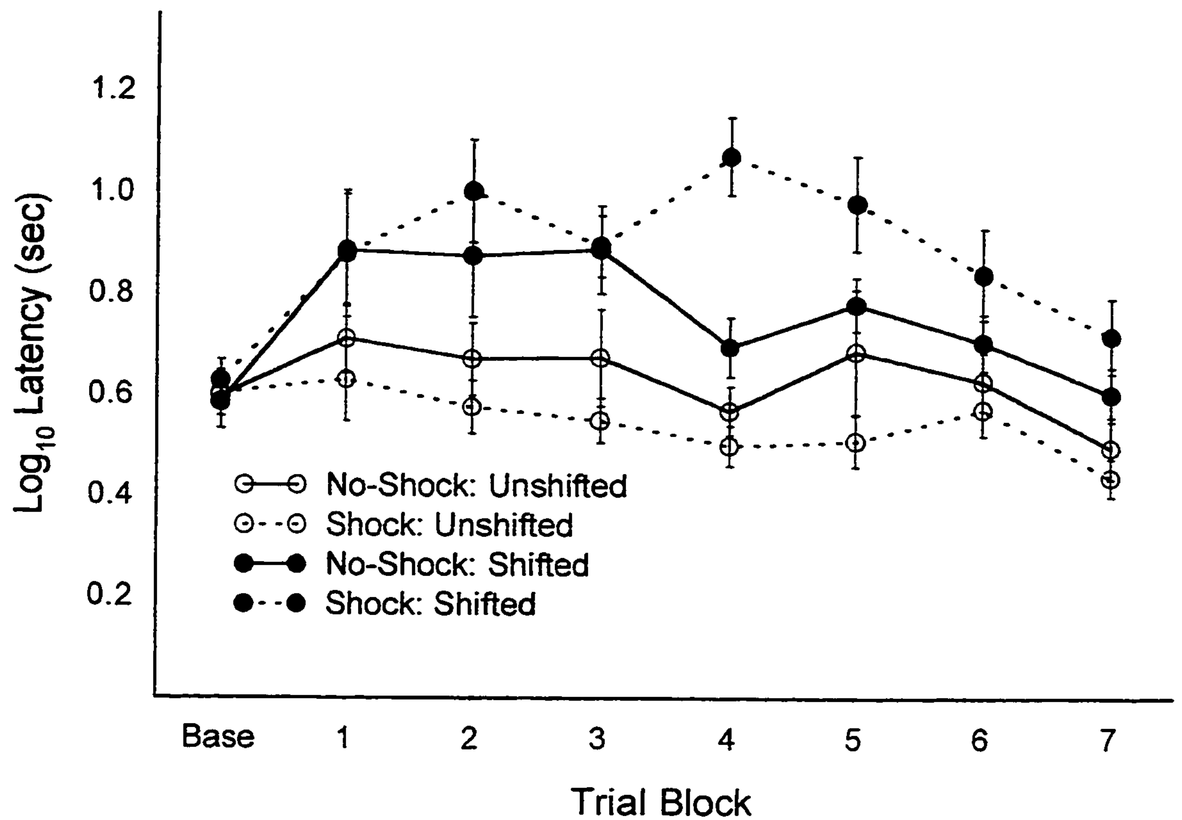


**Figure 8**. Mean runway latencies ($\log_{10}$ transformed) (± s.e.m) in animals trained with a large level of reinforcement and tested with the same (Unshifted) or reduced reinforcement (Shifted). Shock or No-Shock was applied immediately before the first post-shift runway trial and each trial block consists of 6 runway trials.

reward reduction was maintained until post-shift Block 7. Simple-simple effects analysis revealed that while reward reduction increased runway latencies in non-shocked on all post-shift trial blocks, these reached statistical significance only on post-shift Block 3 ($F_{1,27} = 4.30$, $p = .048$). In contrast, among shocked animals reward reduction significantly increased latencies on post-shift Blocks 2 to 7 ($F$s > 7.2, $p$s < .015). Simple-simple effects analysis also revealed that among Unshifted animals, exposure to shock did not significantly alter runway latencies on any trial block ($F$s < 2.8, $p$s, >.10).

A separate repeated measures ANOVA was performed on photocell counts in the novel open-field. As can be seen in Figure 9, shock treatment reduced photocell counts only during the initial 2 minutes in the open-field and produced a small increase in photocell counts in the 10 min time block. This was confirmed by ANOVA. There was no significant main effect of either Shift treatment ($F_{1,27}$ = < 1.0, $p$=.797) or Shock treatment ($F_{1,27}$= 1.53, $p = .226$) nor was there any significant Shift by Shock interaction ($F_{1,27} < 1.0$, $p = .966$). There was, however, a significant main effect of Time ($F_{4,24} = 26.69$, $p < .001$) and a significant Shock by Time interaction ($F_{4,24} = 5.89$, $p = .002$). The Shift by Time interaction was not significant ($F_{4,24}$ = 2.13, $p = .108$). Subsequent simple effects tests for the Shock by Time interaction revealed that Shock treatment reduced photocell counts during the first time block ($F_{1,27} = 12.03$, $p = .002$) and produced a nonsignificant increase in photocell counts at 10 min ($F_{1,27} = 3.75$, $p = .063$). Shock did not influence locomotion at any other

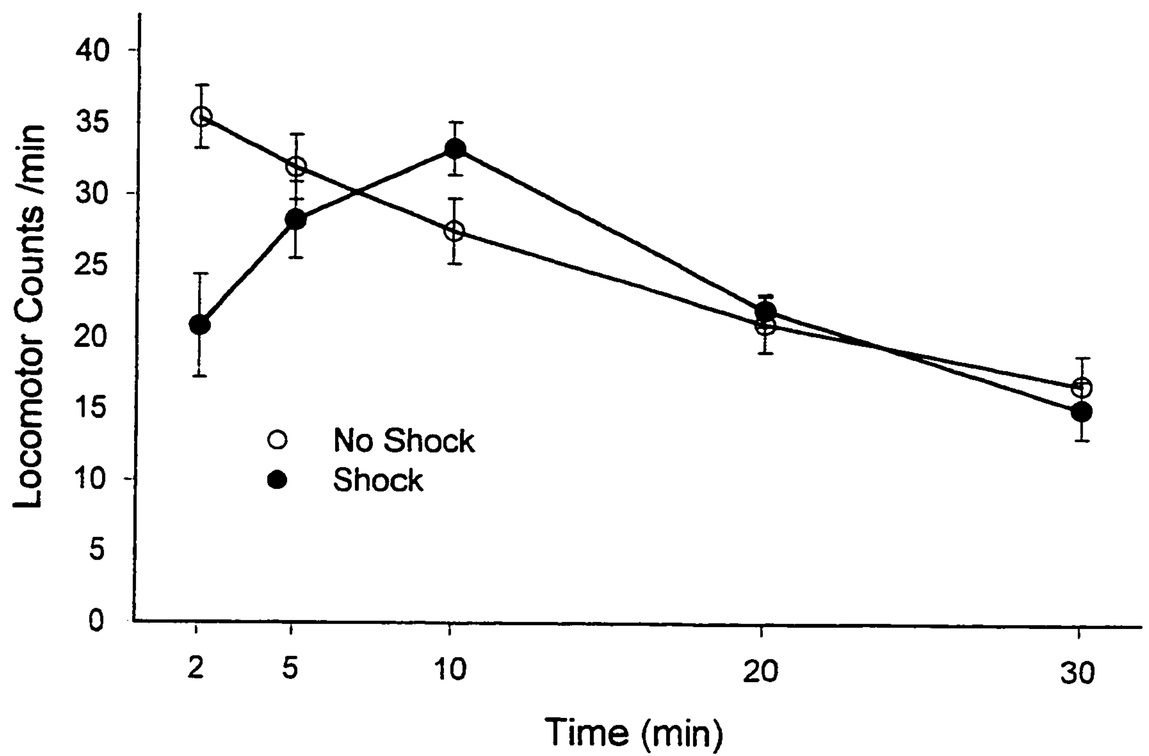


**Figure 9.** Mean locomotor counts/min (± s.e.m) in a novel open-field among animals exposed to either Shock or No-Shock 28 days earlier. Animals had been previously tested in the runway.

time block ($F$s < 2.0, $p$s > .15). We had expected that experience with reward reduction would alter novelty-induced locomotion in the first few minutes of the test and would exaggerate the impact of shock on locomotion. As shown in Figure 10, reward reduction did not alter locomotion in the first 2 minutes among non-shocked animals; however, among shocked animals, experience with reward reduction potentiated the reduction in novelty-induced locomotion induced by shock. Contrast interaction tests confirmed that Shift treatment had no impact on locomotion among non-shocked animals ($F_{1,27} = 2.10$, $p = .159$) but significantly decreased locomotion in the first 2 minutes among shocked animals ($F_{1,27} = 11.73$, $p = .002$). The experience with reward reduction did not influence novelty-induced locomotion in shocked animals at any other time block ($F$s < 4.1, $p$s > .05).

**Discussion**

All animals learned to traverse the runway to obtain food reinforcement as indicated by decreases in latencies over the 12 days of training. Reducing reinforcer magnitude from 15 pellets to 1 pellet increased runway latencies in both shocked and non-shocked groups indicating that the rats were sensitive to the shift in reward magnitude.

Footshock did not exert any significant impact on runway responding among animals trained and tested with the same level of reinforcement. It therefore appears that, with the parameters employed, shock has no effect on the appetitive response to

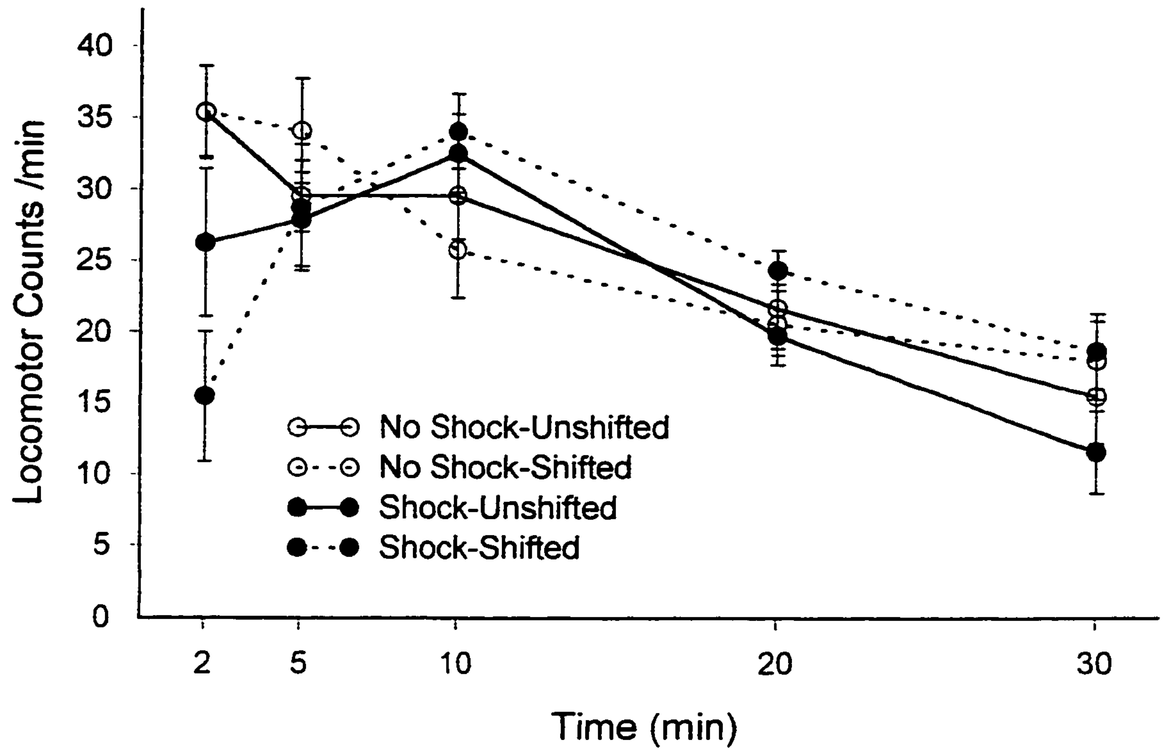


**Figure 10**. Mean locomotor counts/min (± s.e.m) in a novel open-field among animals exposed to either Shock or No-Shock 28 days earlier. Animals had been previously tested in the runway under unchanged (Unshifted) or reduced (Shifted) reinforcement conditions.

food reinforcement. In contrast, while footshock did not alter the magnitude of the response to reward reduction, it did significantly prolong the duration of the response to reward reduction. While reward reduction increased runway latencies in non-shocked animals on the first 3 post-shift blocks of trials, this increase was evident in shocked animals up to the seventh post-shift trial block. Because each trial block consisted of 2 days of testing, footshock prolonged the response to reward reduction by 6 days.

The runway results suggest that exposure to footshock has little influence on appetitive responding for food reinforcement and that the effects of shock are evident only when an aversive stimulus (i.e., reduced reinforcer magnitude) is added to the appetitive response. Note that, unlike extinction studies where the reinforcer is completely omitted (this may be viewed as the most extreme form of reinforcer reduction), in the current study animals continue to be reinforced for traversing the runway even after reward reduction. That the animals continue to run to the goal box after reinforcer magnitude has been reduced (albeit at a slower speed) indicates that new low level of reinforcement does support appetitive responding. Thus, because appetitive responding is maintained by the reduced level of reinforcement and because shock has no impact on appetitive responding in unshifted animals, the shock-induced enhancement in the response to reinforcer reduction is most likely due to a heightened response to the aversive reinforcer reduction.

Lastly, novelty-induced locomotion was also altered by prior exposure to footshock. The temporal pattern of shock-induced reductions in novelty-induced

locomotion was similar to that noted in Experiment 1c (i.e., locomotion was reduced only in the earliest part of the test). That footshock produces a similar temporal pattern of response disruption in both Experiment 1c and the current study attests to the robust nature of the shock-induced reduction in novelty-induced locomotion.

## EXPERIMENT 2B

Experiment 2a indicated that footshock produced no effect on responding for food reinforcement but enhanced the response to reward reduction. One possible explanation is that footshock influences the response to any change in reward magnitude rather than specifically enhancing the response to reward reduction. In this case, it would be expected that footshock would enhance the response to an increase in reinforcer magnitude in a manner similar to that seen following a reduction in reinforcer magnitude. A second possibility is that the enhanced response to reward reduction observed in Experiment 1a may actually be secondary to the effects of footshock on appetitive responding for food when small levels of reinforcement are used. For instance, the shock-induced enhancement of the increase in runway latencies produced by reward reduction may reflect a reduction in the appetitive response to the low level of reinforcement rather than an enhanced response to the reward reduction per se. This would suggest that the results of Experiment 2a may be related to a stress-induced decrease in the reinforcing value of small magnitude reinforcers.

Experiment 2b was conducted to assess both of these possibilities. The procedures were identical to that employed in Experiment 2a, except reward magnitude was increased rather than decreased and 20 days of runway training were employed instead of 12 days. This was done because with the low reward magnitude used in this study more training is required to obtain stable runway responding. Animals were trained with a low level of reinforcement (1 pellet), exposed to footshock, and tested with the same or increased reinforcer magnitude. If footshock alters the response to any change

in reinforcer magnitude, then footshock should alter runway responding when reward magnitude is either increased or decreased. Similarly, if footshock alters runway responding only when low levels of reinforcement are used, then footshock should alter runway responding in animals trained and tested with a constant low level of reinforcement. Based upon the hypothesis that stressors will preferentially enhance responsiveness to aversive stimuli, we expect that footshock will exert no impact on the response to an increase in reward magnitude. Similarly, we expect that shock will not alter runway responding in animals trained and tested with a low level of reinforcement.

**Materials and Method**

*Subjects:* Thirty-two male Long-Evans rats weighing 250-275 g served as subjects. Housing conditions were identical to those used in Experiment 2a. Animals were allowed 14 days to acclimatize to the housing facilities before testing began. Purina Rat Chow and water were freely available throughout the study except where indicated.

*Apparatus*: The runway, shock apparatus, food reinforcer, and open-field was exactly as described in Experiment 2a.

*Procedure*: Procedures were identical to Experiment 2a with the following exception. All animals were trained with 1 pellet in the goal box on each of 3 trials per day for 20 days. Twenty-four hr after the last training day, animals were matched on the basis of average running speed (weighted average) and exposed to either 30

min footshock or to no shock. Half the animals in each Shock treatment group were then tested in the runway with 15 pellets in the goal box instead of 1 pellet (Shifted groups) while the remaining animals continued to receive 1 pellet in the goal box. Shock parameters were identical to those used in Experiment 2a. Open-field testing was conducted 14 days after the last runway test (28 days after shock exposure).

*Data Analysis*: Mean latency to traverse the runway for blocks of 6 trials (i.e., latencies of 2 days of 3 trials) were computed as in Experiment 2a. Raw latency scores were transformed with a $\log_{10}$ transformation for subsequent data analysis. Statistical procedures were identical to those used in Experiment 2a.

**Results**

Transformed runway latencies for blocks of 6 trials for the No-shock and Shock groups over the 20 days of training are shown in Figure 11. Repeated measures ANOVA indicated that there were no significant differences between the Shock treatment groups ($F$s< 1.0, $p$s >.80) nor were there any significant interactions ($F$s< 2.0, $p$s, >.16). There was, however, a significant Blocks effect ($F_{9,20}$= 10.23, $p$ < .001) indicating that runway latencies decreased over the course of training. Thus, all treatment groups did learn to traverse the runway for 1 pellet in the goal box and latencies were comparable between treatment groups prior footshock or the change in reward magnitude.

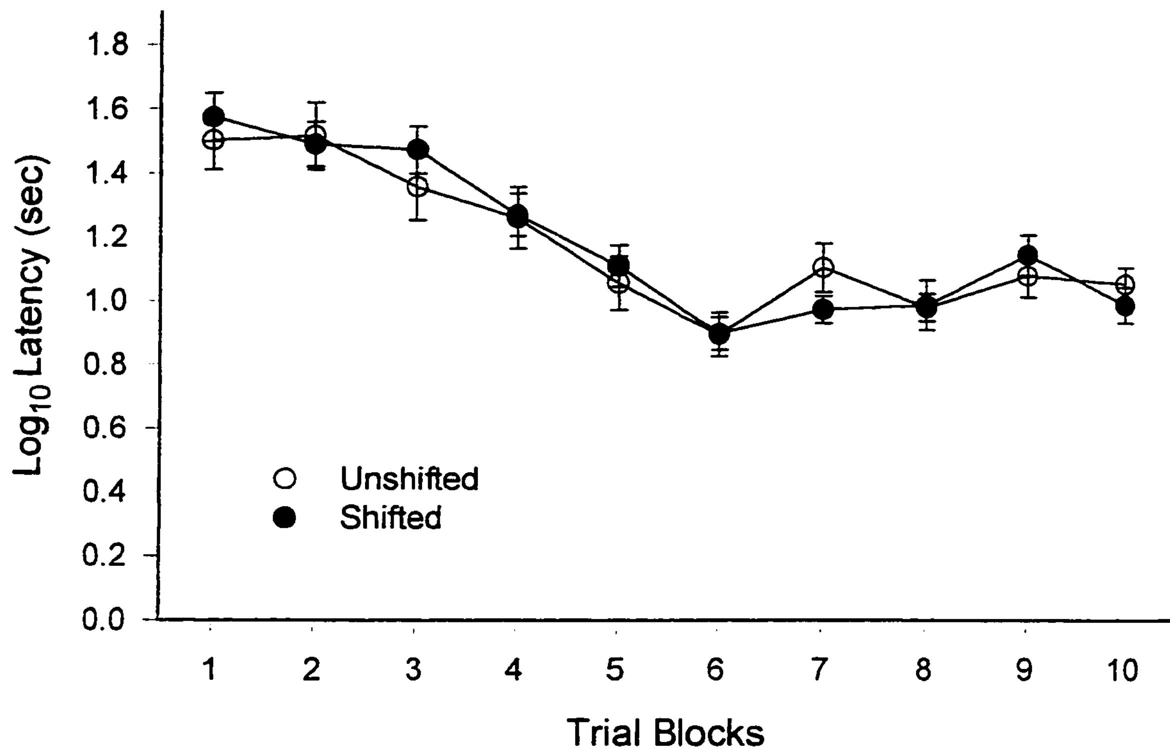


**Figure 11**. Mean runway latencies ($\log_{10}$ transformed) (± s.e.m) during the 20 days of runway acquisition (3 trials per day) in animals assigned to the Unshifted and Shifted reinforcement conditions. All animals were trained with 1 pellet in the goal box on each trial for runway acquisition training.

Transformed post-shift latencies were analyzed with repeated measures ANOVA. A weighted baseline latency score was also included in this analysis. This baseline was computed from the last 6 days of training using the same coefficients as in Experiment 2a. ANOVA on transformed latencies scores following reward increase revealed a main effect of Shift treatment ($F_{1,28}$=7.49, $p$=.011), a main effect of Blocks ($F_{6,181}$=22.71, $p$<.001), but a Shift by Blocks interaction ($F_{6,181}$ = 2.18, $p$ < .05; Huynh-Feldt adjusted degrees of freedom) and a significant Stress by Blocks interaction ($F_{6,181}$= 2.16, $p$ < .05). Figure 12 shows that, although runway latencies tended to decrease in all groups, the decrease in latencies was largest for animals in the Shifted groups regardless of shock treatment. As can be seen in Figure 13, runway latencies decreased in both Shifted and Unshifted groups following the increase in reward magnitude. Simple effects analysis of Shift by Blocks interaction, revealed that the reduction in runway latencies was larger among shifted animals than unshifted animals at post-shift Block 4 ($F_{1,28}$=4.77, $p$=.037), post-shift Block 5 ($F_{1,28}$=9.65, p=.004), post-shift Block 6 ($F_{1,28}$=6.37, $p$=.018) and post-shift Block 7 ($F_{1,28}$=11.21, $p$=.002). Simple effects analysis of the Stress by Blocks interaction revealed that there was a trend for larger runway latencies among shocked animals at post-shift Block 5 ($F_{1,28}$=4.0, $p$=.055). Shock treatment did not significantly alter runway latencies at any other post-shift block ($F$s<3.0, $p$s>.10).

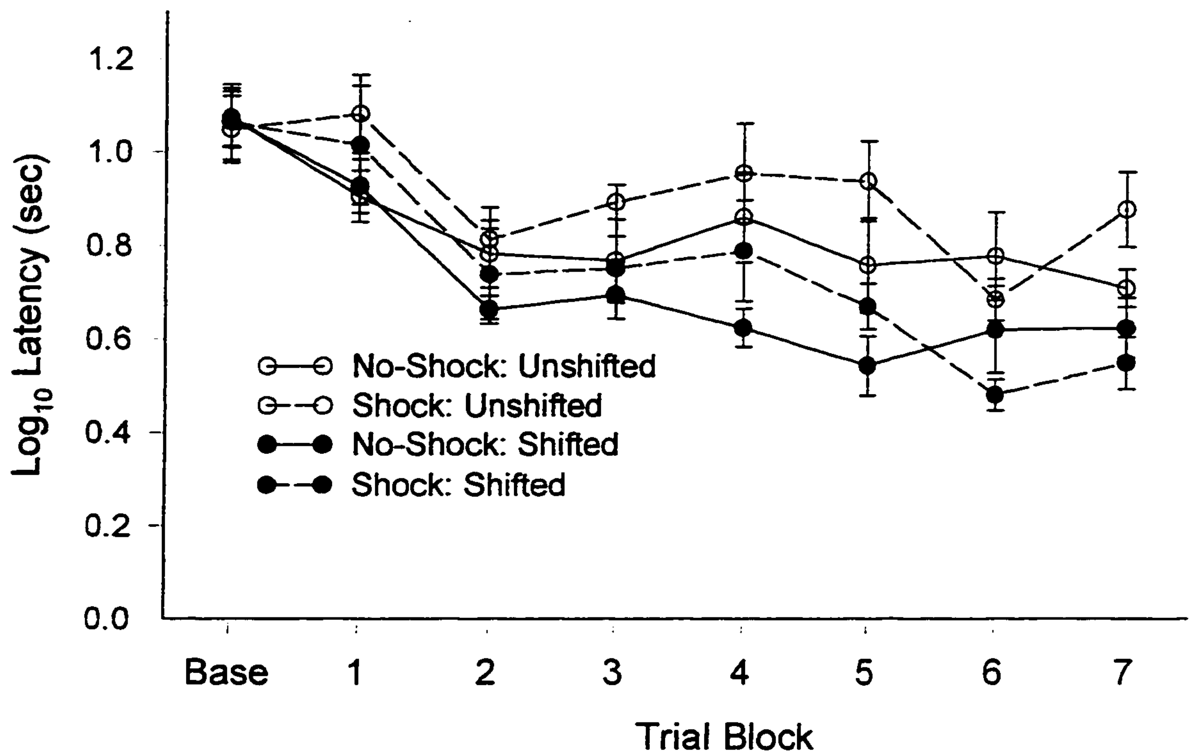


**Figure 12**. Mean runway latencies ($\log_{10}$ transformed) (± s.e.m) in animals trained with a small level of reinforcement and tested with the same (Unshifted) or increased reinforcement magnitude (Shifted). Animals were exposed to either Shock or No-Shock immediately before the first post-shift runway trial. Each trial block consists of 6 runway trials.

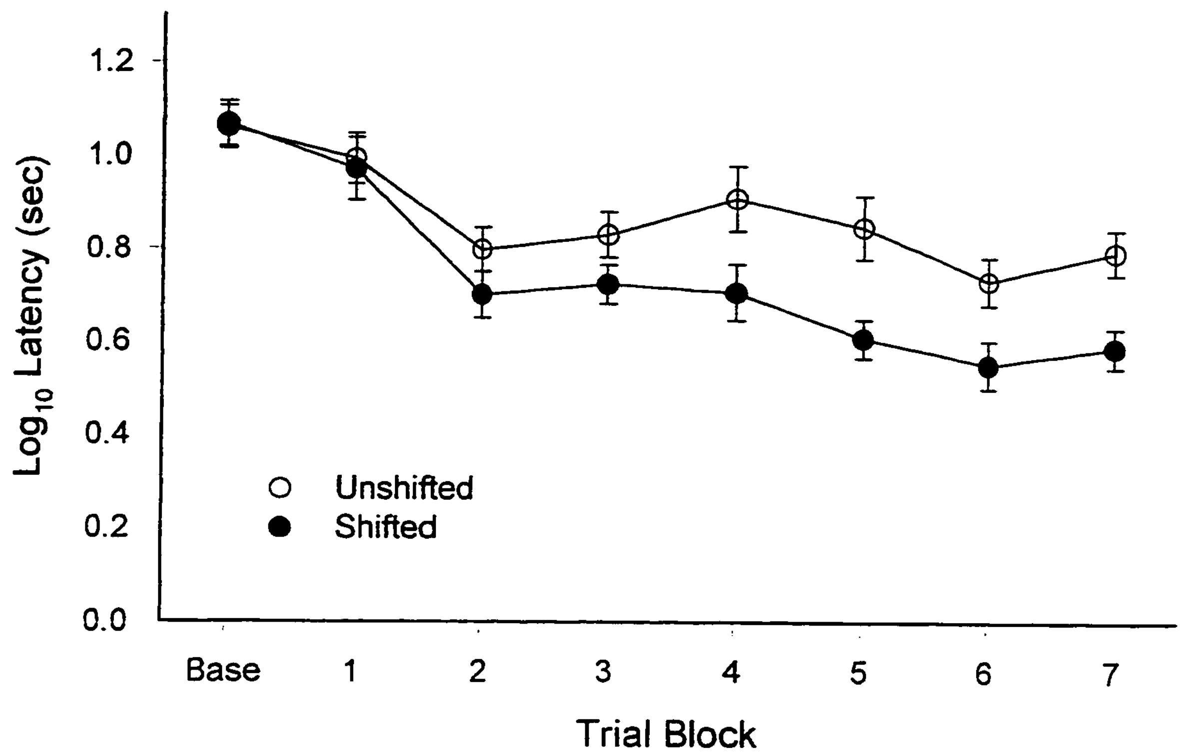


**Figure 13**. Mean runway latencies ($log_{10}$ transformed) (± s.e.m) in animals trained with a small level of reinforcement (1 pellet) and tested with the same (Unshifted) or increased reinforcement (Shifted). Base refers to latencies averaged over the last 6 days of runway training.

A separate repeated measures ANOVA was conducted on photocell counts in the open-field. ANOVA revealed a significant main effect of Blocks ($F_{5,24}$=52.25, $p$<.001) but no other main effects or interactions were significant ($F$s <2.5, $p$s >.14). As seen in Figure 14, the blocks effects indicated that novelty-induced locomotion significantly decreased over the course of the 30 min open-field test.

**Discussion**

Animals trained with a low level of reward (i.e., 1 pellet) learn to run to the goal box as indicated by decreasing runway latencies over the training period. Similarly, increasing reward magnitude following training reduced runway latencies indicating that animals do respond to the increase in reward magnitude.

Consistent with the results of Experiment 2a, exposure to footshock did not influence runway latencies among animals where reward magnitude was unchanged. Taken together with Experiment 2a, these results indicate that footshock alters the response to the low level of reinforcement only when animals had previous experience with a higher level of reinforcement. These results indicate that footshock does not alter the response to food reinforcement regardless of the absolute level of reinforcer magnitude. Thus, the footshock-induced enhancement in the response to reward reduction found in Experiment 2a cannot be attributed to shock effects on low-level reinforcers.

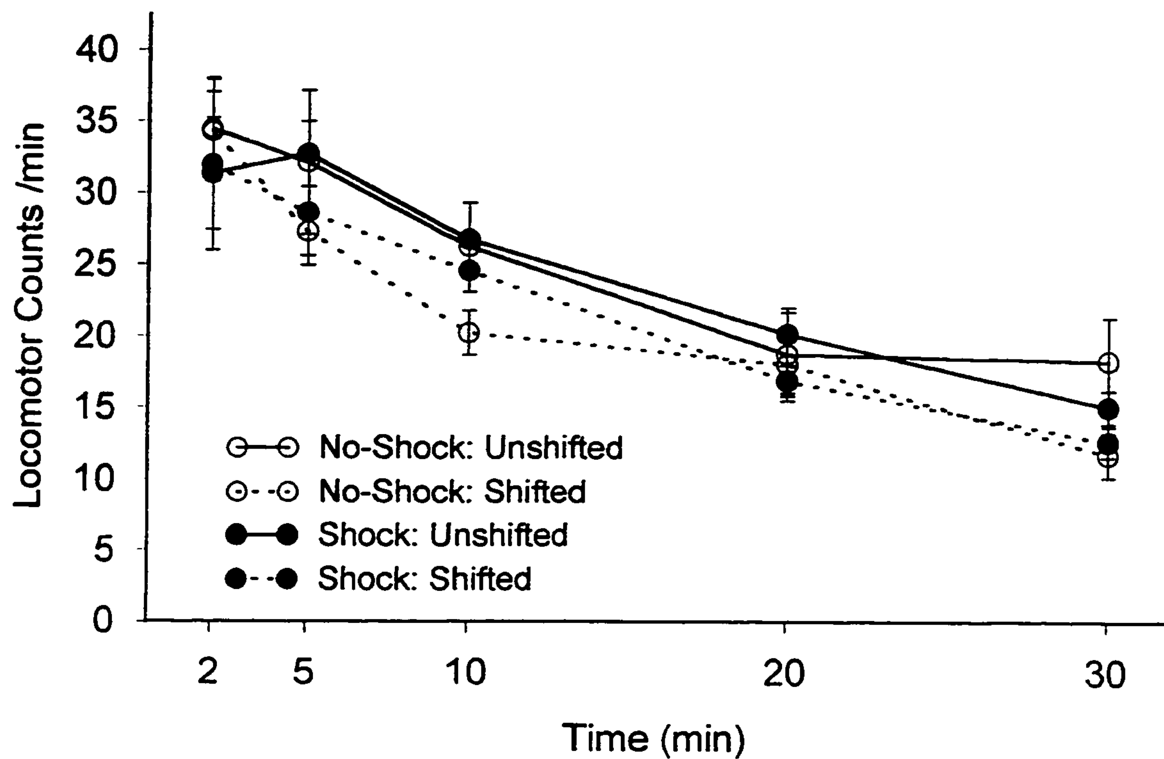


**Figure 14**. Mean locomotor counts/min (± s.e.m) in a novel open-field among animals exposed to either Shock or No-Shock 28 days earlier. Animals had been tested in the runway under unchanged (Unshifted) or increased (Shifted) reinforcement conditions.

Unlike the effects of footshock on the response to a decrease in reinforcer magnitude, footshock exerted no effects on the response to an increase in reinforcer magnitude. Thus, the enhanced response to reward reduction observed in experiment 2a cannot be attributed to a general effect of footshock on any change in reinforcer magnitude. Footshock appears to selectively enhance the response to a reduction in reinforcer magnitude without altering the response to either unchanged reinforcer magnitude or increased reinforcer magnitude.

In the current study, footshock did not influence novelty-induced locomotion. This result contrasts with that observed in Experiments 1c and 2a. Since training and testing conditions in the current study were almost identical to those of Experiment 2a, it seems unlikely that this discrepancy can be explained by procedural differences. The primary difference between the current study and Experiment 2a is the direction of the reward shift. There is, however, some indication that the handling involved in runway training and testing may have attenuated the effects of shock on novelty-induced locomotion. For instance, the combination of reward reduction and exposure to footshock appears to have produced the largest reduction in novelty-induced locomotion in Experiment 2a. This suggests that the handling involved in runway training and testing may attenuate the effects of footshock on novelty-induced locomotion and that exposure to aversive reward reduction may counteract this handling effect. The lack of impact of footshock on novelty-induced locomotion in the current study may reflect that, as in Experiment 2a, handling attenuates the impact of

footshock on novelty-induced locomotion. Unlike Experiment 2a, however, increasing reward magnitude is not aversive and therefore the reward shift in the current experiment  would not counteract the handling effect. This may contribute to the lack of effect of footshock on novelty-induced locomotion in the current study as well as the shock effect in Experiment 2a.

## EXPERIMENT 3A

As discussed earlier, exposure to a number of stressors can increase the self-administration of reinforcing drugs such as ETOH, heroin, fentanyl, morphine, amphetamine and cocaine (Beck & O'Brien, 1980; Deminiere et al.1992; Goeders & Guerin, 1994; Nash & Maickel, 1985; Shaham, Alvares, Nespor & Grunberg, 1992; Shaham, Klein, Alvares & Grunberg, 1993; Shaham & Stewart, 1994; Volpicelli, Ulm & Hopson, 1990). Since the self-administration of these drugs is thought to be mediated by their inherent reinforcing properties (Wise & Bozarth, 1987; Wise & Rompre, 1989), the drug self-administration tasks are especially useful to assess the impact of stressors on responses to appetitive stimuli. The current study employed drug self-administration to evaluate the impact of a commonly used stressor (repeated restraint) on the acquisition and maintenance of appetitive responding for cocaine reinforcement.

Existing data indicates that stressors increase cocaine self-administration (Goeders & Guerin, 1994; Ramsey & van Ree, 1993) and enhance behavioral and biochemical responses to cocaine (Ishizuka, Rockhold, Hoskins & Ho, 1990; Kalivas & Duffy, 1989; Prasad, Sorg, Ulibarri & Kalivas, 1995; Pudiak & Bozarth, 1994; Sorg & Kalivas, 1991). Since stressors enhance the response to cocaine, the current study employed a low dose of cocaine (0.125 mg/kg/infusion) because it maximizes the likelihood of detecting stressor induced increases in responsiveness to self-administered cocaine. Moreover, the two existing studies that have assessed the effects of stressors on cocaine self-administration also employed this dose of cocaine

(Goeders & Guerin, 1994; Ramsey & van Ree, 1993) thereby permitting comparison of the current study with these previous studies.

Unlike Experiments 1 and 2, repeated restraint stress was used instead of footshock. Restraint was selected for a number of reasons. First, restraint stress, like other stressors, increases dopaminergic function (Carlson, Fitzgerald, Keller & Glick, 1991; Herman, Guillonneau, Dantzer, Scatton & Semerdjian-Rouquier, 1982; Imperato, Angelucci, Casolini, Zocchi & Puglisi-Allegra, 1992; Kalivas & Duffy, 1989; Puglisi-Allegra, Imperato, Angelucci & Cabib, 1991; Puglisi-Allegra, Kempf, Schleef & Cabib, 1991; Seegal, 1981) and cocaine self-administration is thought to be subserved by dopaminergic systems (Koob, 1992; Wise & Bozarth, 1987). Second, previous studies have shown that repeated immobilization (an extreme form of restraint) can increase the self-administration of morphine and fentanyl (Shaham, 1993; Shaham, Klein, Alvares & Grunberg, 1993). Lastly, administration regulations at the facility where this study was conducted (Texas A & M University) precluded the use of footshock.

Since most studies that have examined the relationship between exposure to stressors and drug self-administration have reported that stressors enhance the acquisition rate but not optimal response (Deminiere et al.1992; Goeders & Guerin, 1994; Haney, Maccari, LeMoal, Simon & Piazza, 1995; Piazza, Deminiere, LeMoal & Simon, 1989; Piazza, Deminiere, LeMoal & Simon, 1990), both the rate of acquisition as well as asymptotic response rates for cocaine self-administration were assessed. On the basis of existing data indicating that a number of stressors can increase drug self-

administration, we expected that exposure to repeated restraint would facilitate the acquisition of cocaine self-administration and enhance the response rate following acquisition.

**Materials and Method**

*Subjects*: Forty male Sprague-Dawley rats (Harlan, TX) weighing between 350 and 400 g at the time of surgery served as subjects. Rats were individually housed in standard plastic cages and maintained on a 12 hr ON: 12 hr OFF light-dark cycle. All animals were permitted at least one week to acclimatize to the housing facilities prior to surgery. Purina Rat Chow and water were freely available in home cages throughout the study.

*Apparatus*: Restraint was applied by wrapping animals in soft towels and securing them with electrical tape. Both the head and tail of the rat were left exposed. Self-administration testing was conducted in 16 operant boxes (Med Associates, model ENV-001) equipped with two levers. Depression of one of the levers (the active lever) resulted in a 0.1 ml infusion of cocaine HCl (.125 mg/kg/infusion) over a 12 sec period. A light located over the active lever was also illuminated during the 12 sec drug infusion. Responding on the other lever (inactive lever) was recorded but had no other consequences. Drug delivery and recording of responses were controlled by OPN software (Spencer & Emmett-Ogelsby, 1985) running on two microcomputers.

*Procedure:* Following acclimatization, all animals were implanted with intrajugular catheters. Surgery was performed under anesthesia induced by separate

injections of pentobarbitol (20 mg/kg i.p.) and ketamine (60 mg/kg i.p.). A silastic catheter was attached to the right external jugular vein and passed subcutaneously to an incision on the top of the skull. The free end of the catheter was attached to a 22 gauge stainless steel tube which was then anchored to the skull with dental acrylic and secured with four screws. Animals were permitted 4 to 7 days to recover from surgery. Following surgery, catheter patency was maintained by injecting a 0.1 ml solution containing heparin (1.25 units/ml), penicillin G sodium (25,000 units/ml) and streptokinase (1900 units/ml) through the catheter each day.

Following recovery from surgery, animals were matched on the basis of body weight and assigned to one of two stressor treatments: Restraint or No-restraint. Rats assigned to the Restraint group were removed from their home cages, transported to a separate room, and tightly wrapped in a soft towel for 30 min. Non-restrained animals were taken out of their home cages, briefly handled, and immediately returned to their home cages. The restraint treatment was repeated daily for the next four days for a total of five days. Self-administration testing began seven days after the last restraint exposure. Immediately prior to each daily self-administration test, catheter patency was verified by drawn blood through the catheter and injecting 0.1 ml of the heparin solution into the catheter. Each animal was then placed in the operant chamber and given a priming injection of cocaine (.125 mg/kg/infusion) at the start of daily 2 hr test sessions. Subsequent infusions were delivered on a fixed-ratio 1 (FR-1) schedule following depression of the active lever. Immediately following self-administration tests, catheters were again flushed with 0.1 ml of the heparin solution.

Self-administration testing continued daily for the next 20 days. Catheters were checked after 10 and 20 days by injecting pentobarbitol (20 mg/kg) through the catheter and checking for loss of the righting reflex.

*Data Analysis*: Only animals that had functioning catheters for the entire 20 day test period were included in data analysis. Sample sizes were 11 for Non-restrained rats and 15 for Restrained rats. Separate repeated measures ANOVAs were conducted on responses on the active and the inactive lever. In addition, because the number of levels of the repeated measures factor (i.e., test days=20) exceeded the number of subjects in the Non-restrained treatment group (i.e., n=11), a further repeated measures ANOVA was conducted on active lever responses that were blocked over 2 days of self-administration testing, yielding 10 blocks of 2 days per block.

**Results**

Response rates on both the active and inactive levers for both groups is shown in Figure 15. Restraint treatment had no significant impact on responding for cocaine injections (active lever) and both treatment groups learned to self-administer cocaine over days of testing. ANOVA confirmed that active lever responding increased over days ($F_{9,16} = 7.65$, $p < .001$) and that restraint treatment had no impact on active lever responding ($F_{1,24} = .04$, $p = .84$).

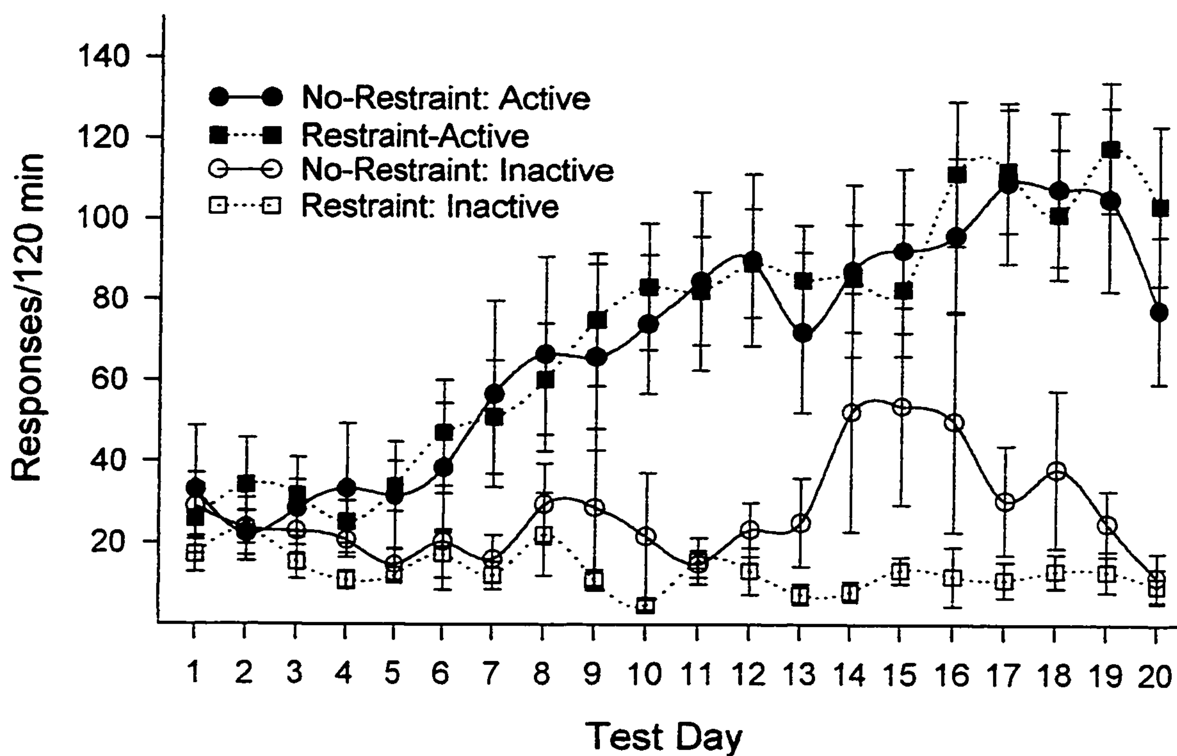


**Figure 15.** Mean (± s.e.m) response rates on the Active and Inactive levers over 20 days of testing in animals exposed to five days of either Restraint or No-Restraint. Responses on the Active lever resulted in injections of cocaine (0.125 mg/kg/infusions) while responses on the Inactive lever did not produce cocaine injections.

Figure 15 also shows response rates on the inactive lever. As expected, inactive lever responding was reasonably constant throughout the 20 day test period. ANOVA confirmed that inactive lever responding did not vary over test Days ($F_{9,16}$ = 1.42 $p$ = .256). There was some indication that inactive lever responding increased in the non-restrained control animals after day 14. Inspection of the response patterns for these animals indicated that this was due to an increase in inactive lever responding in one animal on days 14 to 16. This increase in inactive lever responding was associated with a transient increase in cocaine self-administration on the same days. Moreover, ANOVA on inactive lever responses revealed that the Restraint by Days interaction was not statistically significant ($F_{9,16}$ = 1.29, $p$ = .315).

**Discussion**

Contrary to our expectations, repeated restraint exerted no impact on either the acquisition or the maximal response rates for a low dose of cocaine. The lack of impact of restraint is somewhat surprising since there were a number of reason to expect that restraint would enhance cocaine self-administration. For instance, other stressors such as footshock (Goeders & Guerin, 1994) and emotional stress (Ramsey & van Ree, 1993) appear to increase the acquisition of cocaine self-administration. In addition, a variety of stressors including tail-pinch, restraint, exposure to novelty and social competition have been reported to increase amphetamine self-administration (Deminiere et al.1992; Deroche, Piazza, LeMoal & Simon, 1993; Haney, Maccari,

LeMoal, Simon & Piazza, 1995; Piazza, Deminiere, LeMoal & Simon, 1990). Since cocaine and amphetamine self-administration appear to be mediated by dopaminergic mechanisms (Robinson & Berridge, 1993; Wise & Bozarth, 1987; Wise & Rompre, 1989), it was expected that stressors would exert comparable effects on cocaine and amphetamine self-administration. Moreover, cross-sensitization has been demonstrated between a number of stressors including restraint and both amphetamine- and cocaine-stimulated locomotion (Badiani, Browman & Robinson, 1995; Badiani, Cabib & Puglisi-Allegra, 1992; Deroche et al.1992; Leyton & Stewart, 1990; MacLennan & Maier, 1983). Because cross-sensitization between stressors and both amphetamine and cocaine appear to occur under similar circumstances, one would expect that stressors would also produce comparable effects on the self-administration of cocaine and amphetamine. The results of the current study suggest that this may not be the case.

Only two previous studies have assessed the effects of stressors on self-administration responding for cocaine (Goeders & Guerin, 1994; Ramsey & van Ree, 1993). Using the same dose of cocaine as the current study (0.125 mg/kg/infusion), one study found that footshock enhanced cocaine self-administration (Goeders & Guerin, 1994) while the other reported that footshock did not alter cocaine self-administration (Ramsey & van Ree, 1993). Because these two studies and the current study employed the same dose of cocaine, discrepancies in the effects of stressors cannot be attributed to drug dose. It should be noted that Ramsey & van Ree (1993) reported that psychological stress enhanced the acquisition of cocaine self-administration for 0.125 mg/kg/infusion; however, as pointed out earlier, their data do

not appear to justify this conclusion. Accordingly, the Goeders & Guerin study (1994) appears to be the only report of stressor-induced increases in cocaine self-administration.

Differences in stressor parameters may account for the discrepant results. Goeders & Guerin (1994) exposed rats to 50 shocks/day during 9 days in a Geller-Seifter task (i.e., shock was contingent on food-reinforcer responding) prior to starting self-administration testing as well as during each of 3-5 days of self-administration testing at each of 5 cocaine doses. They reported that while response-contingent shock exerted no impact on cocaine self-administration, response-independent shock increased cocaine self-administration of the 0.125 mg/kg/infusion dose (Goeders & Guerin, 1994). Since this was the second cocaine dose tested, the increase in cocaine self-administration occurred after a minimum of 12 days of shock. In contrast, Ramsey & van Ree (1993) reported that cocaine self-administration was not affected in rats exposed to 10 footshocks immediately prior to each of 5 daily self-administration sessions. The inconsistent results between these studies are difficult to reconcile because both the timing of the exposure to shock as well as the number of shock session differ between these studies. However, it appears that exposure to a number of other stressors prior to self-administration testing enhances the acquisition of both cocaine and amphetamine self-administration (Deminiere et al.1992; Deroche, Piazza, LeMoal & Simon, 1993; Haney, Maccari, LeMoal, Simon & Piazza, 1995; Piazza, Deminiere, LeMoal & Simon, 1990). These results suggest that it is the timing of stressor exposure that may be the critical factor. This would account for the increased

cocaine self-administration reported by Goeders & Guerin (1994) but the lack of increase reported by Ramsey & van Ree (1993).

Because others have found that exposure to stressors administered prior to self-administration testing increased drug self-administration (Deminiere et al.1992; Deroche, Piazza, LeMoal & Simon, 1993; Haney, Maccari, LeMoal, Simon & Piazza, 1995; Piazza, Deminiere, LeMoal & Simon, 1990; Rouge-Pont, Piazza, Kharouby, LeMoal & Simon, 1993), we had expected that exposure to restraint prior to self-administration testing would also increase cocaine self-administration. Restraint, however, did not alter cocaine self-administration. While it is possible that the restraint treatment used was not effective in altering the acquisition of cocaine self-administration, this seems unlikely given that other stressors such as tailpinch (Piazza, Deminiere, LeMoal & Simon, 1990), social stress (Haney, Maccari, LeMoal, Simon & Piazza, 1995), and exposure to novelty (Rouge-Pont, Piazza, Kharouby, LeMoal & Simon, 1993) increase self-administration. It seems unlikely that the restraint procedure we employed is less stressful than these stressors.

Other studies using shock parameters almost identical to those used by Ramsey and van Ree (1993) have found that footshock increases self-administration responding for heroin and reinstates heroin responding in extinguished animals (Shaham & Stewart, 1994; Shaham & Stewart, 1995). These latter results suggest that the shock parameters employed by Ramsey & van Ree (1993) are in fact effective in influencing drug self-administration responding. Given these results, it is difficult to understand

how the same stressor regimen is effective in increasing the reinforcing efficacy of heroin but not that of cocaine.

Lastly, previous studies that have assessed the impact of footshock on cocaine self-administration employed animals that were food-deprived (Goeders & Guerin, 1994; Ramsey & van Ree, 1993), a treatment known to alter the self-administration of stimulants like cocaine (Glick, Hinds & Carlson, 1987; Papasava & Singer, 1985), amphetamine (Glick, Hinds & Carlson, 1987) and phenteramine (Papasava, Singer & Papasava, 1985) as well as opiates (Carroll, France & Meisch, 1979; Carroll, Pederson & Harrison, 1986). Thus, at the least, the shock-induced increase in cocaine self-administration reported by Goeders & Guerin (1994) must be viewed as the effects of the interaction of food deprivation and footshock on cocaine self-administration. Indeed, it has been shown that food deprivation reduces the threshold dose of cocaine required to support self-administration (Papasava & Singer, 1985). The fact that Goeders & Guerin detected shock-induced increases in cocaine self-administration only at the lowest dose tested (non-shocked animals did not self-administer this dose of cocaine in their study) is consistent with a stressor-induced enhancement in the effects of food deprivation, and the shock-induced increase in cocaine self-administration may be secondary to this effect.

## EXPERIMENT 3B

Experiment 3a suggested that 5 days of restraint prior to self-administration testing exerted no impact on the acquisition or maintenance of cocaine self-administration. Previous studies have shown that restraint increases the self-administration of fentanyl, and morphine (Shaham, 1993; Shaham, Alvares, Nespor & Grunberg, 1992; Shaham, Klein, Alvares & Grunberg, 1993). It is possible that the specific restraint parameters chosen were not effective in altering responsiveness to cocaine. The current study attempted to assess this possibility by evaluating the locomotor stimulating effects of cocaine in rats exposed to the same restraint stress regimen. If this restraint regimen is effective in potentiating the locomotor response to cocaine, then it would be unlikely that cocaine self-administration was unaffected by restraint because the restraint regimen itself was an ineffective stressor.

### Materials and Method

*Subjects*: Seventy-five male Sprague-Dawley rats weighing 278-362 g on the first day of restraint treatment served as subjects. All animal were individually housed in standard hanging wire cages and maintained on a 12 hr ON: 12 hr OFF light-dark cycle. Purina Rat Chow and water were always freely available in home cages.

*Apparatus*: Restraint was applied exactly as in Experiment 3a. The open-field was identical to the one used in Experiment 1c.

*Procedures*: Following 14 days acclimatization to the colony room, animals were matched on the basis of body weight and assigned to either Restraint treatment or No-

restraint treatment. Animals assigned to Restraint treatment were transported to a separate room where they were restrained as in Experiment 3a for 30 min. Non-restrained animals were simply removed from their home cages, briefly handled and then returned to their home cages. Restraint treatment was repeated on each of the next four days. Seven days after the last restraint session, animals within each Restraint treatment group were randomly assigned to one of four Drug treatments: 0, 5, 10 or 20 mg/kg cocaine HCl. Animals were individually transported from the housing facilities to the open-field test room, injected i.p. with the appropriate drug dose and placed in the novel open-field for a 30 min test. Locomotor counts were recorded at 2, 5, 10, 20 and 30 min.

*Data Analysis:* Locomotor counts were standardized as locomotor counts/min as in Experiment 1c. These standardized counts were then analyzed with a repeated measures ANOVA with follow-up simple effects and specific contrasts. The influence of restraint on weight gain was analyzed with repeated measures ANOVA on body weight before and after restraint.

**Results**

Repeated measures ANOVA on body weight revealed that body weight increased over the duration of the restraint phase ($F_{2,72} = 1365.33$, $p < .001$). There was no main effect of Restraint ($F_{1,73} < 1.0$, $p > .90$) nor did restraint influence the pattern of weight gains over the restraint period ($F_{2,72} = .604$, $p = .549$).

ANOVA on photocell counts revealed a significant main effect of Drug ($F_{3,67}$= 7.46, $p < .001$), a trend for a main effect of Restraint ($F_{1,67}$ = 3.24, $p = .076$) but no Drug by Restraint interaction ($F_{3,67}$= 1.52, $p = .218$). As shown in Figure 16, locomotor counts decrease over the 30 min open-field test. This was confirmed by a significant main effect of Time ($F_{4,64}$ = 41.48, $p < .001$). Neither the Restraint by Time nor the Drug by Time interactions were significant ($F_{12,170}$ = 1.02, $p = .432$ and $F_{4,64}$ = .29, $p = .883$, respectively). The Restraint by Drug by Time interaction approached statistical significance ($F_{12,170}$ = 1.65, $p = .081$). In light of this trend and because we had specifically expected that restraint would enhance the response to cocaine, specific contrast-interaction tests were computed to compare the impact of cocaine among non-restrained and restrained animals.

As seen in Figure 17, the highest does of cocaine (20 mg/kg) increased locomotion in both non-restrained (Figure 17A) and restrained animals (Figure 17B). While this dose of cocaine increased locomotion at each time block in non-restrained animals ($F$s > 9.59, $p$s < .003), this dose increased locomotion in restrained animals only at the 10, 20 and 30 min time blocks ($F$s > 4.40, $p$s < .04). Similarly, the 10 mg/kg dose significantly increased locomotion at 5, 10, 20 and 30 min time blocks in restrained animals ($F$s > 5.1, $p$s < .03) but only at the 5 min time block in non-restrained animals ($F_{1,67}$ = 6.03, $p = .017$). The 5 mg/kg dose of cocaine increased locomotion only in the non-restrained animals and only at the first time block ($F_{1,67}$ = 7.55, $p = .008$).

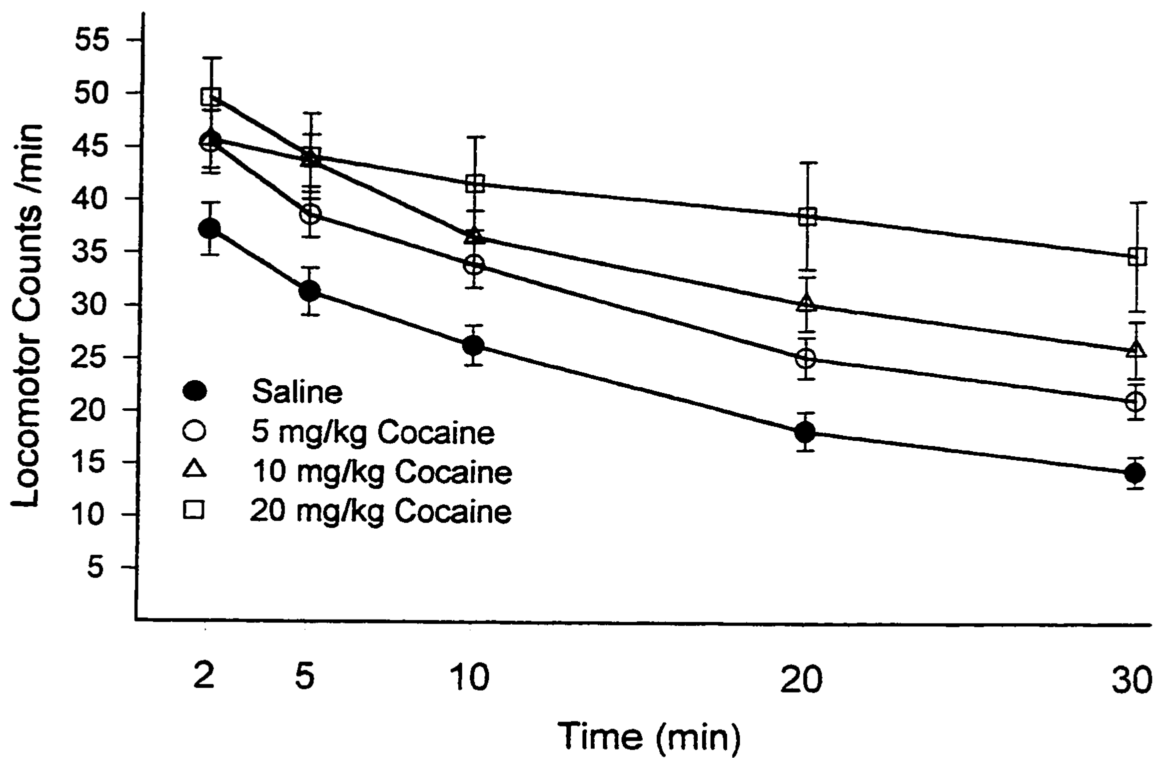


**Figure 16**. Mean locomotor counts/min (± s.e.m) in a novel open-field among animals injected with saline, 5, 10, or 20 mg/kg cocaine. Drugs were injected immediately before the 30 min open-field test.

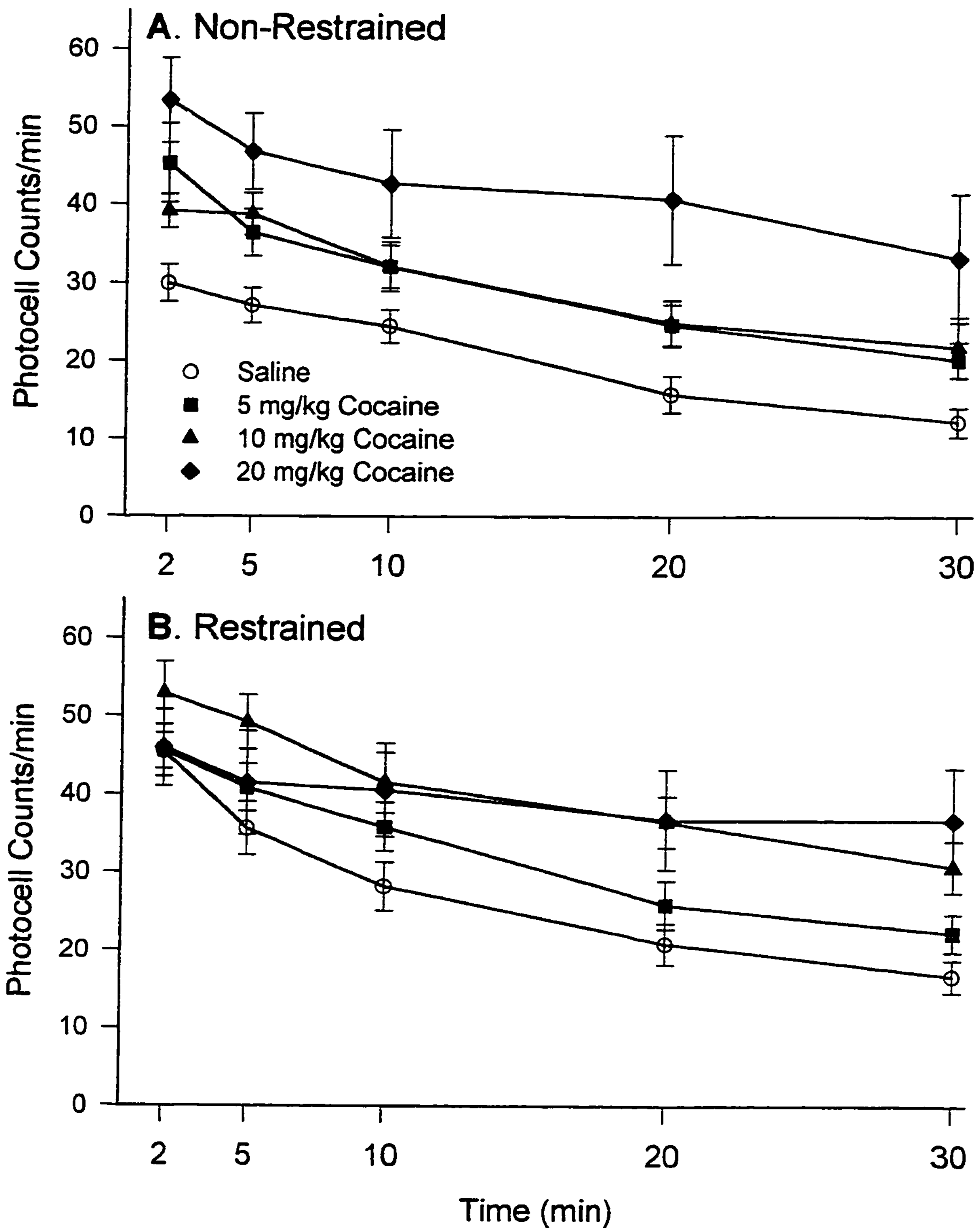


**Figure 17.** Mean locomotor counts/min (± s.e.m) in a novel open-field among animals injected with saline, 5, 10, or 20 mg/kg cocaine. Animals had been previously exposed to five days of either Restraint (B) or No-Restraint (A) seven days before the 30 min open-field test.

The results appear to indicate that restraint attenuates the locomotor stimulating effects of the 5 and 20 mg/kg dose of cocaine in the initial 2 min block. However, this is most likely an artifact of the increase in locomotion produced by restraint in this time block ($F_{1,67} = 7.64$, $p = .007$). Thus, the lack of effectiveness of cocaine in increasing locomotion in restrained animals in the early part of the test reflects the fact that locomotor scores are increased by restraint and this increase either masks the effects of cocaine or indicates a ceiling effect.

**Discussion**

The results from this study indicate that five days of restraint produces a modest change in novelty-induced locomotion. Restraint increases locomotion only in the initial 2 min block of the open-field test. In both non-restrained and restrained animals, the highest dose employed (20 mg/kg) significantly increased locomotor scores. This result is consistent with previously reported results (Boyle, Gill, Smith & Amit, 1991; Maisonneuve & Glick, 1992; Witkin & Goldberg, 1990). The low dose of cocaine produced a small non-significant increase in locomotion regardless of restraint treatment. Others have also reported that this dose of cocaine does not substantially alter locomotion (Boyle, Gill, Smith & Amit, 1991).

Restraint does appear to alter the locomotor response to the intermediate dose of cocaine. For instance, the 10 mg/k dose increased locomotion among restrained animals but not among non-restrained animals. In contrast, in restrained animals, the intermediate dose produces effects comparable to the high dose of cocaine (see Figure

17B). Thus, the intermediate dose appears to function like the low dose for unrestrained animals but like the high dose for restrained animals. As such, these results suggest that the restraint procedures used are effective in altering responsiveness to cocaine.

## EXPERIMENT 3C

Experiments 3a and 3b assessed the impact of restraint on the response to cocaine using both drug self-administration and novelty-induced locomotion. Unlike the earlier studies (Experiments 1 and 2), these studies employed Sprague-Dawley rats rather than Long-Evans rats. A close look at the open-field data from Experiments 1, 2 and 3 suggest that the pattern of novelty-induced locomotion over the course of the 30 min test appears to vary between Long-Evans and Sprague Dawley rats. For instance, the rate of decrease in locomotion (which provides an index of habituation rate) seems to be greater for Long-Evans rats than Sprague-Dawley rats. Others have also found that these commonly used strains of rats exhibit differences in reactivity to sensory stimuli (Glowa & Hansen, 1994). For instance, Long-Evans rats exhibit a larger acoustic startle response than Sprague-Dawley rats and a faster rate of habituation to startle stimuli (Glowa & Hansen, 1994). These results suggest that Long-Evans rats may be more susceptible to aversive stimuli than are Sprague-Dawley rats. As such, the ineffectiveness of restraint stress already reported may be related to the more stress tolerant nature of Sprague-Dawley rats.

To address this issue, we took advantage of the availability of the Sprague-Dawley rats used in Experiment 3b to assess the development and maintenance of amphetamine-induced conditioned taste aversion. If the Sprague-Dawley rats are more stress-tolerant than Long-Evans rats then they should exhibit less taste neophobia and a reduced conditioned avoidance of saccharin relative to Long-Evans rats.

**Materials and Method**

*Subjects*: Subjects consisted of the same subjects that were employed in Experiment 3b. Housing conditions were as described in Experiment 3b.

*Apparatus*: All fluid consumption testing was conducted exactly as described in Experiment 1a. Similarly, saccharin concentration (0.1%) and amphetamine doses (2.0 mg/kg) were identical to those used in Experiment 1a.

*Procedures*: All animals were left untreated in their home cages for 17 days after the open-field test described in Experiment 3b. Twenty-four hr later all animals were placed on a restricted water schedule for 12 days as described in Experiment 1a. CTA conditioning began on the next day. CTA procedures were exactly as described for Experiment 1a..

*Data Analysis*: Both saccharin intake and water intake were analyzed with separate repeated measures ANOVAs with follow-up simple effects tests as appropriate.

**Results**

Because subjects had been previously treated with cocaine as part of Experiment 3b, a preliminary ANOVA was conducted on saccharin intake to determine the impact of cocaine on saccharin intake. This ANOVA revealed that cocaine did not exert any significant effect on saccharin intake ($F_{3,59} = .29$, $p = .829$). Similarly, interactions involving this factor failed to reach statistical significance ($F$s < 1.4, $p$s > .15).

Accordingly, this factor was dropped from subsequent analyses on saccharin and water intake.

Figure 18 shows saccharin intake before and after saccharin-amphetamine pairing. ANOVA revealed a significant main effect of Amphetamine ($F_{1.70} = 253.83$, $p < .001$), a significant Amphetamine by Days interaction ($F_{6.65} = 113.12$, $p < .001$) as well as a significant Days effect ($F_{6.65} = 73.02$, $p < .001$). Simple effects test revealed there was no significant difference between fluid intake among the saline- and amphetamine-injected animals on baseline water intake ($F_{1.70} = .13$, $p = .724$) or initial saccharin intake on PD1 ($F_{1.70} = 2.32$, $p = .705$). Saccharin intake was significantly reduced in amphetamine-injected animals for all subsequent saccharin tests ($F$s > 64, $p$s < .001). These results indicate that one saccharin-amphetamine pairing significantly suppresses saccharin intake and that following a second pairing, saccharin intake is suppressed for at least four extinction trials.

Figure 18 also shows that fluid intake is reduced on the first saccharin presentation indicating that for this strain of rat saccharin neophobia is reflected as a decrease in fluid intake relative to baseline water intake. Comparisons between baseline fluid intake and saccharin intake on PD1 indicated that fluid intake was significantly reduced for either saline- ($F_{1.70} = 128.20$, $p <001$) or amphetamine- ($F_{1.70} = 122.12$, $p < .001$) injected animals. Following this initial reduction in fluid intake,

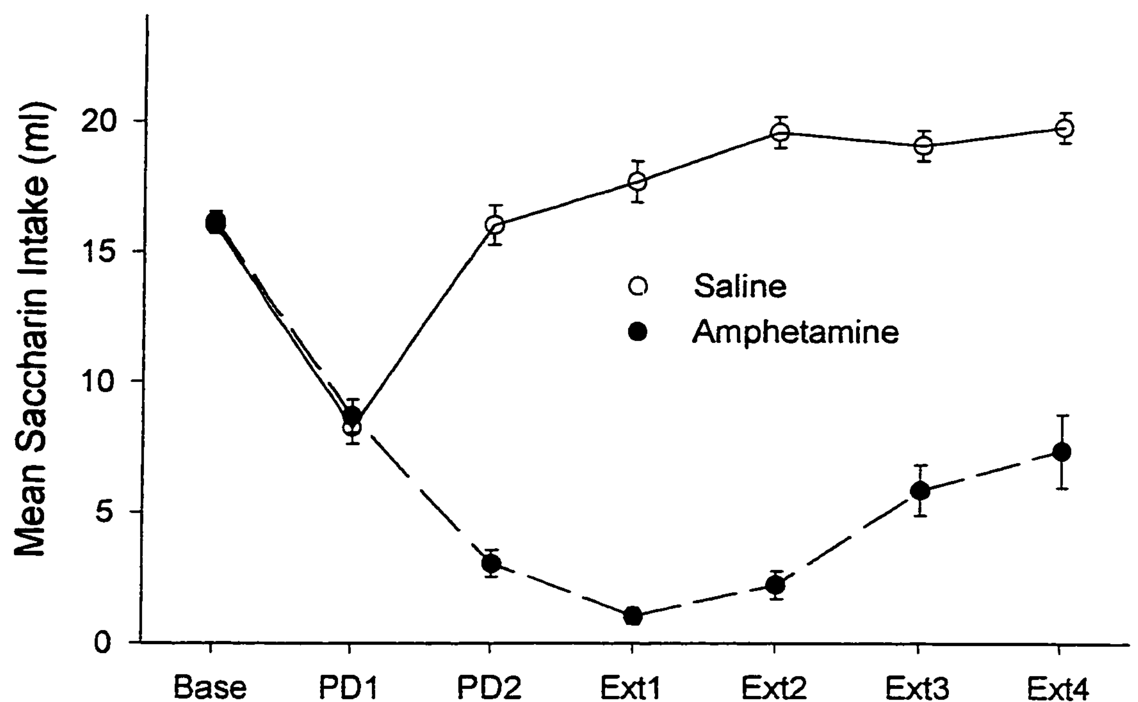


**Figure 18**. Mean (± s.e.m) water (Base) and saccharin consumption (PD1 to EXT4) in Sprague-Dawley rats injected with saline or amphetamine (2.0 mg/kg) following the first saccharin presentation (PD1). Two saccharin-amphetamine conditioning trials were conducted (PD1 and PD2) and followed by four extinction trials (Ext1 to Ext4).

saccharin intake in saline-injected rats recovered to baseline intake levels on PD2 ($F_{1,70}$ = .06, $p$ = .803) and actually exceeded baseline water intake on all subsequent saccharin test ($F$s > 11.0, $p$s < .002). In the case of amphetamine-injected animals, saccharin intake was always less than baseline water intake ($F$s > 60, $p$s < .001). Restraint was also included as a factor in the ANOVA. However, restraint did not influence saccharin intake ($F_{1,70}$ = .13, $p$ = .719) nor did it interact with any other factor ($F$s < 11.3 , $p$s > .28).

A separate ANOVA on water intake for days between saccharin presentation revealed a significant main effect of Amphetamine ($F_{1,59}$ = 40.25, $p$ < .001), Days ($F_{5,55}$ = 47.87, $p$ < .001) as well as an Amphetamine by Days interaction ($F_{5,55}$ = 27.86, $p$ < .001). Neither restraint nor previous cocaine treatment influenced water intake ($F_{1,59}$ = 2.16, $p$ = .147 and $F_{3,59}$ = .44 $p$ = .722, respectively). ANOVA revealed a significant Cocaine by Stress by Day interaction ($F_{15,152}$ = 2.28, $p$ = .006); however simple effect tests indicated that this interaction was not significant at any test day ($F$s < 3, $p$s > .08). ANOVA also revealed a significant Cocaine by Amphetamine by Day interaction ($F_{15,152}$ = 2.17, $p$ = .010). Follow-up simple effects tests indicated that the Cocaine by Amphetamine interaction was significant only on Day 17 ($F_{3,59}$= 2.77, p = .050). A close look at mean water intake on Day 17 indicated that among rats that had received the highest dose of cocaine in Experiment 3b, water intake was slightly decreased in saline-injected animals but increased in amphetamine-injected animals. Because of the transient and small nature of this result, this effect is not considered to be of substantial interest.

As shown in Figure 19. amphetamine-injected animals consumed more water that saline-injected animals on all water days following the first saccharin-amphetamine pairing (Day 13 occurs 24 hr after PD1). Simple effects analysis revealed that water intake was significantly increased in amphetamine-treated rats on Days 15, 17, 19 and 21 ($F$s > 32, $p$s < .001) and approached significance on Day 13 ($F_{1,59} = 3.54$, $p = .065$). This increase in water intake among amphetamine-treated animals most likely reflects the dehydration in these animals because of the extreme nature of the conditioned avoidance of saccharin. Indeed, frequency plots showed that more than 80% of the amphetamine-injected rats drank less that 3 ml of saccharin following the first and second amphetamine injections and that more than 50% of these animals consumed less that 3 ml of saccharin on the fourth extinction trial.

**Discussion**

Sprague-Dawley rats exhibited a significant avoidance of saccharin following a single saccharin-amphetamine pairing. Prior treatment with restraint or cocaine had no significant impact on this CTA. These animals also displayed a significant neophobia upon initial presentation of the novel saccharin solution. Again, neither restraint nor cocaine treatment exerted any impact on this neophobia.

Based on existing data indicating that Long-Evans rats are more reactive to aversive stimuli (Glowa & Hansen, 1994), we had expected that the conditioned avoidance of saccharin intake in Sprague-Dawley rats would be less than that seen in Long-Evans rats (see Experiments 1a and 1b). The results indicate, however, that

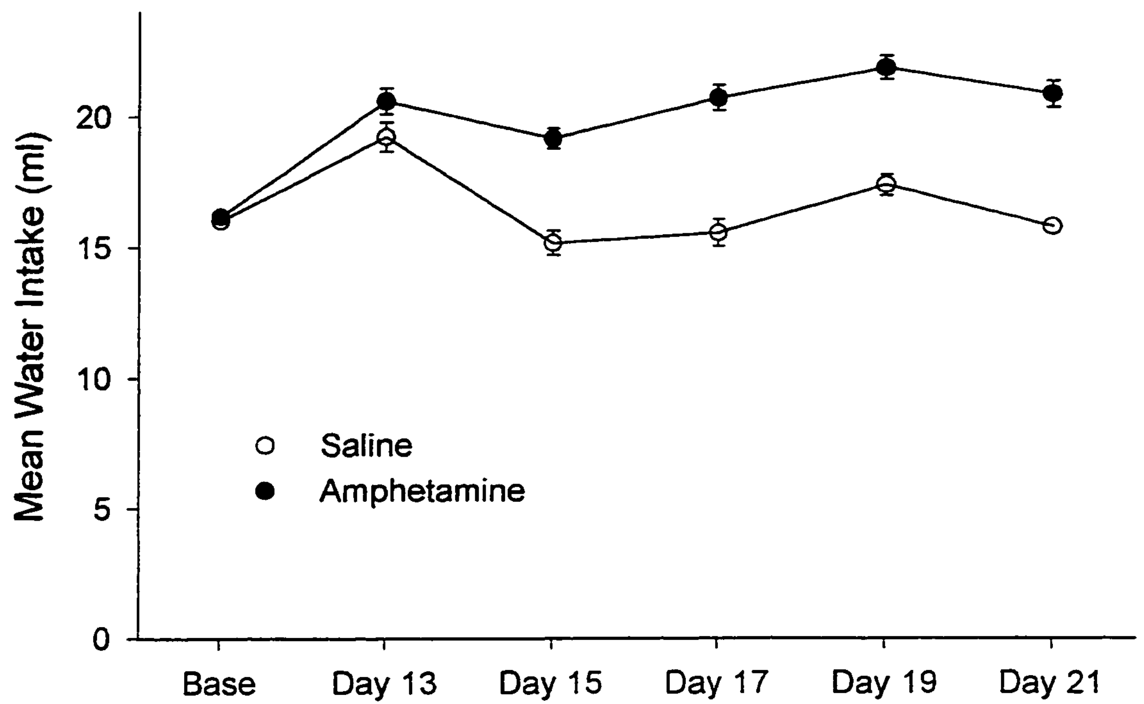


**Figure 19**. Mean (± s.e.m) water intake on days between saccharin presentations in animals injected with saline or amphetamine. Base to Day 21 refers to water intake on days preceding PD1 to Ext4, respectively.

Sprague-Dawley rats are much more sensitive to the conditioned avoidance of saccharin than are Long-Evans rats. For instance, the same dose of amphetamine produced a 50% reduction in saccharin intake among Long-Evans rats (see Figures 1 and 2) following two saccharin-amphetamine pairings while the identical treatment almost completely suppressed saccharin intake in Sprague-Dawley rats. The extreme sensitivity of Sprague-Dawley rats to amphetamine CTA is demonstrated by the fact that more than 90% of amphetamine-injected animals consumed less than 2 ml of saccharin following the second saccharin-amphetamine pairing (i.e., Ext1). We did not observed such severe reductions in saccharin intake in Long-Evans rats in Experiments 1a and 1b.

As was discussed earlier, there is evidence to indicate that novelty, including taste novelty, appears to be aversive. If, as had been suggested by others (Glowa & Hansen, 1994) Long-Evans rats are more reactive to aversive stimuli, it would be expected that Long-Evans rats would exhibit a larger neophobic response to a novel saccharin. The results of the current study indicate that this is not the case. While neophobia in Long-Evans rats is expressed primarily as reduced saccharin intake on first presentation relative to subsequent saccharin presentations (see Experiments 1a and 1b), in Sprague-Dawley rats saccharin neophobia is expressed as a substantial reduction in fluid intake between initial saccharin presentation and both baseline water intake as well as subsequent saccharin intake. It is also unlikely that the pattern of neophobia observed in Sprague-Dawley rats reflects that the concentration of saccharin used is unpalatable for this strain of rat since saline-injected animals actually increased

saccharin intake above baseline water intake following the first saccharin presentation. That the reduction in fluid intake is restricted to the first presentation of saccharin indicates that the saccharin solution was not unpalatable. Thus, it appears that Sprague-Dawley rats exhibit a larger neophobic reaction to saccharin than Long-Evans rats.

Taken together, the results of this study indicate that Sprague-Dawley rats are more sensitive to a novel saccharin solution and exhibit a larger and more persistent conditioned avoidance of saccharin. Since these measures reflect sensitivity to aversive novelty as well as the conditioned avoidance of an aversive taste solution, it appears that Sprague-Dawley rats are actually more rather than less sensitive to at least some aversive stimuli.

Lastly, it should be noted that prior restraint exerted no significant impact on fluid intake. These results are not surprising given the long delay between the last exposure to restraint and fluid consumption tests (24 days).

# EXPERIMENT 4

Experiment 3a assessed the impact of exposure to restraint on responding for cocaine reinforcement. The results indicated that repeated restraint did not alter cocaine self-administration, although, as shown in Experiment 3b, restraint did alter the locomotor response to cocaine. Experiment 4 assessed the impact of restraint on responding for a second drug reinforcer - ethanol. As has already been discussed, a large number of studies have shown that stressors can increase the intake of ethanol. Since ethanol has been shown to serve as an effective drug reinforcer (Koob, 1992; Koob & Bloom, 1988; Lewis & June, 1990; Samson & Harris, 1992), the stress-induced increase in ETOH intake may reflect a stress-induced increase in the reinforcing value of ETOH, as has been proposed for other self-administered drugs (Goeders & Guerin, 1994; Shaham, 1996; Shaham & Stewart, 1994; Shaham & Stewart, 1995).

It had also been suggested that ethanol intake may be, at least partly, mediated by the ability of ETOH to attenuate the behavioral and physiological responses to stressors (Cappell, 1972; Conger, 1951; Hodgson, Stockwell & Rankin, 1979; Kalant, 1990) rather than increasing the reinforcing value of ETOH. One indirect way to test whether stressors increase or decrease the reinforcing value of ETOH is to manipulate the availability of ETOH during exposure to stressors. For instance, if ETOH attenuates the impact of stressors, then permitting access to ETOH during the period of stressor exposure should attenuate the impact of stressors when compared with animals that are not permitted access to ETOH during the period of stressor exposure.

In contrast, if exposure to stressors increases the reinforcing value of ETOH, then the availability of ETOH during the period of restraint should exert no impact on the stress-induced increase in ETOH intake.

The current study had the following objectives. First, the consistency of the effect of repeated restraint on the self-administration of ETOH versus cocaine was evaluated. Second, the impact of the availability of ETOH during the stressor period on the effect of restraint on ETOH intake in the post-stressor period was also evaluated. In addtion, novelty-induced locomotion was tested following the completion of ETOH testing to determine the effects of restraint on novelty-induced locomotion. This also permitted the assessment of the relationship between ETOH intake and novelty-induced locomotion.

**Materials and Method**

*Subjects*: Forty-nine male Long-Evans rats (Charles River, St Constant, Quebec) weighing 229-289 g served as subjects. Animals were housed as in Experiment 1 and acclimatized to the colony room for 7 days with Purina Rat Chow and water freely available. All consumption measures were obtained during the second quarter of the light cycle.

*Apparatus*: Fluids were available to animals for 23 hr each day in two 75 ml plastic tubes with ball bearing spouts attached to the front of the cage. Ethanol was prepared fresh each day by diluting 95% ethanol with the appropriate volume of tap water. Restraint was applied in foam-padded wire mesh restrainers that fit snugly

around each rat. Non-restrained animals were placed in a separate room in chambers similar to their home cages. Fluid consumption was measured by determining the difference between the weight of the tubes at the start and end of the 23 hr period. This difference represents the volume of water consumed in the 23 hr period. In the case of ETOH, the volume of fluid consumed was determined from the weight difference by adjusting the weight of ETOH to take into account the density of ethanol relative to water (0.816) as well as the specific concentration of the ethanol solution. Body weights were recorded every second day immediately before replacing the tubes. The open-field was identical to the one used in Experiment 3b.

*Procedures*: The entire study was conducted in three phases: acquisition phase, restraint phase, and post-restraint phase. Following acclimatization to the housing facilities, each animal was provided with two drinking tubes. One tube was filled with ethanol and the second tube was filled with water. On alternate days, both tubes were filled with water. ETOH was presented in a series of ascending concentrations starting with 2% and incrementing by 2% following two presentations at each concentration until a final concentration of 8% was reached. The position of the ETOH tube was alternated on every second presentation to prevent the development of a position bias. Animals were then maintained on a schedule of alternate day presentation of a choice between water and 8% ETOH for seven presentations. Ethanol consumption after seven presentations of 8% ETOH was then calculated as grams of absolute ETOH consumed per kilogram of body weight. Subjects were matched on the basis of g/kg ETOH consumption and assigned to one of two treatments: seven days of 60 min/day

Restraint or No-restraint treatment. Each Restraint treatment group was then subdivided such that half the animals in each group continued to receive 8% ETOH on alternate days throughout the seven days of restraint (ETOH-Available) while the remaining animals were given only water throughout the restraint period (ETOH-Unavailable). Thus, animals assigned to the ETOH-Available treatment received 4 presentations of a choice between water and 8% ETOH during the restraint period. Following the restraint period all animals were returned to the alternate day schedule of a choice between 8% ETOH and water for 4 additional ETOH presentations. Water bottles were then returned to the cages and animals were permitted free access to water until the end of the study. Seven days after the last ethanol presentation animals were individually transported to the open-field room. Half the animals in each of the four treatment groups were injected i.p with 0.5 mg/kg d-amphetamine sulfate and the remaining animals were injected with saline. Immediately following injections, animals were placed in the open-field and locomotor counts were recorded at 2, 5, 10, 20 and 30 min.

*Data Analysis:* Ethanol consumption was computed as g/kg body weight. Both ethanol consumption as well as total fluid intake were analyzed with repeated measures ANOVAs. Because we specifically expected that the impact of restraint on post-stress ETOH intake would be altered by the availability of ETOH during the 7 day restraint period, simple-simple effects test for the influence of restraint on ETOH intake for both ETOH availability treatment groups were conducted. Locomotor counts were analyzed with a repeated measures ANOVA that included restraint and

amphetamine treatments. A second analysis on locomotor counts was conducted to determine the relationship between ETOH intake and novelty-induced locomotion. Experiment 3b showed that repeated restraint increases novelty-induced locomotion. If restraint increases ETOH intake, then ETOH intake should also modify the impact of restraint on novelty-induced locomotion. To assess this, two separate hierarchical regression analyses were conducted on locomotion in the first (2 min) and last (30 min) time blocks of the open-field test. For this analysis, in addition to the Restraint and Amphetamine factors, ETOH intake was also included. Predictor variables were entered in three steps. Block 1 included Restraint treatment, Drug injections, and their interaction. Block 2 included ETOH intake (g/kg) averaged over the last two days of ethanol intake. This was included rather than the baseline ETOH intake because it incorporates the effects of restraint on ETOH intake. To reduce intercorrelations and the attendant increase in instability of regression coefficients, ETOH intake was standardized using $z$ transformation. Block 3 included the ETOH intake by Restraint and ETOH intake by Drug interactions. This analytical approach was employed since it permits the evaluation of the contribution of ETOH consumption to explaining open-field locomotion beyond that already explained by both the restraint and drug treatments. The two-way interactions involving ETOH intake were entered last (Block 3) since interactions must be entered after main effects. Finally, a protected $t$ test approach was employed in the regression analysis (Cohen & Cohen, 1983).

**Results**

Figure 20 shows body weights for all treatment groups for each ethanol (8%) consumption day. As expected, all treatment groups increased body weight over days. ANOVA on body weights from the start of the restraint period until the final ETOH presentation indicated that neither Restraint ($F_{1,45} < 1.0$, $p = .970$) nor the availability of ETOH ($F_{1,45} < 1.0$, $p = .559$) influenced weight gains. As expected, there was a significant effect of Days ($F_{7,39} = 152.2$, $p < .001$) indicating that animals increased body weights over days. No interactions were significant (*F*s < 1.0, *p*s > .50).

Figure 21 illustrates the influence of restraint and availability of ETOH on post-restraint ETOH intake (g/kg). As can be seen, ETOH intake was increased on the first post-stress day but only in the restrained animals that were not permitted access to ETOH during the restraint period. A repeated measures ANOVA that included baseline ETOH intake and the 4 post-restraint ETOH test days revealed a main effect of Days ($F_{4,42} = 4.27$, $p = .005$) but no main effects of either Restraint ($F_{1,45} = 1.26$, $p = .267$) or ETOH-Availability ($F_{1,45} = .36$, $p = .554$). Similarly, the Restraint by ETOH-Availability interaction was not significant ($F_{1,45} = 1.34$, $p = .253$). There was, however, a significant Restraint by Days interaction ($F_{4,42} = 3.29$, $p = .020$). The ETOH-Availability by Restraint by Days interaction approached statistical significance ($F_{4,42} = 2.51$, $p = .056$). Simple-simple effects tests at each day indicated that among animals where ETOH was available during the restraint period, restraint did not significantly influence ETOH intake on any post-stress day (*F*s < 1.20, *p*s > .25). In contrast, in animals where ETOH was not available during the restraint period,

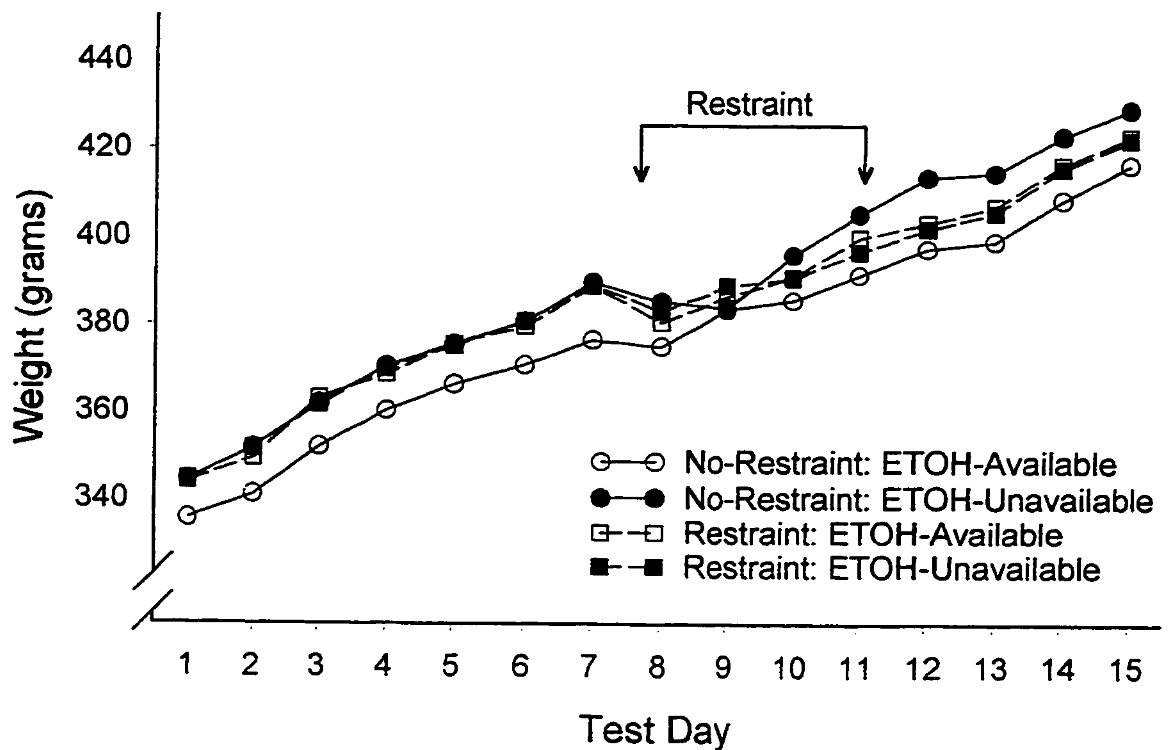


**Figure 20**. Mean body weights (± s.e.m) among animals consuming 8% ETOH prior to restraint, during the restraint period, and following the restraint period. For half the animals ETOH was not available during the 7 day restraint period (ETOH-Unavailable) while the remaining animals had access to ETOH (ETOH-Available).

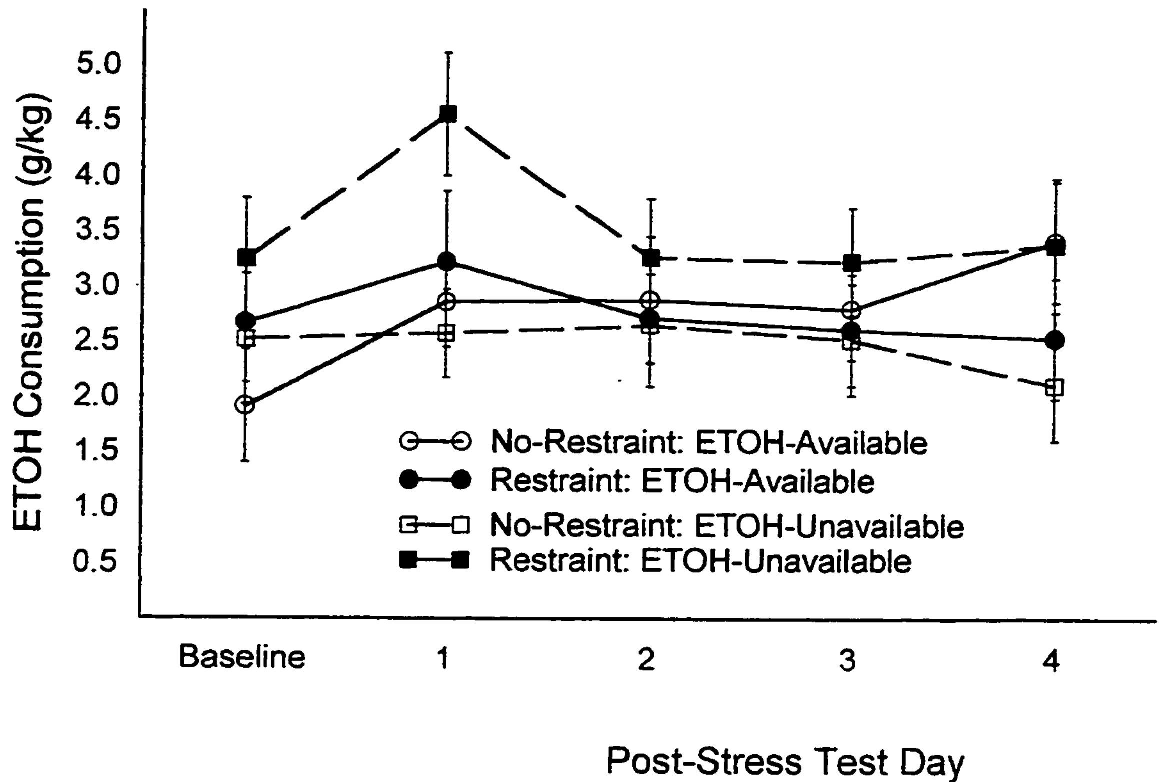


**Figure 21**. Mean (± s.e.m) ETOH intake before (Baseline) and following the restraint period (post-stress test days) among animals than had access to ETOH during the restraint period (ETOH-Available) and animals that did not have access to ETOH during the restraint period (ETOH-Unavailable).

restraint increased ETOH intake on the first post-stress day ($F_{1,45} = 7.45, p = .009$) but not on any other day (*F*s < 2.70, *p*s > .10).

It is possible that restraint did in fact increase ETOH intake among groups with ETOH available during the restraint period but the increase may have occurred during the restraint period itself. A separate ANOVA on ETOH intake among animals with ETOH available during the restraint period revealed no main effects of either Restraint ($F_{1,22} = .04, p = .834$) or Days ($F_{3,66} = 1.88, p = .141$) (see Figure 22). There was, however, a trend for a Restraint by Days interaction ($F_{3,20} = 2.64, p = .077$). Follow-up simple effects tests for the effect of restraint at each day did not reveal any significant effects (*F*s < 1.1, *p*s > .30). Thus, it appears that restraint does not influence ETOH intake during the restraint period.

Figure 23 presents total fluid consumption in the restraint and post-restraint periods. Although there was a slight increase in total fluid consumption on the last ETOH consumption test, separate ANOVAs on total fluid intake during the restraint period and after the restraint period indicated that total fluid consumption was not influenced by either Restraint or ETOH-Availability (*F*s < 2.6, *p*s > .10).

Figure 24 shows that restraint did not exert any significant impact on novelty-induced locomotion, although, as expected amphetamine increased locomotor counts. ANOVA confirmed that amphetamine increased locomotion ($F_{1,34} = 20.37, p < .001$) and indicated that the impact of amphetamine was dependent on the time block ($F_{4,31} = 4.59, p = .05$). As can be seen from Figure 24, this indicates that amphetamine

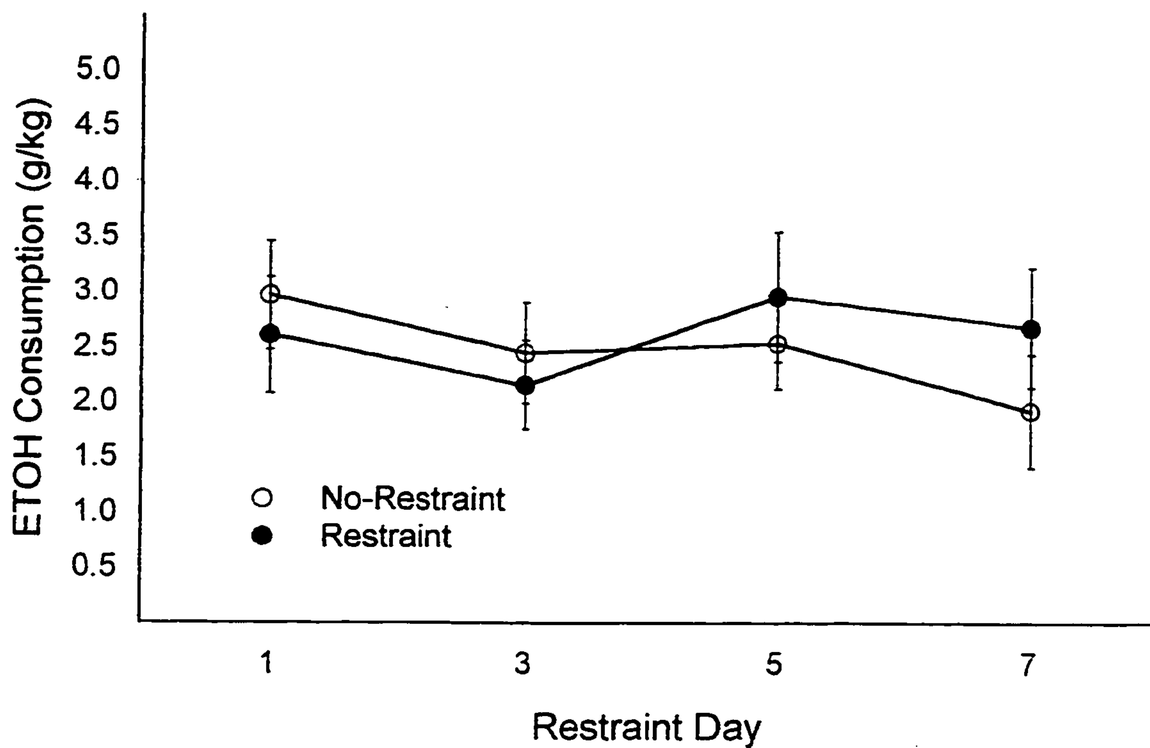


**Figure 22**. Mean (± s.e.m) ETOH intake during the seven day restraint period among animals exposed to Restraint or No-Restraint. Only data from animals that had access to ETOH during the seven day restraint period (ETOH-Available group) are shown.

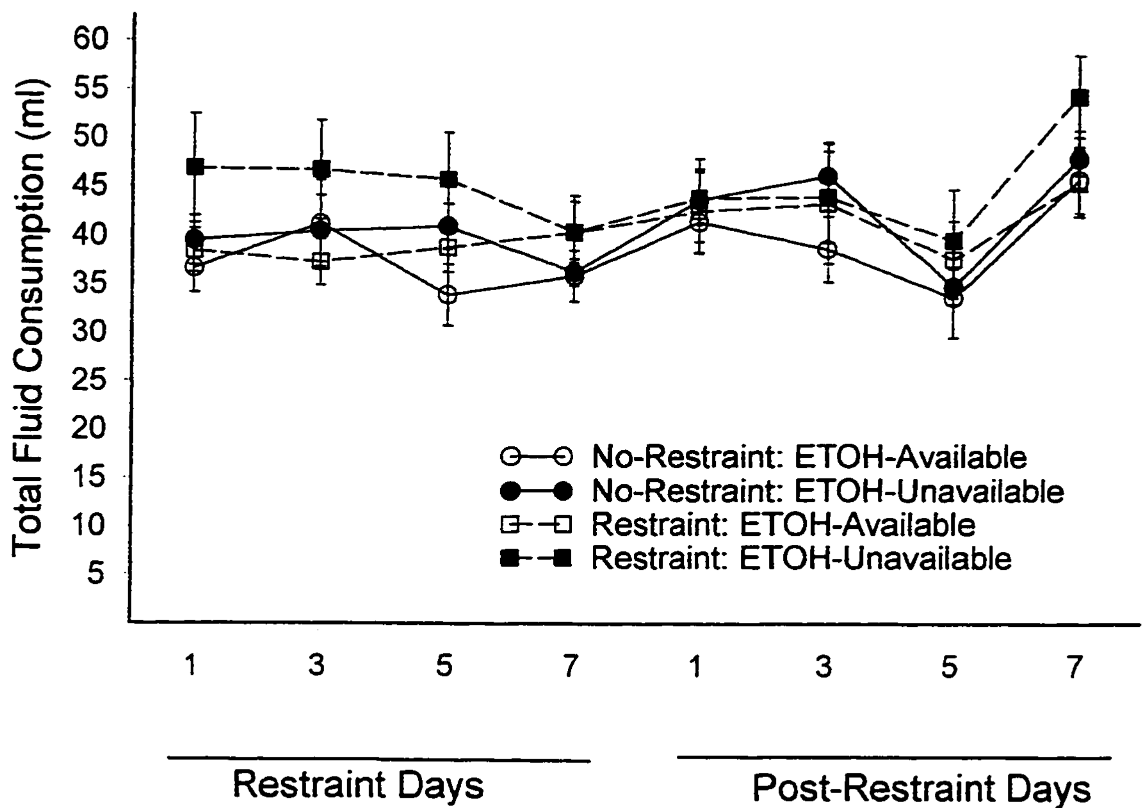


**Figure 23**. Mean (± s.e.m) total fluid intake on ETOH consumption test days in Restraint and No-Restraint animals that has access (ETOH-Available) or were deprived of ETOH (ETOH-Unavailable) during the seven days of exposure to restraint.

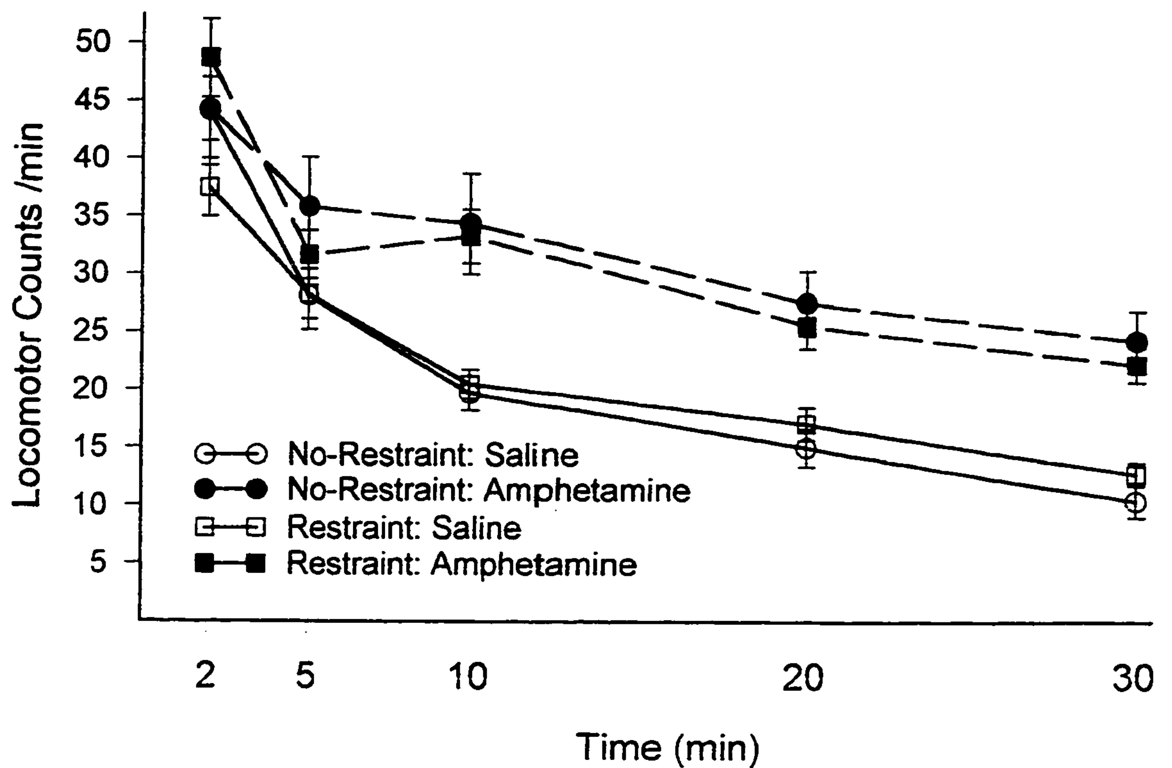


**Figure 24**. Mean (± s.e.m) locomotor counts/min in a novel open-field among Restrant and No-Restraint animals injected with either saline or amphetamine (0.5 mg/kg). The last restraint session occurred 15 days prior to the open-field test and drug injections occurred immediately before open-field testing.

exerted its' stimulating effects primarily after 5 min. Neither the main effect of Restraint ($F_{1,34} < 1.0$, $p = .736$) nor the Restraint by Time interaction reached significance ($F_{4,31} < 1.0$, $p = .901$). Lastly, the three-way interaction failed to reach statistical significance ($F_{4,31} = 1.43$, $p = .246$) indicating that the effects of amphetamine over the course of the 30 min test was not altered by Restraint.

Separate regression analyses on locomotor counts in the first 2 min and the last 10 min of the open-field test indicated that ETOH intake (from the last two ETOH presentations) was positively correlated with open-field locomotion ($t$s > 2.9, $p$s < .04). For initial locomotion (2 min) no other factors or interactions were significant. A different pattern of results emerged, however, for locomotion in the last time block of the open-field test.

Figure 25 illustrates the results of the regression analysis on locomotor counts from the 30 min time block. The overall regression equation accounted for a substantial amount of variance in locomotion (adjusted $R^2 = .570$, $F_{6,30} = 8.96$, $p < .0001$). As expected amphetamine injections increased locomotion ($F_{6,30} = 21.97$, $p = .0001$). However, restraint treatment did not influence locomotion ($F_{6,\ 30} = 3.55$, $p = .551$). As seen in Figure 25, as ETOH intake increased, locomotion also increased ($F_{6,30} = 4.88$, $p = 035$); however, the influence of ETOH intake on locomotion was significantly influenced by restraint treatment. Indeed, restraint treatment completely eliminated the positive relationship between ETOH intake and locomotion in non-restrained animals (Restraint by ETOH intake interaction ($F_{6,30} = 6.77$, $p = .0143$).

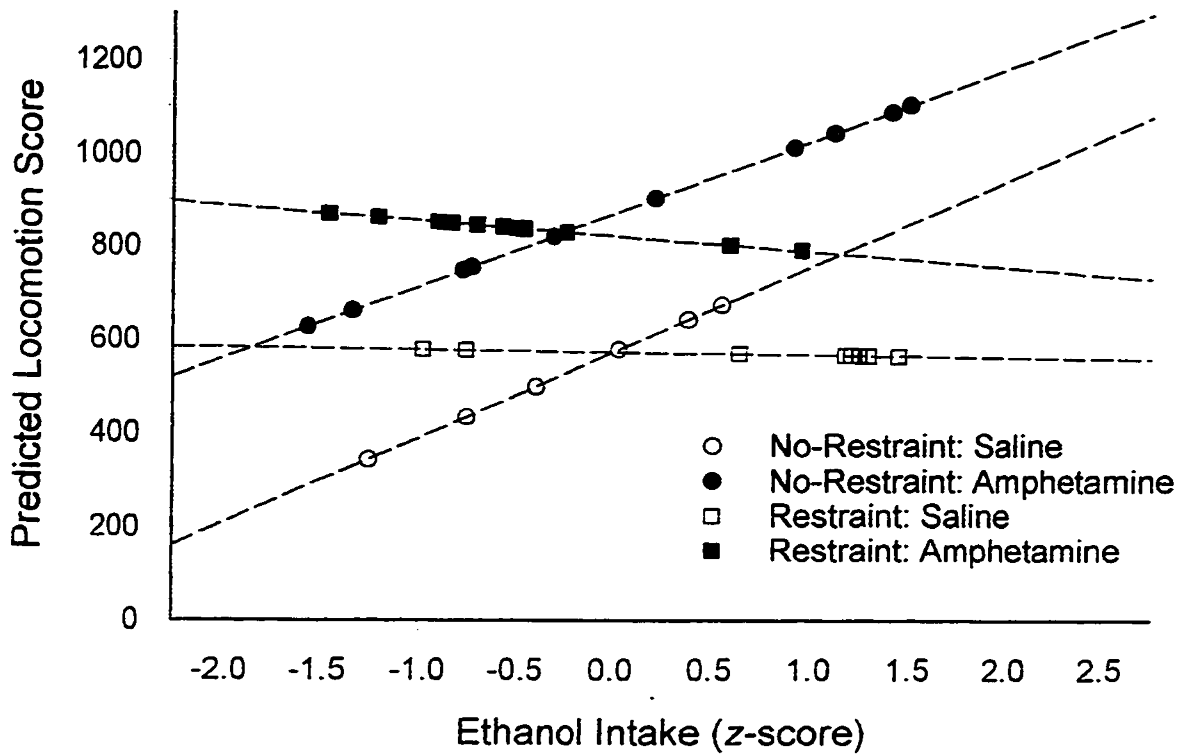


**Figure 25.** Regressed locomotor scores as a function of restraint treatment and ETOH intake (standardized ).

This was confirmed by indices of unique variance ($s_r^2$) for ETOH intake and the restraint by ETOH intake interaction that were almost identical but of opposite sign (.059 and -.081, respectively). Finally, while amphetamine injection accounted for the largest amount of locomotion variance (26.2%), ETOH intake accounted for 5.9% of the variance and the Restraint by ETOH intake interaction accounted for 8.1% of the variance. Together, these factors accounted for 14% of the variance in novelty-induced locomotion.

**Discussion**

Exposure to seven days of restraint does not alter weight gains or total fluid consumption. Similarly, depriving rats of ETOH during the seven day restraint period has no impact on weight gains or total fluid intake. Consistent with previously reported results (Nash & Maickel, 1985; Nash & Maickel, 1988; Rockman, Hall & Glavin, 1986), repeated restraint stress increases ETOH intake in the post-stress period but not during the seven days of restraint. Moreover, the restraint-induced increase in ETOH intake was evident only among animals that did not have the opportunity to consume ETOH during the restraint period.

The increase in ETOH intake in the post-restraint period is consistent with results reported by other labs (Derr & Lindblad, 1980; Krishnan, Nash & Maickel, 1991; Rockman, Hall & Glavin, 1986; Rockman, Hall, Hong & Glavin, 1987). When compared to the results of Experiment 3a, however, it appears that restraint may exert a different impact on ETOH and cocaine self-administration. For instance, repeated

restraint increased ETOH intake in the current study but exerted little effect on cocaine self-administration in Experiment 3a.

If stressor-induced increases in ETOH intake reflect attempts to reduce the impact of restraint by increasing ETOH intake (i.e., negative reinforcement mechanism), then it would be expected that eliminating this means of coping with the restraint stress would result in increased ETOH intake. While this appears to be the case, it should be noted that the post-restraint increase in ETOH intake is transient. It is possible that the transient nature of the increase in ETOH intake reflects that, in the absence of further restraint, animals no longer employ ETOH as a means of reducing the impact of the stressors. This does make intuitive sense as there would seem to be little utility of using ETOH to reduce stressor effects when the stressor treatment is no longer applied.

Restraint does not appear to influence locomotion in the open-field at either the initial time block (2 min) or the last time block (30 min). There is a positive relationship between ETOH intake and locomotion at both time blocks. This is consistent with reports that novelty-induced locomotion is a significant predictor of the propensity to self-administer other drugs such as amphetamine (Deminiere et al.1992; Deroche, Piazza, LeMoal & Simon, 1993; Piazza, Deminiere, LeMoal & Simon, 1989; Piazza, Deminiere, LeMoal & Simon, 1990). However, the current results indicate that restraint alters the relationship between locomotion and ETOH intake in the last time block but not the initial time block. Indeed, while the positive relationship between ETOH intake and locomotion is uninfluenced by restraint in the first time block, it is

eliminated by restraint in the last time block. These data suggest that the relationship between locomotion and ETOH intake may be independent of the novel aspect of the open-field since the same relationship emerges when the open-field is most novel and following 20 min exposure to it. Moreover, that restraint eliminates the ETOH intake/locomotion relationship in the last time block suggests that the aversiveness of the open-field is not a relevant factor since it would be expected that restraint would enhance the response to aversive novelty and therefore exert a greater impact on the ETOH/locomotion relationship in the first time block of the open-field test.

One possible explanation for these results may be that the relationship between drug self-administration and locomotion actually reflects a relationship between habituation to a novel environment (i.e., novel open-field) and habituation to a novel drug in the self-administration test. This hypothesis would be consistent with reports that novelty-induced locomotion is related to the propensity to acquire drug self-administration but not the maintenance of drug self-administration (Bisaga & Kostowski, 1993; Deminiere et al.1992; Deroche, Piazza, LeMoal & Simon, 1993; Piazza, Deminiere, LeMoal & Simon, 1989; Piazza, Deminiere, LeMoal & Simon, 1990).

## EXPERIMENT 5

Experiment 5 was designed to further test the hypothesis that exposure to stressors enhances reactivity to aversive stimuli but not reactivity to appetitive stimuli. In order to do this, two strains of rats that appear to differ in their reactivity to novel and aversive stimuli were used. These strains were selected for a number of reasons. First, the results from the earlier experiments provide a basis on which to compare the results of the current study, thereby providing some degree of validation for the behavioral measures. Second, these two rat strains are among the most commonly used rats strains for behavioral studies and, as such, the results have applicability to a broad range of studies. Third, while the results of Experiments 3c, 1a and 1b are suggestive of a strain difference in taste neophobia, differences in water deprivation schedules between these studies preclude direct comparison. The current study will provide direct comparisons of taste neophobia. Fourth, Sprague-Dawley rats exhibit a smaller acoustic startle response than Long-Evans rats (Glowa & Hansen, 1994). Since acoustic startle is thought to reflect fearfulness and anxiety (Brown, Kalish & Farber, 1951; Davis, 1992; Davis, Hitchcock & Rosen, 1989) and exposure to footshock has been shown to potentiate acoustic startle responses (Brown, Kalish & Farber, 1951; Davis, Hitchcock & Rosen, 1989), these data suggest that these strains differ in sensitivity to aversive stimuli.

Sprague-Dawley and Long-Evans rats were compared on a number of the measures used in the earlier studies. Specifically, the strains were compared on taste neophobia, amphetamine CTA and novelty-induced locomotion. The CTA procedure

also permits the assessment of strain differences in the appetitive response to saccharin. The present study will also compare these strains in an additionnal test - the light/dark emergence test. This procedure is based upon the natural tendency of rats to avoid brightly-lit exposed areas and is thought to measure fearfulness or anxiety (Czech & Green, 1992; Rodgers & Shepard, 1993; van der Staay, Kerbusch & Raaijmekers, 1990). Furthermore, this test has been shown to be sensitive to anti-anxiety drugs (Rodgers & Shepard, 1993). Thus, this test permits the direct evaluation of strain differences in reactivity to aversive stimuli independent of the other behavioral measures. Based upon the results of the earlier studies, it is expected that Sprague-Dawley rats will exhibit a behavioral profile similar to that seen in stressed animals. Specifically, we expect that Sprague-Dawley rats will exhibit greater taste neophobia, a larger amphetamine CTA and less novelty-induced locomotion. Also, it is expected that latencies to emerge into the lighted compartment of the light/dark chamber will be greater in Sprague-Dawley rats that Long-Evans rats. It is not expected that the strains will differ in the appetitive response to saccharin.

**Materials and Method**

*Subjects and Apparatus:* Subjects consisted of 21 male Long-Evans and 21 male Sprague-Dawley rats weighing 308-368 g and 321-425 g, respectively, on the first saccharin test (PD1). Apparatuses for fluid consumption testing and open-field testing were identical to those used in Experiments 1a and 3c. Drug injections were also identical to those employed in Experiment 3c.

*Procedures*: CTA testing was conducted as described in Experiment 3c except that the water deprivation schedule was 10 days instead of 12 days. Animals from each strain were randomly assigned to saline or amphetamine (2.0 mg/kg) treatment and received 2 saccharin-amphetamine pairing as previously described. Extinction testing for the amphetamine CTA, however, was extended to 12 extinction tests and water was provided on days between saccharin consumption tests. Following the last extinction test, water bottles were returned to the cages and all animals were permitted free access to water for the next 14 days. Open-field testing was conducted on the next day as described for Experiment 1c. Photocell counts were recorded at 2, 5, 10, 20 and 30 min. Animals were returned to their home cages immediately following the open-field test. Twenty-four hours later, animals were individually transported to a separate room and tested in the modified shuttle box. This test consisted of individually placing each animal in the light side of the two-chamber shuttle box. Care was taken to ensure that animals were facing away from the door separating the light and dark chambers when they were placed in the chamber. The latency to cross into the dark chamber was recorded manually with a digital stopwatch. The latency was recorded as the time it took the animal to move three paws into the dark chamber. The animal was then permitted to cross from the dark chamber into the light chamber. Again, the latency was measured as the time it took the animal to move three paws into the light chamber. Once the animal crossed into the light chamber, it was removed from the shuttle box and returned its home cage. The two compartment

shuttle box was then lightly wiped with a dilute ethanol solution prior to testing the next animal.

*Data Analysis*: Baseline water intake was computed as described in Experiment 3c. Fluid consumption data was analyzed with a repeated measures ANOVA that included baseline water intake and all 14 saccharin intake tests. Open-field data was analyzed as in Experiment 3c. Emergence latency data was analyzed with ANOVA.

**Results**

An initial ANOVA on body weights revealed that Sprague-Dawley rats were significantly heavier than Long-Evans rats ($F_{1,38} = 19.51$, $p < .001$). Since fluid intake is expected to be proportional to body weight, a simple effects test on baseline water intake was conducted. This analysis revealed that Sprague-Dawley rats consumed significantly more water than Long-Evans rats ($F_{1,38} = 18.56$, $p < .001$). The greater fluid intake in Sprague-Dawley rats may simply reflect that these are larger animals than Long-Evans rats. Thus, any comparisons of fluid intake across strains must be adjusted for differences in body weight. To accommodate for this, fluid intake values were standardized on the basis of body weight. Since body weight data was not recorded on each saccharin test, separate regression analyses were conducted for each treatment cell (i.e., Strain by Drug combinations) to generate body weights for each saccharin consumption test ($R^2$ was greater than .98 for each treatment cell). These predicted body weights were then used in the calculation of fluid consumption per kg

of body weight (i.e., ml fluid intake/ kg body weight). All subsequent analyses on fluid intake were then conducted with these standardized consumption values.

Saccharin consumption data were analyzed with a 2 x 2 x 15 repeated measures ANOVA. As can be seen in Figure 26, saccharin-amphetamine pairing reduced subsequent saccharin consumption. This was confirmed by a significant main effect of Drug treatment ($F_{1,38}$= 15.99, $p$ <.001). A significant Drug by Days interaction ($F_{14,25}$ = 49.92, $p$ < .001) also indicated that the effect of Drug on saccharin intake varied over test days. Simple effects analysis revealed that saccharin intake was suppressed in amphetamine-injected animals from PD2 to EXT6 ($F$s > 5.0, $p$s < .023) and on EXT8 ($F_{1,38}$ = 4.89, $p$ = .033). Simple effect tests indicated that there were no difference between amphetamine- and saline- injected animals on baseline water intake ($F_{1,38}$ = .14, $p$ = .710) or PD1 ($F_{1,38}$ = .20, $p$ = .656). Moreover, there were no strain differences in baseline water intake ($F_{1,38}$ = 3.61, $p$ = .065) indicating that strain differences in absolute fluid intake were eliminated when intake was standardized on the basis of body weight.

ANOVA also revealed a significant Strain by Drug by Days interaction ($F_{14,25}$ = 2.39, $p$ = .028) indicating that amphetamine-induced suppression of saccharin intake differed between the two strains (see Figure 27). As can be seen in Figure 27A and confirmed by simple-simple effects tests, saccharin-amphetamine pairing produced a significant suppression in saccharin intake in Long-Evans rats from the PD2 to EXT3 ($F$s > 10.0, $p$ < .005) but not thereafter ($F$s < 2.3, $p$s > .14). In contrast, saccharin-amphetamine pairing significantly reduced saccharin intake in Sprague-Dawley rats

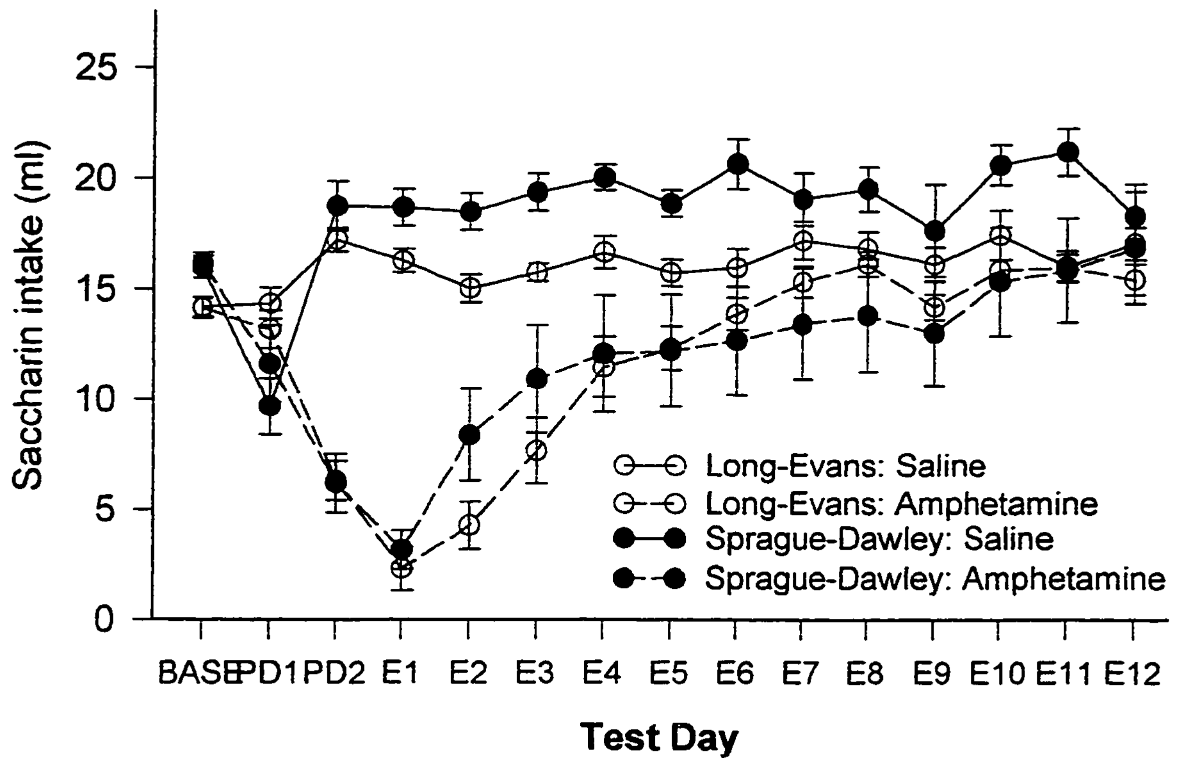


**Figure 26.** Mean (± s.e.m) water (BASE) and saccharin intake among Long-Evans and Sprague-Dawley rats injected with saline or amphetamine (2.0 mg/kg) following the first saccharin presentation (PD1). Two saccharin-amphetamine pairings were conducted (PD1 and PD2) and were followed by 12 extinction trials (E1 to E12).

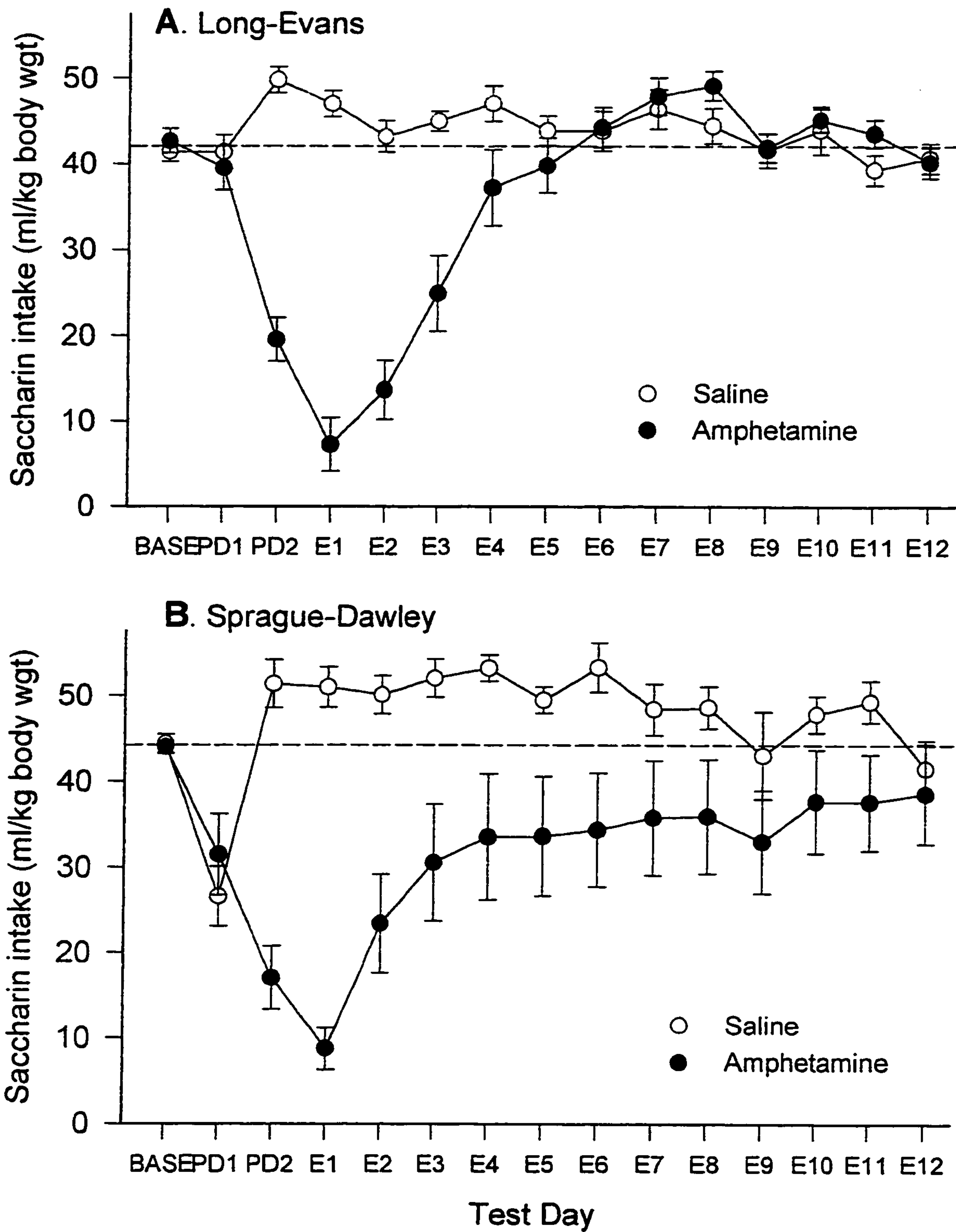


**Figure 27**. Mean (± s.e.m) water and saccharin intake in Long-Evans (A) and Sprague-Dawley (B) rats before and after saccharin-amphetamine pairing. Data are presented are identical to data from Figure 26 but presented separately for each rat strain for clarity.

from PD2 to EXT8 ($F$s > 5.3, $p$s < .04) and on EXT11 ($F_{1,38}$ = 5.94, $p$ = .020) (see Figure 27B). The maximum suppression in saccharin intake was evident following the second saccharin-amphetamine pairing. There was, however, no difference between the strains in saccharin intake following the first or second amphetamine injections ($F$s < 1.0, $p$s > .45). Figure 27 also shows that saccharin neophobia differs between the two rats strains. Initial saccharin intake is reduced relative to baseline water intake in Sprague-Dawley (see Figure 27B) rats but not Long-Evans rats (Figure 27A). Simple effects tests indicated that this strain difference in initial saccharin intake relative to baseline water intake was significant ($F_{1,38}$ = 10.74, $p$ = .002).

A separate repeated measures ANOVA on photocell counts in the open-field revealed a significant main effect of Strain ($F_{1,38}$= 13.95, $p$ =.001) and a significant main effect of Time ($F_{4,147}$= 221.52, $p$ <.001). Figure 28 illustrates that, as expected, locomotor counts decrease over the course of the 30 min open-field test. Figure 28 also shows that Sprague-Dawley rats exhibit fewer locomotor counts that Long-Evans rats. Simple effects analysis revealed that Sprague-Dawley rats exhibit fewer locomotor counts than Long-Evans rats at all time blocks except the 5 min time block ($F$s > 4.0, $p$s < .05 except for 5 min ($F_{1,38}$=.13, $p$ =.720).

Figure 29 shows emergence latencies in the light-dark emergence test. Separate ANOVAs on emergence latencies indicated that there were no strain differences in the latency to enter the dark chamber ($F_{1,38}$ = 1.59, $p$ = .215) but there was a trend for

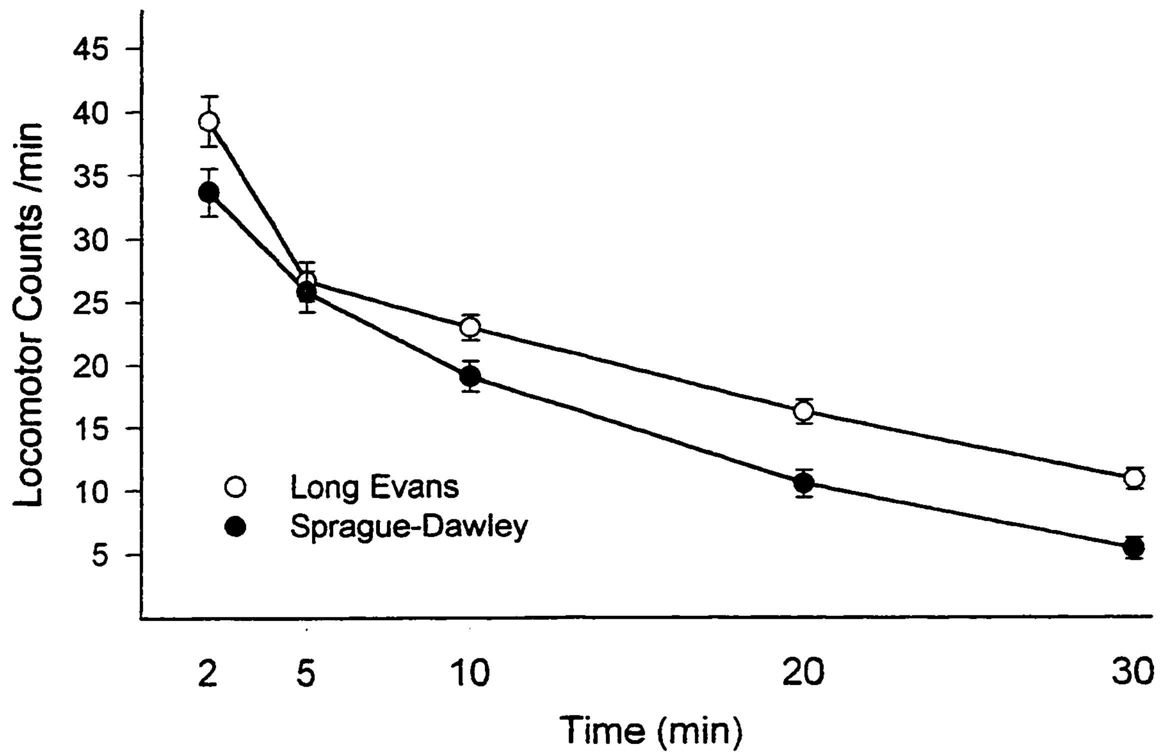


**Figure 28**. Mean (± s.e.m) locomotor counts/min in a novel open-field in Long-Evans and Sprague-Dawley rats previously tested for amphetamine CTA. Open-field testing was conducted 14 days after the last extinction trial.

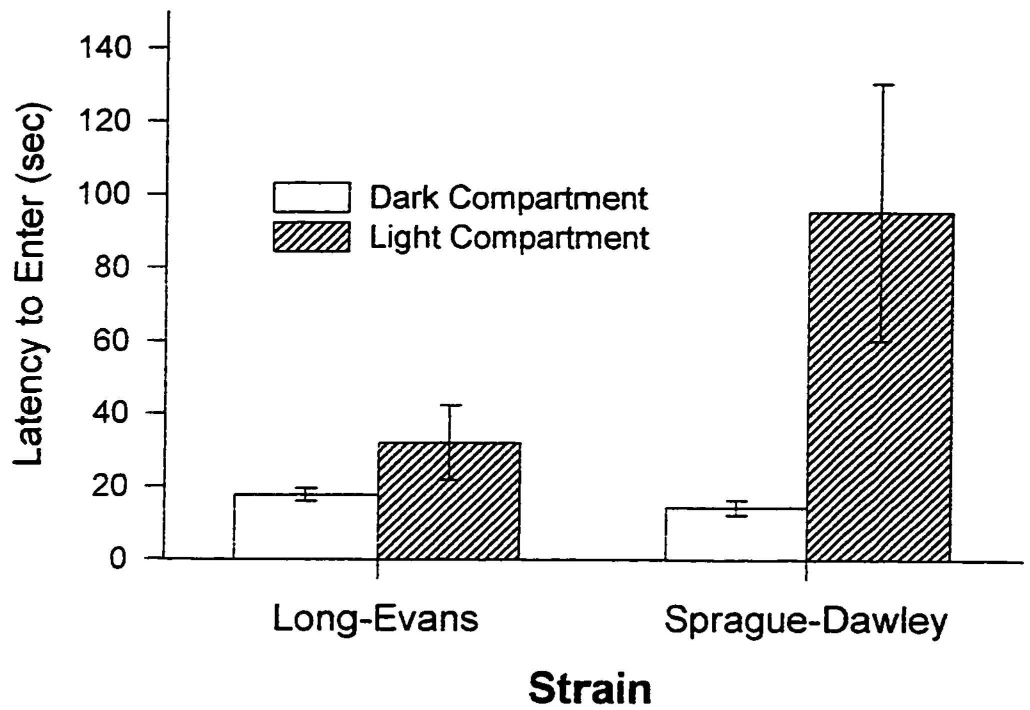


**Figure 29**. Mean (± s.e.m) latency to enter the dark and lighted compartment of the light/dark chamber in Long-Evans and Sprague-Dawley rats.

Sprague-Dawley rats to have longer latencies to enter the lighted compartment ($F_{1,38}$ = 2.98, $p$ .092). Prior amphetamine treatment exerted no significant impact ($F$s < 3.0, $p$s > .10) nor was there any significant Drug by Strain interaction ($F\text{s}_{1,38} < 2.1$, $p\text{s} >$ .15).

As already mentioned, Sprague-Dawley animals were larger than Long-Evans animals. Figure 30 shows that weight gains over the course of the CTA study differed between the two strains and that amphetamine injections appear to reduce body weights. ANOVA on body weight indicated that Sprague-Dawley rats were significantly larger than Long-Evans rats ($F_{1,38} = 19.51$, $p < .001$) and that amphetamine injections significantly reduced body weight ($F_{1,38} = 4.60$, $p = .038$). In addition, the influence of both strain and amphetamine varied over Days ($F_{3,36} = 2.89$, $p = .049$ and $F_{3,36} = 38.35$, $p < .001$, respectively). Simple effects tests indicated that Sprague-Dawley rats were larger than Long-Evans rats on each day ($F$s > 11.0, $p$s < .002). Amphetamine-injected animals weighed significantly less than saline-injected animals on PD2 ($F_{1,38} = 6.78$, $p = .013$) and Day 10 ($F_{1,38} = 14.20$, $p = .001$) (Day 10 occurred 24 hr before EXT4). Although from Figure 30, it appears that amphetamine exerted a larger effect on weight gains in Long-Evans rats than Sprague-Dawley rats, the Strain by Drug by Days interaction was not significant ($F_{3,36} = 1.46$, $p = .240$). Similarly, the Strain by Drug interaction was not significant ($F_{1,38} = 2.36$, $p = .133$).

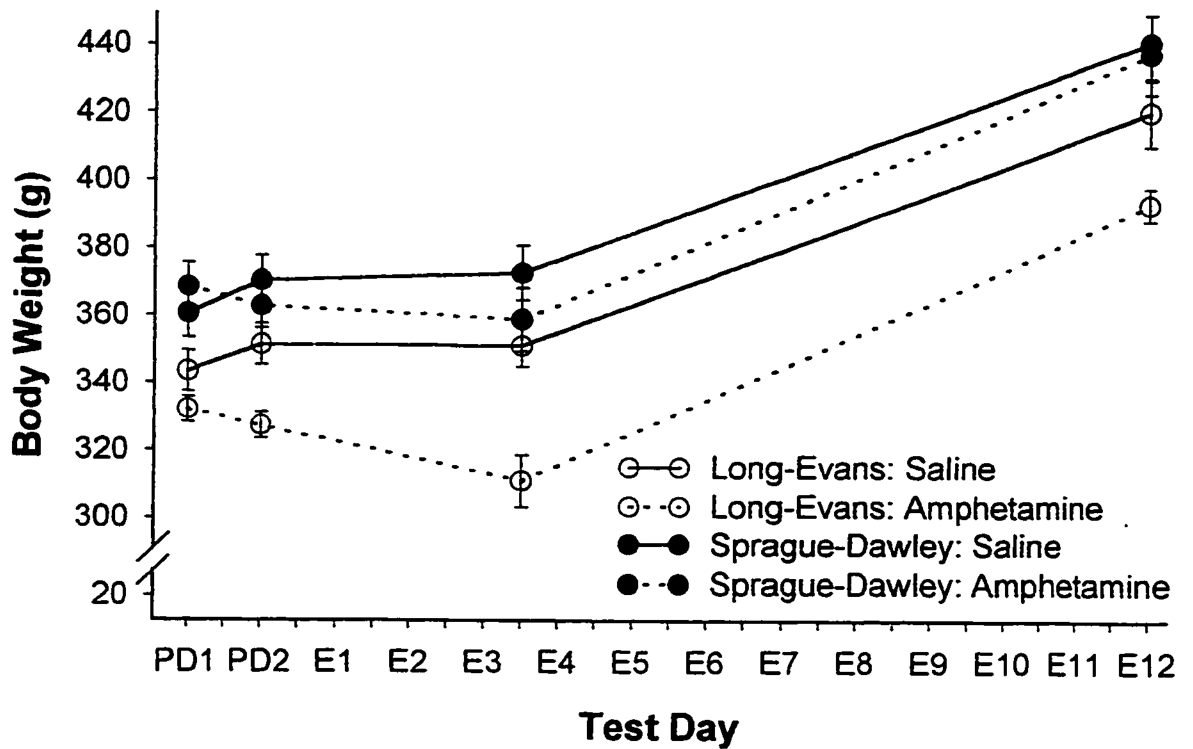


**Figure 30.** Mean (± s.e.m) body weight in Long-Evans and Sprague-Dawley rats over the course of CTA training and testing. Drug treatments indicated in the figure refer to saccharin-drug parining conditions on pairing days 1 and 2 (PD1 and PD2).

Following separate analyses of data derived from the three behavioral tests, an overall multivariate analysis of variance (MANOVA) was conducted on the multiple dependent measures to assess the impact of the Strain and Drug factors. This strategy was employed because the three different behavioral test procedures used were all intended to measure differences in reactivity to novel or aversive stimuli. The integration of these dependent measures into the MANOVA permits the assessment of a behavioral profile based upon all measures. In addition, given the multiple dependent measures, MANOVA is a more powerful analytical procedure to detect additive treatment effects that are often undetectable with ANOVA (Cohen & Cohen, 1983).

Because of the large number of observations from the three behavioral tests, it was necessary to compute composite measures of saccharin intake and open-field locomotion for the MANOVA. For the CTA results three composite measures were computed. Saccharin neophobia was calculated as the ratio of fluid intake on the first presentation of saccharin (i.e., PD1) relative to baseline water intake. The two composite measures of amphetamine CTA were computed as a) the average saccharin intake on the first three extinction tests divided by baseline water intake ([E1+E2+E3]/3/baseline $H_2O$]) and b) the average saccharin intake on the second three extinction tests ([E4+E5+E6]/3/baseline $H_2O$]). These two composite variables were selected because they provide a composite index of the rate of extinction of the amphetamine CTA. Open-field data included in the MANOVA was restricted to the first time block (2 min) and the last time block (30 min). These two variables were

included because these two time blocks reflect the extremes of the novelty of the open-field. Both the latency to enter the dark compartment and the lighted compartment from the emergence latency test were included in the MANOVA. Significant main effects and interactions were followed by Roy-Bargmann stepdown $F$ tests (Pedhazer, 1982). Unlike univariate $F$ test, this procedure partials out intercorrelations between dependent variables and therefore eliminates the inflation in Type I error rates associated with correlations between dependent variables.

The results of the MANOVA confirmed the results of the previously reported ANOVAs. MANOVA revealed a significant main effect of Drug ($F_{7,32} = 21.86$, $p < .001$), a significant main effect of Strain ($F_{7,32} = 8.95$, $p < .001$) and a significant Strain by Drug interaction ($F_{7,32} = 3.18$, $p = .011$). Follow-up stepdown $F$ tests indicated that the source of the main effect of Drug was the two composite CTA variables. Amphetamine-saccharin pairing significantly decreased saccharin intake averaged over the first three extinction tests ($F_{1,33} = 84.27$, $p < .001$) as well as the second three extinction tests ($F_{1,32} = 15.07$, $p < .001$). Stepdown $F$ tests also revealed that the rat strains were different on a number of measures. Sprague-Dawley rats exhibited significantly less locomotion that Long-Evans rats at both the 2 min ($F_{1,38} = 4.31$, $p = .045$) and 30 min time blocks ($F_{1,37} = 16.84$, $p < .001$) of the open-field test. The strain also differed on taste neophobia ($F_{1,34} = 10.06$, $p = .003$) reflecting that Sprague-Dawley rats exhibited a greater avoidance of novel saccharin than Long-Evans rats. While there was no difference between strains in the latency to enter the dark compartment of the light-dark chamber ($F_{1,36} = 1.13$, $p = .296$), Sprague-Dawley

rats were significantly slower to emerge from the dark chamber into the light chamber ($F_{1,35} = 5.12$, $p = .030$). MANOVA also revealed a significant Strain by Amphetamine interaction ($F_{7,32} = 3.17$, $p = .011$). Stepdown $F$ tests indicated that the source of this interaction was the second composite saccharin intake variable (i.e., average of EXT4 to EXT6) ($F_{1,32} = 12.91$, $p = .001$) confirming that the rate of extinction of the amphetamine CTA was slower in Sprague-Dawley than Long-Evans rats.

Taken together, the results of the MANOVA confirmed the results from the ANOVAs conducted separately on each dependent variable (i.e., data from each behavioral test). In addition, the MANOVA also indicated that the strains differed in the latency to emerge from the dark but not the lighted compartment of the light-dark chamber.

**Discussion**

Experiment 5 showed that there are significant differences between Sprague-Dawley and Long-Evans rats. Both saccharin neophobia as well as the duration of the amphetamine CTA were significantly greater in Sprague-Dawley rats than Long-Evans rats. Moreover, the differences in saccharin intake cannot be attributed to differences in body weight. It is unlikely that the greater neophobic response to novel saccharin among Sprague-Dawley rats is due to differences in sensory reactivity to the saccharin since among saline-injected animals saccharin intake (adjusted for body weight) does not differ between the two strains after the initial presentation of saccharin. In

addition, it should be noted that the pattern of saccharin neophobia found in the current study is consistent with the neophobic responses noted in these strains in Experiments 1a, 1b and 3c. Others have also reported that these two strains do not differ in their preference for saccharin (Fregly & Rowland, 1992). Thus, it appears that the novel aspect of the saccharin determines the saccharin intake on initial presentation and that these strains differ in responsiveness to the novel saccharin.

There was also a substantial difference between strains in amphetamine CTA. While the maximum suppression in saccharin intake following saccharin-amphetamine pairing did not differ between strains, Sprague-Dawley rats exhibited suppressed saccharin intake for longer than Long-Evans rats. One possible explanation is that Sprague-Dawley rats are more sensitive to the effects of amphetamine than Long-Evans rats. This seems rather unlikely since it would be expected that, under such conditions, the maximum suppression in saccharin intake would be greater in Sprague-Dawley rats. That the maximum CTA was comparable between strains suggest that this is not the case. Moreover, amphetamine actually had a greater impact on weight gains in Long-Evans rats than in Sprague-Dawley rats suggesting that Long-Evans rats are more sensitive to the effects of amphetamine than Sprague-Dawley rats.

The current results also indicate that the duration of the water deprivation schedule does influence the amphetamine-conditioned suppression in saccharin intake. For instance, in Experiments 1a and 1b, Long-Evans rats deprived for 6 and 8 days exhibited a maximum conditioned suppression in saccharin intake of approximately 50%, while in the current study saccharin intake was suppressed by 85%. Similarly,

in Sprague-Dawley rats saccharin intake in amphetamine-injected rats was suppressed by 80% in the current study, while in Experiment 3c where the water deprivation schedules was 12 days instead of 10 days, maximum suppression in saccharin intake was greater than 99%. It appears, therefore, that as the water deprivation schedule is increased the extent of the conditioned suppression in saccharin is also increased. Note, however, that the degree of saccharin neophobia does not appear to be related to the water deprivation schedule (compare Figures 1 and 2 with Figure 27A). The increased magnitude of the amphetamine CTA may be related to a potentiation of the effects of amphetamine as the schedule of fluid deprivation is increased since others have reported that deprivation schedules can potentiate the effects of amphetamine (Valencia-Flores, Velazquez-Martinez & Villarreal, 1990).

The two strains also differ in novelty-induced locomotion and the latency to emerge from the dark compartment of the light-dark chamber. We had expected that these strains would differ in novelty-induced locomotion but that the differences would vary over the course of the 30 min open-field test. If the Sprague-Dawley rats are more reactive to novel environments, it would be expected that the difference between strains would be most evident when the environment is most novel. Based on previous studies in which shock alters novelty-induced locomotion only in the early part of the open-field test (see Experiments 1c, 2a,), it had been expected that the difference in novelty-induced locomotion would be most evident in the early part of the open-field test. While the MANOVA revealed that novelty-induced locomotion did differ between strains, locomotion in the first and last time blocks were both different

between strains. This result suggests that the temporal nature of novelty-induced locomotion may not be sufficiently sensitive to detect differences between strains. This is also difficult to determine since it appears that the baseline level of locomotion in Sprague-Dawley rats is consistently lower than in Long-Evans rats.

The light-dark emergence test indicated that Sprague-Dawley rats have longer latencies to enter the lighted compartment than Long-Evans rats. There was no difference between strains in the latency to enter the dark compartment. That the latencies to enter the dark compartment did not differ suggests that the results are not due to general differences in locomotion. Since the latency to enter the lighted compartment has been shown to be sensitive to pharmacological manipulations of anxiety levels (Czech & Green, 1992; Rodgers & Shepard, 1993), these results indicate that Sprague-Dawley animals are more reactive to the anxiety-inducing lighted chamber than Long-Evans rats.

Taken together, the results of the current study indicate that Long-Evans and Sprague-Dawley rats consistently differ on measures of reactivity to novelty and aversive stimuli. The MANOVA revealed that the behavioral responses to novelty (i.e., saccharin neophobia, novelty-induced locomotion) and aversive stimuli (i.e., conditioned avoidance of saccharin, latency to enter the lighted compartment) differ in the same direction between strains and provide empirical validation for the notion that novel stimuli are in fact aversive for animals. More importantly, these results indicate that Sprague-Dawley rats are more sensitive to aversive stimuli than Long-Evans rats. Therefore, the lack of efficacy of restraint in altering cocaine self-administration in

Sprague-Dawley rats cannot be attributed to the insensitivity of this strain of rat to aversive stimuli such as restraint. Indeed, the results of the current study suggest that Sprague-Dawley rats should be more sensitive to stressors than Long-Evans rats.

# GENERAL DISCUSSION

The present series of experiments were conducted to determine if aversively- and appetitively-motivated behaviors are differentially sensitive to the effects of stressors. This was done by comparing the effects of footshock and restraint stress in a series of behavioral tests that provide measures of responding to aversive and appetitive stimuli. In addition, based upon data suggesting that novel stimuli may have aversive qualities, the effects of these stressors on responding to novel stimuli were assessed.

Table 1 provides a summary of the results of theses studies. The CTA studies demonstrated that exposure to footshock facilitated the acquisition of the conditioned avoidance of saccharin intake and enhanced saccharin neophobia. There was no indication in either of these studies that footshock altered the post-neophobic consumption of saccharin in saline-treated animals. Two runway studies showed that exposure to footshock prolonged the response to a reduction in reward magnitude but had no impact on runway responding when reward magnitude was either increased or unchanged. Experiment 3 indicated that exposure to repeated restraint did not alter cocaine self-administration response rates although the same restraint treatment enhanced the locomotor stimulating effects of an intermediate dose of cocaine. Experiment 4 demonstrated that restraint increased ethanol intake but only among animals that had been deprived of ETOH during the seven day period of restraint exposure. Moreover, this increase in ETOH intake was transient, appearing only on the first post-restraint ETOH consumption test.

**Table 1.** Summary of effects of stressors on responding for aversive, novel and appetitive stimuli (**Symbols**: ↑, increase; ↔, no effect, ↓, decrease).

| Measure | Stressor | Effect of Stressor | Study |
|---|---|---|---|
| **Appetitive Measures** | | | |
| Runway latencies in Unshifted Groups | | | |
| Large reward (15 pellets) | Shock | ↔ | 2a |
| Small reward (1 pellet) | Shock | ↔ | 2b |
| Cocaine self-administration | Restraint | ↔ | 3a |
| ETOH consumption | | | |
| ETOH available during restraint | Restraint | ↔ | 4 |
| ETOH deprived during restraint | Restraint | ↑ | 4 |
| Saccharin intake in saline-injected rats | Shock | ↔ | 1a, 1b |
| **Novel Measures** | | | |
| Saccharin Taste Neophobia | Shock | ↑ | 1b |
| | Restraint | ↔ | 3c |
| Novelty-induced locomotion | Shock | ↓ for 5 min | 1c, 2a |
| | Restraint | ↔ | 2b |
| Cocaine-induced locomotion | Restraint | ↑ (10 mg/kg) | 2b |
| ETOH intake/Locomotion correlation | Restraint | ↓ | 4 |
| **Aversive Measures** | | | |
| Amphetamine CTA | Shock on PD1 | ↔ | 1a |
| | Shock before PD1 | ↑ | 1b |
| | Restraint | ↔ | 3c |
| Runway latency following reward reduction | Shock | ↑ | 2a |
| **Strain Comparison** (Sprague-Dawley vs Long-Evans) | | | |
| Saccharin Taste Neophobia | Sprague-Dawley > Long-Evans | | 5 |
| Amphetamine CTA | | | |
| Acquisition | Sprague-Dawley = Long-Evans | | 5 |
| Resistance to Extinction | Sprague-Dawley > Long-Evans | | 5 |
| Saccharin Intake (saline-injected animals) | Sprague-Dawley = Long-Evans | | 5 |
| Novelty-induced Locomotion | Sprague-Dawley < Long-Evans | | 5 |
| Latency to Enter Lighted Compartment | Sprague-Dawley > Long-Evans | | 5 |

Novelty-induced locomotion was also assessed in a number of these studies. While footshock consistently decreased locomotion in a novel open-field, this decrease was evident only in the initial five minutes of the open-field test. Restraint did not appear to exert any effect on novelty-induced locomotion. However, restraint was effective in eliminating the positive relationship between locomotion in the novel open-field and ETOH consumption. Finally, relative to Long-Evans rats, the more reactive Sprague-Dawley rat strain exhibited a more pronounced saccharin neophobia, more protracted conditioned avoidance of saccharin, less novelty-induced locomotion and greater anxiety as indexed by the emergence latency test.

Taken together, the results of the current series of studies provide a consistent picture. Exposure to stressors appear to enhance the response to both novel and aversive stimuli without altering the response to appetitive stimuli.

**Stress and Aversive Stimuli**

Exposure to footshock appears to enhance the response to aversive stimuli. Both the conditioned avoidance of saccharin and the increase in runway latencies produced by reward reduction were enhanced by exposure to footshock. It should be noted that the shock-induced enhancement in amphetamine CTA was evident only when exposure to footshock occurred a number of days prior to saccharin-amphetamine pairing. Moreover, the shock-induced enhancement of amphetamine CTA was evident on PD2 indicating that the stress-induced potentiation of saccharin avoidance was transient.

In addition to increasing the conditioned avoidance of saccharin, exposure to footshock also enhanced the response to a reduction in reward magnitude. As already outlined, reward reduction appears to have many of the characteristics of aversive stimuli. Footshock did not affect the increase in runway latencies in the early stages following reward reduction; however, the increased runway latencies produced by reward reduction were more persistent in shocked animals. It also seems that the impact of footshock was restricted to a reduction in reward magnitude and did not generalize to any change in reward magnitude since shock was without effect when reward magnitude was increased. These data may indicate that footshock impedes the normal process of adaptation to the reduction in reward magnitude (i.e., habituation to the reward reduction). Such a delay in habituation would explain why footshock prolonged the duration of response to reward reduction but did not increase the magnitude of it.

A unique aspect of the runway procedure is that the aversive stimuli is almost entirely internally generated. Reward reduction is aversive because animals detect a mismatch between the expected magnitude of reinforcement and the delivered level of reinforcement. This differs from conventional aversively-motivated paradigms in which aversive stimuli is externally applied (e.g., shuttle escape or bar press escape tasks where shock is externally applied). Thus, this procedure provides an important tool to assess the impact of prior stressor experience on sensitivity to an internally-generated psychological stressor.

**Stress and Novelty**

Exposure to footshock altered the neophobic response to a novel saccharin solution as well as the pattern of locomotion in a novel open-field. These open-field data are consistent with earlier reports that shock decreases locomotion in a novel open-field (Campbell & Candland, 1961; Carli, Prontera & Samanin, 1989; Lemoine, Armando, Brun, Segura & Barontini, 1990; van Dijken, Mos, van der Heyden & Tilders, 1992; van Dijken, Tilders, Olivier & Mos, 1992; van Dijken, van der Heyden, Mos & Tilders, 1992; Weyers, Bower & Vogel, 1989). In addition, the current results add to existing data showing that shock-induced decreases in novelty-induced locomotion are evident up to 28 days after exposure to footshock (van Dijken, Mos, van der Heyden & Tilders, 1992; van Dijken, Tilders, Olivier & Mos, 1992). Moreover, these decreases in novelty-induced locomotion were evident even when CTA and runway testing occur between shock exposure and open-field testing. Thus, the shock-induced reductions in novelty-induced locomotion appear to persist over a considerable period of time and are not easily disrupted by intervening behavioral treatments.

Unlike previous studies where locomotion was tested for only 5 min, the current studies tested locomotion for 30 min and revealed that the effect of shock is restricted to the early portion of the open-field test. Although there are numerous reports showing that shock disrupts locomotion in brief open-field tests (i.e., 5 min) (Lemoine, Armando, Brun, Segura & Barontini, 1990; van Dijken, Mos, van der Heyden & Tilders, 1992; van Dijken, Tilders, Olivier & Mos, 1992), few studies have examined the time course of these shock effects in longer open-field tests. This is an important

issue for two reasons. First, it demonstrates that assessing the effects of stressors such as shock on novelty-induced locomotion should not employ total locomotion scores cumulated over long test periods. Because shock effects are consistently observed only in the initial 5 min of the test, total locomotion scores over longer time periods may mask the effects of stressors and lead to the erroneous conclusion that locomotion is not affected by shock. Second, the pattern of results obtained suggest that the effects of shock are related to alterations in the response to the novel aspect of the open-field.

Like novelty-induced locomotion, it appears that footshock alters the response to saccharin only when the saccharin solution is novel. Experiment 1a demonstrated that when footshock follows the initial presentation of saccharin, there was no indication that shock influenced saccharin intake. However, in Experiment 1b where footshock preceded the initial saccharin presentation, saccharin neophobia was enhanced. Such a shock-induced reduction in saccharin intake has also been reported by others (Dess, 1992; Dess, 1993; van Dijken, Mos, van der Heyden & Tilders, 1992). However, unlike other novel sweet solutions such as sucrose or glucose, saccharin appears to possess inherent aversive qualities in addition to its appetitive properties (Dess, 1993). This raises the possibility that the effect of shock on saccharin neophobia may reflect the impact of shock on this inherent aversive property. Indeed, it has been suggested that shock-induced alterations in saccharin intake are mediated by such a mechanism rather than alterations in the appetitive response to saccharin (Dess, 1993). While this is a possibility, it seems rather unlikely because shock decreased saccharin intake on

the first saccharin presentation (i.e., increased saccharin neophobia) but did not alter post-neophobia saccharin intake. Moreover, when exposure to shock occurred after the initial saccharin presentation it did not alter saccharin consumption. Our results are therefore more consistent with shock-induced enhancements in the aversive response to novelty rather that shock-induced enhancements in the inherent aversive qualities of saccharin.

Taken together, the neophobia and open-field data indicate that footshock altered the behavioral response to taste stimuli and environmental stimuli only when these stimuli were novel. Exposure to saccharin prior to shock eliminated the effects of footshock on saccharin consumption. Similarly, the impact of shock on locomotion abated with prolonged exposure to the novel open-field.

As was suggested for the prolonged response to reward reduction, stressor-induced alterations in saccharin neophobia and novelty-induced locomotion may be related to the effects of stressors on the processing of information about novel stimuli. A shock-induced impairment in the acquisition or processing of information about novel stimuli may results in a delay in habituation to such stimuli. Thus, stressed animals would exhibit behavioral responding consistent with more protracted novelty rather than with enhanced or heightened novelty. This would be consistent with data indicating that exposure to stressors reduced the rate of habituation to novel objects (Rosellini & Widman, 1989) decrease preference for unfamiliar stimuli (Mitchell, Osborne & O'Boyle, 1985; Sheldon, 1968; Williams, 1972) and induce stimulus perseveration (i.e., protracted responding to a stimulus) (Anisman, Hahn, Hoffman & Zacharko, 1985;

Prince & Anisman, 1984). This would also be consistent with the hypothesis that nove stimuli contain some inherent aversive qualities and that stressors enhance responsiveness to the aversive features of novel stimuli. Further studies assessing the impact of stressors on the time course of responding to novel stimuli would be particularly useful to address this hypothesis.

**Stress and Appetitive Stimuli**

It appears that footshock exerted little impact on appetitive responding in any of the tasks employed. For instance, while footshock enhanced saccharin neophobia, it did not alter saccharin consumption when saccharin was not novel. Similarly, footshock did not alter runway latencies where reward magnitude was unchanged. The runway studies also indicated that the effects of footshock on appetitive responding in the runway was not influenced by the absolute level of reinforcement. For instance, when reward magnitude was not changed footshock exerted no effect on runway responding for either the large level of reward or the low level of reward. These results indicate that footshock did not alter the motivational properties of food reinforcement regardless of the level of reward magnitude.

Consistent with the lack of effects of shock on appetitive responding in the CTA and runway studies, there was no indication that restraint stress altered appetitive responding measured by cocaine self-administration, although the restraint procedures employed were effective in altering the locomotor response to cocaine. The effects of restraint on cocaine self-administration may have been masked by the stressfulness of

surgical procedures. Previous studies, however, have shown that exposure to tailpinch and social stress (i.e., aggressive encounters) prior to surgery increase amphetamine and cocaine self-administration (Haney, Maccari, LeMoal, Simon & Piazza, 1995; Piazza, Deminiere, LeMoal & Simon, 1990; Rouge-Pont, Piazza, Kharouby, LeMoal & Simon, 1993). One would expect that the masking effect of surgery would be even less likely when surgery precedes exposure to stressors. Since we exposed animals to restraint after surgery, it seems unlikely that the surgery masked the effects of restraint in Experiment 3a but do not mask the effect of tailpinch and social stress when they precede surgery.

Results from drug self-administration cannot unambiguously determine whether stress-induced changes in response rates indicate an increase or decrease in the reinforcing value of the drug reinforcer. While the most convincing evidence for stress-induced increases in the reinforcing properties of appetitive reinforcers is derived from self-administration studies that employed the progressive ratio paradigm and the reinstatement paradigm (Shaham & Stewart, 1994; Shaham & Stewart, 1995), other factors may be operating in these studies. For instance the progressive ratio paradigm involves continually incrementing the fixed-ratio reinforcement schedule and it has been reported that increments in fixed-ratio response requirements for water appears to be stressful, as measured by plasma corticosterone levels (Goldman, Coover & Levine, 1973). Moreover, other data indicates fixed-ratio reinforcement schedules increase resistance to extinction relative to continuous reinforcement schedules (Williams, Gray, Snape & Holt, 1989). Since one of the consequences of exposure to

stressors is increased resistance to extinction (Chen & Amsel, 1977; Fallon, 1971; Nation & Boyagian, 1981), it is not unreasonable to suggest that the stress-induced increase in the heroin breakpoint may be related to a stress-induced enhancement in resistance to extinction. Because the breakpoint measure provides an index of the number of nonreinforced responses animals will make (nonreinforced responses must be made because the FR schedule is incremented throughout the progressive ratio paradigm), it is in fact a measure of resistance to extinction. Given the nature of this behavioral measure and that stressors increase resistance to extinction, it is therefore possible that the stress-induced increase in the breakpoint is an extinction phenomenon rather than a reflection of a change in the reinforcing value of the heroin.

Stressor-induced increased resistance to extinction, however, is not likely to play a role in reinstatement studies. There is some question of the specificity of stressor effects in reinstatement tests since shock has been shown to reinstate extinguished responding in aversively-motivated (Riccio & Spear, 1991) and other appetitively-motivated tasks (Deutsch & Howarth, 1962). That shock produces reinstatement in both appetitively- and aversively-motivated tasks suggests either that reinstatement procedures measure factors other than appetitive incentive motivational factors or appetitive incentive motivation is present in aversively-motivated tasks. In addition, recent data has shown that reinstated responding produced by shock and noncontingent heroin injections appear to be dissociable on biochemical and behavioral grounds (Shaham & Stewart, 1996). This dissociation suggests that shock may be producing reinstatement by some process independent of altered incentive motivation or increased

reinforcing value of appetitive reinforcers. Thus, while there is little doubt that footshock can reinstate responding for appetitive reinforcers, it is not clear that shock-induced response reinstatement is mediated by alterations in reinforcing value of the drug reinforcers.

Unlike cocaine self-administration, responding for ETOH was increased following exposure to repeated restraint stress. This result is consistent with numerous other reports that stressors can increase ETOH intake (Mills, Bean & Hutcheson, 1977; Nash & Maickel, 1985; Pohorecky, 1990; Volpicelli, Ulm & Hopson, 1990). That the repeated restraint regimen used altered ETOH intake provides further evidence that restraint was an effective stressor. It should be noted that repeated restraint increased ETOH intake when restraint was applied following acquisition of ETOH consumption while restraint was applied prior to acquisition for the cocaine self-administration study. Thus, the timing of exposure to restraint relative to acquisition or maintenance of drug reinforced responding may influence the impact of restraint. This seems unlikely, however, since other data indicate that exposure to mild stressors prior to self-administration testing facilitate the acquisition of amphetamine self-administration (Rouge-Pont, Piazza, Kharouby, LeMoal & Simon, 1993). Similarly, exposure to footshock after acquisition of heroin self-administration also increases self-administration responding (Shaham & Stewart, 1994). Because existing research shows that exposure to stressors either before or after acquisition of self-administration responding can enhance drug self-administration responding, differences in the timing of restraint exposure cannot account for our results.

We also assessed the role of ETOH intake during the period of exposure to restraint on the post-stress increase in ETOH intake. We found that the stress-induced increase in ETOH consumption was evident only when ETOH was not available during the stressor exposure period. These results suggest that voluntary ETOH intake during the period of stressor exposure can attenuate the effect of restraint and is consistent with other data indicating that experimenter-administered ETOH attenuates the effects of stressors (De Turck & Vogel, 1982; Milakofsky, Miller & Vogel, 1989; Vogel, Deutch & Miller, 1986). While it may be argued that the increase in ETOH intake following restraint reflects a stress-induced increase in the reinforcing value of ETOH, this seems unlikely since restraint did not increase ETOH intake among animals that had ETOH available during the period of restraint. Moreover, a stress-induced increase in the reinforcing value of ETOH would be expected to increase ETOH intake both during and after the restraint period. Accordingly, there is little reason to attribute the transient increase in ETOH intake to a change in the reinforcing impact of ETOH.

It has been shown that novelty-induced locomotion predicts the rate of acquisition of amphetamine self-administration (Deroche, Piazza, LeMoal & Simon, 1993; Piazza, Deminiere, LeMoal & Simon, 1989; Piazza, Deminiere, LeMoal & Simon, 1990). Since mild stressors like tailpinch enhance the acquisition of amphetamine self-administration, it has been suggested that the relationship between novelty-induced locomotion and amphetamine self-administration reflects a relationship between sensitivity to the mildly stressful nature of a novel environment and the propensity to

self-administer drugs like amphetamine (Rouge-Pont, Piazza, Kharouby, LeMoal & Simon, 1993). The current results suggest that this may not be the case. While we did observe the same relationship between novelty-induced locomotion and ETOH intake as others have seen between novelty-induced locomotion and amphetamine self-administration (Matthies, 1989; Deroche, Piazza, LeMoal & Simon, 1993; Piazza, Deminiere, LeMoal & Simon, 1989; Piazza, Deminiere, LeMoal & Simon, 1990), we did not observe any relationship between restraint and novelty-induced locomotion.

If the relationship between novelty-induced locomotion and drug self-administration reflects the relationship between the sensitivity to mild stressors and drug self-administration, then it should be possible to observe this sensitivity when evaluating the relationships between both restraint stress and ETOH self-administration and between restraint stress and locomotion. The results reported in Experiment 4 showed the expected relationship between ETOH intake and novelty-induced locomotion. This study also showed a relationship between restraint stress and ETOH consumption. However, there was no evidence of a relationship between restraint and novelty-induced locomotion. Moreover, restraint actually eliminated the relationship between ETOH consumption and locomotion. These results suggest that the stressfulness of a novel environment is not the relevant aspect of the novel environment that is correlated with the propensity to self-administer drugs. Furthermore, studies showing a relationship between novelty-induced locomotion and drug self-adminstration have usually used total locomotion scores cumulated over long locomotion tests (e.g., 2-3 hr: see (Piazza, Deminiere, LeMoal & Simon, 1989; Piazza,

Deminiere, LeMoal & Simon, 1990). Since such long duration tests are likely to result in habituation to the novel aspects of the locomotion chamber, these total locomotion scores probably do not reflect the response to novelty. Indeed, our data showed that shock altered novelty-induced locomotion only in the initial minutes of the open-field test when the environment is the most novel. If we are correct in our assertion that shock exerts its effects on locomotion in a novel environment only in the initial minutes because that is when the environment is the most novel and most aversive, then total locomotion scores over 2-3 hr would not reflect reactivity to the stressfulness of the novel environment. Given this, it would seem prudent to view the relationship between locomotion and drug self-administration as independent of novelty per se. Further studies that more accurately measure and manipulate novelty will be required to determining the mechanisms that subserve the relationship between novelty-induced locomotion and drug self-administration.

We found no indications that either shock or restraint altered appetitively-motivated behaviors as measured by saccharin consumption, food-reinforced runway responding in unshifted conditions or cocaine self-administration. These results appear to be inconsistent with other reports that exposure to stressors alters responding for a variety of appetitive reinforcers. There is evidence, however, to suggest that the effects of stressors on responding for appetitive reinforcers may be related to the severity of the stressors regimen. For instance, exposure to mild stressors (e.g., 10 footshocks or tailpinch) increase responding for appetitive reinforcers like heroin (Shaham & Stewart, 1994), morphine (Dib & Duclaux, 1982; Shaham, Alvares, Nespor &

Grunberg, 1992) and fentanyl (Shaham, Klein, Alvares & Grunberg, 1993). In addition, tailpinch has been reported to facilitate the acquisition of amphetamine self-administration (Piazza, Deminiere, LeMoal & Simon, 1990) and increase ICSS responding (Katz & Roth, 1979). More severe stressor treatments (e.g., 60-80 footshocks) that produce the shuttle escape deficits decrease responding for ICSS (Zacharko & Anisman, 1991; Zacharko, Bowers & Anisman, 1984), decrease sucrose consumption (Papp, Willner & Muscat, 1991; Willner, Golembiowska, Klimek & Muscat, 1991) and decrease the consumption of palatable foods (Griffiths, Shanks & Anisman, 1992).

It does appear that the severity of the stressor treatment may be the primary determinant of whether stressors increase or decrease responding for appetitive reinforcers. It is interesting to note that the stressor regimens that have been reported to decrease responding for appetitive reinforcers like ICSS are also effective in producing performance deficits in shuttle escape tasks (Anisman & Zacharko, 1992; Anisman & Zacharko, 1990). Unfortunately, there are no studies that have tested the impact of such stressor regimens on the self-administration of drugs like heroin, amphetamine or cocaine. It would be expected that severe stressors (i.e., those capable of producing shuttle escape deficits) would decrease responding for drug self-administration just as they decrease responding for ICSS.

This hypothesis also implies that the effects of mild stressors (e.g., 10 shock, tailpinch) may be completely determined by prior stressor experience. As already described, exposure to a severe stressor is effective in enhancing both behavioral and

biochemical effects of milder stressors. If exposure to severe stressor potentiates sensitivity to a mild stressor in the aversive test situation, then comparable sensitization processes would be expected to occur in the appetitive situation. Thus, while mild stressors normally increase responding for appetitive reinforcers, they would be expected to decrease responding for appetitive reinforcers if they have been preceded by exposure to a severe stressor.

With regard to the results of the current series of studies, the shock parameters employed were more severe than those used in studies reporting stressor-induced increases in drug self-administration or ICSS but less severe than those used in studies reporting decreased responding for ICSS (Bowers, Zacharko & Anisman, 1987; Kasian, Zacharko & Anisman, 1987; Zacharko, Bowers & Anisman, 1984). These results suggest that appetitive responding is insensitive to stressors of intermediate severity. Despite this, responding to aversive stimuli was disrupted by the same stressors.

**Strain Comparisons**

The results of Experiment 5 indicated that the more reactive Sprague-Dawley rats differed from the Long-Evans rats and that the pattern of differences was consistent with the effects of stressors. Specifically, Sprague-Dawley rats exhibited a larger taste neophobia, enhanced amphetamine CTA, and less novelty-induced locomotion. A similar pattern of results has been previously reported for stress-resistant and stress non-resistant rats (Ismailova, Gasanov, Semenova, Gromova & Fast, 1992). Saccharin consumption following initial neophobia testing did not differ between strains as it did not differ between stressed and non-stressed animals. The emergence latency confirmed that Sprague-Dawley rats are more fearful or anxious than the Long-Evans rats. These results, therefore, indicate that exposure to stressors can produce alterations in behavioral responsiveness that are similar to those seen in strains with inherent differences in reactivity to novel stimuli. As such, these results provide some validation for the hypothesis that stressors influence responding to aversive and novel stimuli by enhancing reactivity to aversive stimuli. These strain differences also suggest that other inherent group differences such as gender, age, etc, may be useful tools in validating hypotheses about the impact of stressors on reactivity to aversive and appetitive stimuli.

Furthermore, the clear differences that we detected between Long-Evans and Sprague-Dawley rats indicate that caution must be exerted when making generalizations between these commonly used rats.

**Role of Amygdala in Mediating Stressor Effects**

Although it was not the intention of the current work to assess the biochemical mechanisms that may mediate the differential sensitivity of aversive and appetitive stimuli to stressors, there is some evidence to suggest that stress-induced alterations in amygdaloid function may mediate the effects of stressors on aversively-motivated behaviors. Indeed, it has been previously suggested that the amygdala is involved in the integration of sensory information into emotional memory (LeDoux, 1993). For instance, stressors have been shown to increase single unit activity (Feenstra, Kalsbeek & van Galen, 1992; Tanaka et al., 1982) as well as increase both dopamine and norepinephrine turnover in the amygdala (Feenstra, Kalsbeek & van Galen, 1992; Tanaka et al., 1982). Moreover, lesions of the amygdala attenuate both novelty-induced and shock-induced increases in dopamine activity in the prefrontal cortex (Davis et al., 1994) and also impair the acquisition and retention of aversively-motivated behaviors such as inhibitory avoidance (Davis, 1992; Liang et al., 1982; Skinner, 1991), acoustic startle (Davis, 1989; Hitchcock, Sananes & Davis, 1989) and conditioned emotional responses (Miller & Grahame, 1991). Given that disrupting amygdala function with lesions impairs aversively-motivated behaviors and that stressors enhance amygdala activity, it would be expected that stressors would enhance or potentiate aversively-motivated behaviors including the aversive response to reward reduction. In fact, it has been shown that reducing amygdala function by injecting lidocaine directly into the amygdala eliminated the response to reward reduction in the runway (Salinas, Packard & McGaugh, 1993) and lesions of the amygdala eliminate consummatory negative

contrast (i.e., reductions in the quality of reinforcers) in a sucrose consumption paradigm (Becker, Jarvis, Wagner & Flaherty, 1984). It has also been suggested that the attenuation of behavioral contrast (a paradigm in which changes in one of two concurrent reinforcement schedules produces effects similar to reward reduction) by amygdala lesions is mediated by the lesion-induced attenuation in the aversive response to the change in the reinforcement schedule (Henke, Allen & Davison, 1972). Based upon these lines of evidence, we proposed that the shock-induced enhancement in the response to reward reduction observed is mediated by such a stress-induced enhancement in amygdala activity.

There is some indication that shock-induced enhancements of saccharin neophobia and amphetamine CTA may also involve amygdala function. For instance, it has been shown that amygdala lesions attenuate taste neophobia and apomorphine-induced CTA (Kesner, Berman & Tardif, 1992). Moreover, similar to the shock-induced enhancement in amphetamine CTA observed in Experiment 1b, shock also facilitates apomorphine CTA (Lasiter & Braun, 1981). These results suggest that the stress-induced enhancements in taste neophobia and amphetamine CTA reported in the present studies may be mediated by the effects of stressors on amygdala function. Such an hypothesis would permit the integration of amygdala lesion studies on reward reduction, behavioral contrast, taste neophobia and apomorphine CTA with the results reported here showing that shock enhanced taste neophobia, amphetamine-CTA, and the response to reward reduction. Moreover, this would also permit incorporation of studies showing that stressors increase single unit activity, and increase NE and

dopamine activity in the amygdala. Accordingly, it is proposed that the enhancements in responsiveness to both novel and aversive stimuli are mediated by amygdala function.

**Conclusions**

The results of the studies reported here indicate that responses to aversive stimuli are more sensitive to the effects of stressors than are responses to appetitive stimuli. These results have implications for appetitively-motivated behaviors where procedural factors (e.g., extinction) may generate subtle aversive stimuli. The results indicate that tests involving the assessment of stressors effects in appetitively-motivated behaviors must take into consideration that enhanced responsiveness to aversive stimuli may be responsible for some behavioral results and that altered responsiveness to appetitive stimuli may be secondary to heightened sensitivity to aversive stimuli. Responses to novel stimuli illustrate the utility of taking into consideration both aversive and appetitive components and that stressors alter responses primarily to the aversive component.

The results also have implications for both the etiology and treatment of stress-related pathologies in humans. For instance, our findings suggest that stress-related pathologies may be the result of sensitized responsiveness of aversive life events and may have relatively little to do with blunted responsiveness to positive events or stimuli. Therapeutic approaches would then be based upon developing strategies to minimize exaggerated responsiveness to aversive events.

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# APPENDIX A: Analysis Tables for Experiment 1A

## Analysis of Variance on Baseline Water Intake

| Source of Variation | Sum of Squares | DF | Mean Square | F | Signif of F |
|---|---|---|---|---|---|
| Main Effects | 15.759 | 2 | 7.880 | 2.874 | .073 |
| SHOCK | 9.116 | 1 | 9.116 | 3.325 | .079 |
| Amphet | 6.130 | 1 | 6.130 | 2.236 | .146 |
| 2-way Interactions | 7.133 | 1 | 7.133 | 2.601 | .118 |
| SHOCK Amphet | 7.133 | 1 | 7.133 | 2.601 | .118 |
| Explained | 22.892 | 3 | 7.631 | 2.783 | .059 |
| Residual | 79.517 | 29 | 2.742 | | |
| Total | 102.409 | 32 | 3.200 | | |

## Analysis of Variance on Water Intake on Days Between Saccharin Tests

Between-Subjects Effects.

Tests of Significance for T1 using UNIQUE sums of squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 461.39 | 28 | 16.48 | | |
| SHOCK | .16 | 1 | .16 | .01 | .922 |
| Amphet | 21.49 | 1 | 21.49 | 1.30 | .263 |
| SHOCK BY Amphet | 1.70 | 1 | 1.70 | .10 | .751 |

Tests involving 'DAYS' Within-Subject Effect.

Mauchly sphericity test, W = .07283
Chi-square approx. = 68.37275 with 14 D. F.
Significance = .000
Greenhouse-Geisser Epsilon = .43951
Huynh-Feldt Epsilon = .52958
Lower-bound Epsilon = .20000

Tests involving 'DAYS' Within-Subject Effect.

AVERAGED Tests of Significance for MEAS.1 using UNIQUE sums of squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1294.56 | 140 | 9.25 | | |
| DAYS | 414.06 | 5 | 82.81 | 8.96 | .000 |
| SHOCK BY DAYS | 48.05 | 5 | 9.61 | 1.04 | .397 |
| Amphet BY DAYS | 81.65 | 5 | 16.33 | 1.77 | .124 |
| SHOCK BY Amphet BY DAYS | 31.99 | 5 | 6.40 | .69 | .630 |

## Analysis of Covariance on Saccharin Intake from PD2 to Ext4.

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 623.62 | 28 | 22.27 | | |
| REGRESSION | 34.14 | 1 | 34.14 | 1.53 | .226 |
| CONSTANT | 35877.00 | 1 | 35877.00 | 1610.86 | .000 |
| SHOCK | 1.95 | 1 | 1.95 | .09 | .770 |
| Amphet | 1002.91 | 1 | 1002.91 | 45.03 | .000 |
| SHOCK BY Amphet | 34.64 | 1 | 34.64 | 1.56 | .223 |

Tests involving 'DAYS' Within-Subject Effect.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1258.84 | 116 | 10.85 | | |
| DAYS | 458.69 | 4 | 114.67 | 10.57 | .000 |
| SHOCK BY DAYS | 54.51 | 4 | 13.63 | 1.26 | .291 |
| Amphet BY DAYS | 246.01 | 4 | 61.50 | 5.67 | .000 |
| SHOCK BY Amphet BY DAYS | 12.40 | 4 | 3.10 | .29 | .887 |

## Simple-Effect Tests for Amphetamine at Each Test Day

Test Day = PD2

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 415.45 | 28 | 14.84 | | |
| REGRESSION | 19.36 | 1 | 19.36 | 1.30 | .263 |
| Amphet | 235.82 | 1 | 235.82 | 15.89 | .000 |

Test Day = Ext1

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 366.85 | 28 | 13.10 | | |
| REGRESSION | 12.29 | 1 | 12.29 | .94 | .341 |
| Amphet | 591.02 | 1 | 591.02 | 45.11 | .000 |

Test Day = Ext2

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 364.33 | 28 | 13.01 | | |
| REGRESSION | 22.10 | 1 | 22.10 | 1.70 | .203 |
| Amphet | 331.94 | 1 | 331.94 | 25.51 | .000 |

Test Day = Ext3

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 259.73 | 28 | 9.28 | | |
| REGRESSION | 1.20 | 1 | 1.20 | .13 | .722 |
| Amphet | 52.37 | 1 | 52.37 | 5.65 | .025 |

Test Day = Ext4
Tests of Significance for T5 using UNIQUE sums of squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 452.88 | 28 | 16.17 | | |
| REGRESSION | 2.41 | 1 | 2.41 | .15 | .702 |
| Amphet | 27.31 | 1 | 27.31 | 1.69 | .204 |

# APPENDIX B: Analysis Tables for Experiment 1B

## Analysis of Variance on Baseline Water Intake and Water Intake on Shock Days

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 294.88 | 23 | 12.82 | | |
| CONSTANT | 24056.49 | 1 | 24056.49 | 1876.38 | .000 |
| SHOCK | .12 | 1 | .12 | .01 | .924 |
| CTADRUG | 8.55 | 1 | 8.55 | .67 | .423 |
| SHOCK BY CTADRUG | 1.66 | 1 | 1.66 | .13 | .722 |

Tests involving 'DAYS' Within-Subject Effect.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 195.54 | 46 | 4.25 | | |
| DAYS | 130.71 | 2 | 65.36 | 15.37 | .000 |
| SHOCK BY DAYS | 8.88 | 2 | 4.44 | 1.04 | .360 |
| CTADRUG BY DAYS | 7.68 | 2 | 3.84 | .90 | .412 |
| SHOCK BY CTADRUG BY DAYS | .14 | 2 | .07 | .02 | .983 |

## Analysis of Variance on Water Intake on Days Between Saccharin Tests

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 406.73 | 23 | 17.68 | | |
| CONSTANT | 48453.51 | 1 | 48453.51 | 2739.96 | .000 |
| SHOCK | 20.51 | 1 | 20.51 | 1.16 | .293 |
| CTADRUG | 33.44 | 1 | 33.44 | 1.89 | .182 |
| SHOCK BY CTADRUG | .29 | 1 | .29 | .02 | .900 |

EFFECT .. SHOCK BY CTADRUG BY DAYS
Multivariate Tests of Significance (S = 1, M = 1 1/2, N = 8 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .70371 | 1.59997 | 5.00 | 19.00 | .208 |

EFFECT .. CTADRUG BY DAYS
Multivariate Tests of Significance (S = 1, M = 1 1/2, N = 8 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .45619 | 4.52990 | 5.00 | 19.00 | .007 |

EFFECT .. SHOCK BY DAYS
Multivariate Tests of Significance (S = 1, M = 1 1/2, N = 8 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .40240 | 5.64334 | 5.00 | 19.00 | .002 |

EFFECT .. DAYS
Multivariate Tests of Significance (S = 1, M = 1 1/2, N = 8 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .30569 | 8.63109 | 5.00 | 19.00 | .000 |

Tests involving 'DAYS' Within-Subject Effect.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 573.39 | 115 | 4.99 | | |
| DAYS | 128.00 | 5 | 25.60 | 5.13 | .000 |
| SHOCK BY DAYS | 36.51 | 5 | 7.30 | 1.46 | .207 |
| CTADRUG BY DAYS | 41.35 | 5 | 8.27 | 1.66 | .150 |
| SHOCK BY CTADRUG BY DAYS | 29.89 | 5 | 5.98 | 1.20 | .314 |

## Analysis of Variance on PD1 Saccharin Intake

| Source of Variation | Sum of Squares | DF | Mean Square | F | Signif of F |
|---|---|---|---|---|---|
| Main Effects | 39.060 | 2 | 19.530 | 2.481 | .106 |
| SHOCK | 36.462 | 1 | 36.462 | 4.633 | .042 |
| CTADRUG | 3.281 | 1 | 3.281 | .417 | .525 |
| 2-way Interactions | .212 | 1 | .212 | .027 | .871 |
| SHOCK CTADRUG | .212 | 1 | .212 | .027 | .871 |
| Explained | 39.272 | 3 | 13.091 | 1.663 | .203 |
| Residual | 181.024 | 23 | 7.871 | | |
| Total | 220.296 | 26 | 8.473 | | |

## Analysis of Covariance on Saccharin Intake from PD2 to Ext4

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 711.18 | 22 | 32.33 | | |
| REGRESSION | 5.10 | 1 | 5.10 | .16 | .695 |
| CONSTANT | 32267.95 | 1 | 32267.95 | 998.20 | .000 |
| SHOCK | 52.80 | 1 | 52.80 | 1.63 | .215 |
| CTADRUG | 1142.83 | 1 | 1142.83 | 35.35 | .000 |
| SHOCK BY CTADRUG | 16.38 | 1 | 16.38 | .51 | .484 |

Tests involving 'DAYS' Within-Subject Effect.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 778.51 | 92 | 8.46 | | |
| DAYS | 296.32 | 4 | 74.08 | 8.75 | .000 |
| SHOCK BY DAYS | 25.55 | 4 | 6.39 | .75 | .557 |
| CTADRUG BY DAYS | 114.02 | 4 | 28.51 | 3.37 | .013 |
| SHOCK BY CTADRUG BY DAYS | 101.40 | 4 | 25.35 | 3.00 | .023 |

## Simple-effect Tests of Drug by Days Interaction

Test Day = PD2

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 175.83 | 22 | 7.99 | | |
| REGRESSION | 8.50 | 1 | 8.50 | 1.06 | .314 |
| CTADRUG | 303.99 | 1 | 303.99 | 38.04 | .000 |

Test Day = EXT1

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 350.70 | 22 | 15.94 | | |
| REGRESSION | 2.70 | 1 | 2.70 | .17 | .685 |
| CTADRUG | 377.48 | 1 | 377.48 | 23.68 | .000 |

Test Day = EXT2

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 356.80 | 22 | 16.22 | | |
| REGRESSION | 7.08 | 1 | 7.08 | .44 | .516 |
| CTADRUG | 306.26 | 1 | 306.26 | 18.88 | .000 |

Test Day = EXT3

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 298.92 | 22 | 13.59 | | |
| REGRESSION | 4.55 | 1 | 4.55 | .34 | .568 |
| CTADRUG | 252.00 | 1 | 252.00 | 18.55 | .000 |

Test Day = EXT4

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 279.14 | 22 | 12.69 | | |
| REGRESSION | 10.57 | 1 | 10.57 | .83 | .371 |
| CTADRUG | 54.43 | 1 | 54.43 | 4.29 | .050 |

## Simple-simple Effects of Shock by Drug by Days Interaction

Test Day = PD2

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 175.83 | 22 | 7.99 | | |
| REGRESSION | 8.50 | 1 | 8.50 | 1.06 | .314 |
| CTADRUG BY SHOCK | 74.62 | 1 | 74.62 | 9.34 | .006 |

Test Day = Ext1

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 350.70 | 22 | 15.94 | | |
| REGRESSION | 2.70 | 1 | 2.70 | .17 | .685 |
| CTADRUG BY SHOCK | 19.51 | 1 | 19.51 | 1.22 | .281 |

Test Day = Ext2

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 356.80 | 22 | 16.22 | | |
| REGRESSION | 7.08 | 1 | 7.08 | .44 | .516 |
| CTADRUG BY SHOCK | 24.10 | 1 | 24.10 | 1.49 | .236 |

Test Day = Ext3

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 298.92 | 22 | 13.59 | | |
| REGRESSION | 4.55 | 1 | 4.55 | .34 | .568 |
| CTADRUG BY SHOCK | 38.21 | 1 | 38.21 | 2.81 | .108 |

Test Day = Ext4

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 279.14 | 22 | 12.69 | | |
| REGRESSION | 10.57 | 1 | 10.57 | .83 | .371 |
| CTADRUG BY SHOCK | 8.42 | 1 | 8.42 | .66 | .424 |

## Simple-simple Effects of Drug for Both Shock and No-Shock Groups

Test Day = PD2
Tests of Significance for T1 using UNIQUE sums of squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 175.83 | 22 | 7.99 | | |
| REGRESSION | 8.50 | 1 | 8.50 | 1.06 | .314 |
| CTADRUG WITHIN NOSHOCK | 47.57 | 1 | 47.57 | 5.95 | .023 |
| CTADRUG WITHIN SHOCK | 302.70 | 1 | 302.70 | 37.87 | .000 |

Test Day = Ext1
Tests of Significance for T2 using UNIQUE sums of squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 350.70 | 22 | 15.94 | | |
| REGRESSION | 2.70 | 1 | 2.70 | .17 | .685 |
| CTADRUG WITHIN NOSHOCK | 331.94 | 1 | 331.94 | 20.82 | .000 |
| CTADRUG WITHIN SHOCK | 103.19 | 1 | 103.19 | 6.47 | .018 |

Test Day = Ext2
Tests of Significance for T3 using UNIQUE sums of squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 356.80 | 22 | 16.22 | | |
| REGRESSION | 7.08 | 1 | 7.08 | .44 | .516 |
| CTADRUG WITHIN NOSHOCK | 94.95 | 1 | 94.95 | 5.85 | .024 |
| CTADRUG WITHIN SHOCK | 224.73 | 1 | 224.73 | 13.86 | .001 |

Test Day = Ext3
Tests of Significance for T4 using UNIQUE sums of squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 298.92 | 22 | 13.59 | | |
| REGRESSION | 4.55 | 1 | 4.55 | .34 | .568 |
| CTADRUG WITHIN NOSHOCK | 56.89 | 1 | 56.89 | 4.19 | .053 |
| CTADRUG WITHIN SHOCK | 217.11 | 1 | 217.11 | 15.98 | .001 |

Test Day = Ext4

Tests of Significance for T5 using UNIQUE sums of squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 279.14 | 22 | 12.69 | | |
| REGRESSION | 10.57 | 1 | 10.57 | .83 | .371 |
| CTADRUG WITHIN NOSHOCK | 12.14 | 1 | 12.14 | .96 | .339 |
| CTADRUG WITHIN SHOCK | 47.16 | 1 | 47.16 | 3.72 | .067 |

# APPENDIX C: Analysis Tables for Experiment 1C

## Analysis of Variance on Open-field Locomotion

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 10189.67 | 29 | 351.37 | | |
| CONSTANT | 114813.10 | 1 | 114813.10 | 326.76 | .000 |
| SHOCK | 1089.11 | 1 | 1089.11 | 3.10 | .089 |
| LOCDRUG | 3840.52 | 1 | 3840.52 | 10.93 | .003 |
| CTADRUG | 938.58 | 1 | 938.58 | 2.67 | .113 |
| SHOCK BY LOCDRUG | 139.99 | 1 | 139.99 | .40 | .533 |
| SHOCK BY CTADRUG | 1176.28 | 1 | 1176.28 | 3.35 | .078 |
| LOCDRUG BY CTADRUG | 40.73 | 1 | 40.73 | .12 | .736 |
| SHOCK BY LOCDRUG BY CTADRUG | 38.76 | 1 | 38.76 | .11 | .742 |

Mauchly sphericity test, W = .21007
Chi-square approx. = 42.77846 with 9 D. F.
Significance = .000
Greenhouse-Geisser Epsilon = .55089
Huynh-Feldt Epsilon = .74199
Lower-bound Epsilon = .25000

EFFECT .. SHOCK BY LOCDRUG BY CTADRUG BY TIME
Multivariate Tests of Significance (S = 1, M = 1 , N = 12 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .76865 | 1.95635 | 4.00 | 26.00 | .131 |

EFFECT .. LOCDRUG BY CTADRUG BY TIME
Multivariate Tests of Significance (S = 1, M = 1 , N = 12 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .93115 | .48060 | 4.00 | 26.00 | .750 |

EFFECT .. SHOCK BY CTADRUG BY TIME
Multivariate Tests of Significance (S = 1, M = 1 , N = 12 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .71853 | 2.54620 | 4.00 | 26.00 | .063 |

EFFECT .. SHOCK BY LOCDRUG BY TIME
Multivariate Tests of Significance (S = 1, M = 1 , N = 12 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .71330 | 2.61256 | 4.00 | 26.00 | .058 |

EFFECT .. CTADRUG BY TIME
Multivariate Tests of Significance (S = 1, M = 1 , N = 12 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .53674 | 5.61017 | 4.00 | 26.00 | .002 |

EFFECT .. LOCDRUG BY TIME
Multivariate Tests of Significance (S = 1, M = 1 , N = 12 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .42089 | 8.94365 | 4.00 | 26.00 | .000 |

EFFECT .. SHOCK BY TIME
Multivariate Tests of Significance (S = 1, M = 1 , N = 12 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .17526 | 30.58772 | 4.00 | 26.00 | .000 |

EFFECT .. TIME
Multivariate Tests of Significance (S = 1, M = 1 , N = 12 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .34292 | 12.45460 | 4.00 | 26.00 | .000 |

Tests involving 'TIME' Within-Subject Effect.
AVERAGED Tests of Significance for MEAS.1 using SEQUENTIAL Sums of Squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 5966.62 | 116 | 51.44 | | |
| TIME | 2083.56 | 4 | 520.89 | 10.13 | .000 |
| SHOCK BY TIME | 7187.83 | 4 | 1796.96 | 34.94 | .000 |
| LOCDRUG BY TIME | 699.75 | 4 | 174.94 | 3.40 | .011 |
| CTADRUG BY TIME | 574.33 | 4 | 143.58 | 2.79 | .030 |
| SHOCK BY LOCDRUG BY TIME | 435.22 | 4 | 108.80 | 2.12 | .083 |
| SHOCK BY CTADRUG BY TIME | 393.87 | 4 | 98.47 | 1.91 | .113 |
| LOCDRUG BY CTADRUG BY TIME | 46.34 | 4 | 11.59 | .23 | .924 |
| SHOCK BY LOCDRUG BY CTADRUG BY TIME | 307.95 | 4 | 76.99 | 1.50 | .208 |

## Simple-effects of Amphetamine, and Shock at each Time

Time = 2 Min
Tests of Significance for T1 using SEQUENTIAL Sums of Squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 3429.35 | 29 | 118.25 | | |
| MWITHIN TIME(1) | 31524.32 | 1 | 31524.32 | 266.58 | .000 |
| CTADRUG | 1.04 | 1 | 1.04 | .01 | .926 |
| LOCDRUG | 631.19 | 1 | 631.19 | 5.34 | .028 |
| SHOCK | 7138.01 | 1 | 7138.01 | 60.36 | .000 |

Time = 5 Min
Tests of Significance for T2 using SEQUENTIAL Sums of Squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 4413.83 | 29 | 152.20 | | |
| MWITHIN TIME(2) | 26721.59 | 1 | 26721.59 | 175.57 | .000 |
| CTADRUG | 988.84 | 1 | 988.84 | 6.50 | .016 |
| LOCDRUG | 1134.52 | 1 | 1134.52 | 7.45 | .011 |
| SHOCK | 894.05 | 1 | 894.05 | 5.87 | .022 |

Time = 10 Min
Tests of Significance for T3 using SEQUENTIAL Sums of Squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 4189.93 | 29 | 144.48 | | |
| MWITHIN TIME(3) | 25178.68 | 1 | 25178.68 | 174.27 | .000 |
| CTADRUG | 178.71 | 1 | 178.71 | 1.24 | .275 |
| LOCDRUG | 99.88 | 1 | 99.88 | .69 | .413 |
| SHOCK | 126.03 | 1 | 126.03 | .87 | .358 |

Time = 20 Min

Tests of Significance for T4 using SEQUENTIAL Sums of Squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 2324.25 | 29 | 80.15 | | |
| MWITHIN TIME(4) | 19293.41 | 1 | 19293.41 | 240.73 | .000 |
| CTADRUG | 16.02 | 1 | 16.02 | .20 | .658 |
| LOCDRUG | 449.50 | 1 | 449.50 | 5.61 | .025 |
| SHOCK BY | 118.75 | 1 | 118.75 | 1.48 | .233 |

Time = 30 Min

Tests of Significance for T5 using SEQUENTIAL Sums of Squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1798.94 | 29 | 62.03 | | |
| MWITHIN TIME(5) | 14178.66 | 1 | 14178.66 | 228.57 | .000 |
| CTADRUG | 425.83 | 1 | 425.83 | 6.86 | .014 |
| LOCDRUG | 1966.01 | 1 | 1966.01 | 31.69 | .000 |
| SHOCK | 161.74 | 1 | 161.74 | 2.61 | .117 |

# APPENDIX D: Analysis Tables for Experiment 2A

## Analysis of Variance on Deprivation Levels for Pre-shift Period

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 4460.30 | 27 | 165.20 | | |
| CONSTANT | 2769897.48 | 1 | 2769897.5 | 16767.31 | .000 |
| SHIFT | 90.92 | 1 | 90.92 | .55 | .465 |
| STRESS | 42.88 | 1 | 42.88 | .26 | .615 |
| SHIFT BY STRESS | 20.42 | 1 | 20.42 | .12 | .728 |

## Diagnostic Statistics

Mauchly sphericity test, W =2.340153E-08
Chi-square approx. = 406.51665 with 65 D. F.
Significance = .000
Greenhouse-Geisser Epsilon = .24045
Huynh-Feldt Epsilon = .29858
Lower-bound Epsilon = .09091

EFFECT .. SHIFT BY STRESS BY DAYS
Multivariate Tests of Significance (S = 1, M = 4 1/2, N = 7 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .55789 | 1.22471 | 11.00 | 17.00 | .343 |

EFFECT .. STRESS BY DAYS
Multivariate Tests of Significance (S = 1, M = 4 1/2, N = 7 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .68370 | .71498 | 11.00 | 17.00 | .710 |

EFFECT .. SHIFT BY DAYS
Multivariate Tests of Significance (S = 1, M = 4 1/2, N = 7 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .70094 | .65937 | 11.00 | 17.00 | .756 |

EFFECT .. DAYS
Multivariate Tests of Significance (S = 1, M = 4 1/2, N = 7 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .01940 | 78.11751 | 11.00 | 17.00 | .000 |

Tests involving 'DAYS' Within-Subject Effect.
AVERAGED Tests of Significance for MEAS.1 using SEQUENTIAL Sums of Squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1205.89 | 297 | 4.06 | | |
| DAYS | 1109.29 | 11 | 100.84 | 24.84 | .000 |
| SHIFT BY DAYS | 34.77 | 11 | 3.16 | .78 | .662 |
| STRESS BY DAYS | 11.21 | 11 | 1.02 | .25 | .993 |
| SHIFT BY STRESS BY DAYS | 37.36 | 11 | 3.40 | .84 | .604 |

## Analysis of Variance on Post-Shift Deprivation Levels

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 10228.88 | 27 | 378.85 | | |
| CONSTANT | 3547325.61 | 1 | 3547325.6 | 9363.47 | .000 |
| SHIFT | 1591.68 | 1 | 1591.68 | 4.20 | .050 |
| STRESS | 44.19 | 1 | 44.19 | .12 | .735 |
| SHIFT BY STRESS | 285.45 | 1 | 285.45 | .75 | .393 |

## Diagnostic Statistics

Tests involving 'DAYS' Within-Subject Effect.
Mauchly sphericity test, W =1.007662E-08
Chi-square approx. = 413.82145 with 90 D. F.
Significance = .000
Greenhouse-Geisser Epsilon = .17767
Huynh-Feldt Epsilon = .21684
Lower-bound Epsilon = .07692

EFFECT .. SHIFT BY STRESS BY DAYS
Multivariate Tests of Significance (S = 1, M = 5 1/2, N = 6 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .71693 | .45558 | 13.00 | 15.00 | .919 |

EFFECT .. STRESS BY DAYS
Multivariate Tests of Significance (S = 1, M = 5 1/2, N = 6 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .41070 | 1.65559 | 13.00 | 15.00 | .174 |

EFFECT .. SHIFT BY DAYS
Multivariate Tests of Significance (S = 1, M = 5 1/2, N = 6 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .36325 | 2.02258 | 13.00 | 15.00 | .097 |

EFFECT .. DAYS
Multivariate Tests of Significance (S = 1, M = 5 1/2, N = 6 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .04050 | 27.33856 | 13.00 | 15.00 | .000 |

Tests involving 'DAYS' Within-Subject Effect.
AVERAGED Tests of Significance for MEAS.1 using SEQUENTIAL Sums of Squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1218.60 | 351 | 3.47 | | |
| DAYS | 741.03 | 13 | 57.00 | 16.42 | .000 |
| SHIFT BY DAYS | 225.83 | 13 | 17.37 | 5.00 | .000 |
| STRESS BY DAYS | 21.02 | 13 | 1.62 | .47 | .943 |
| SHIFT BY STRESS BY DAYS | 9.77 | 13 | .75 | .22 | .998 |

## Analysis of Variance on $Log_{10}$ Transformed Post-shift Latencies

```
Univariate Homogeneity of Variance Tests

Variable .. BAS_T
Cochrans C(7,4) =                                .35105, P =  .735 (approx.)
Bartlett-Box F(3,1300) =                         .26785, P =  .849

Variable .. TBLOCK1
Cochrans C(7,4) =                                .40674, P =  .380 (approx.)
Bartlett-Box F(3,1300) =                        1.05836, P =  .366

Variable .. TBLOCK2
Cochrans C(7,4) =                                .45387, P =  .198 (approx.)
Bartlett-Box F(3,1300) =                        1.73755, P =  .157

Variable .. TBLOCK3
Cochrans C(7,4) =                                .38710, P =  .486 (approx.)
Bartlett-Box F(3,1300) =                        1.28343, P =  .279

Variable .. TBLOCK4
Cochrans C(7,4) =                                .44744, P =  .218 (approx.)
Bartlett-Box F(3,1300) =                        1.07450, P =  .359

Variable .. TBLOCK5
Cochrans C(7,4) =                                .48546, P =  .122 (approx.)
Bartlett-Box F(3,1300) =                        2.02666, P =  .108

Variable .. TBLOCK6
Cochrans C(7,4) =                                .48353, P =  .126 (approx.)
Bartlett-Box F(3,1300) =                         .99971, P =  .392

Variable .. TBLOCK7
Cochrans C(7,4) =                                .56562, P =  .028 (approx.)
Bartlett-Box F(3,1300) =                        2.65841, P =  .047
```

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 3.02 | 27 | .11 | | |
| CONSTANT | 123.43 | 1 | 123.43 | 1104.39 | .000 |
| STRESS | .01 | 1 | .01 | .07 | .796 |
| SHIFT | 3.08 | 1 | 3.08 | 27.53 | .000 |
| STRESS BY SHIFT | .75 | 1 | .75 | 6.67 | .016 |

## Diagnistic Statistics

```
Tests involving 'BLOCKS' Within-Subject Effect.
Mauchly sphericity test, W =       .13986
Chi-square approx. =             48.10048 with 27 D. F.
Significance =                       .007
Greenhouse-Geisser Epsilon =       .61821
Huynh-Feldt Epsilon =              .83267
Lower-bound Epsilon =              .14286

EFFECT .. STRESS BY SHIFT BY BLOCKS
Multivariate Tests of Significance (S = 1, M = 2 1/2, N = 9 1/2)
```

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .64709 | 1.63617 | 7.00 | 21.00 | .180 |

EFFECT .. SHIFT BY BLOCKS

Multivariate Tests of Significance (S = 1, M = 2 1/2, N = 9 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .35891 | 5.35863 | 7.00 | 21.00 | .001 |

EFFECT .. STRESS BY BLOCKS

Multivariate Tests of Significance (S = 1, M = 2 1/2, N = 9 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .67370 | 1.45302 | 7.00 | 21.00 | .237 |

EFFECT .. BLOCKS

Multivariate Tests of Significance (S = 1, M = 2 1/2, N = 9 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .21805 | 10.75814 | 7.00 | 21.00 | .000 |

Tests involving 'BLOCKS' Within-Subject Effect.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 6.64 | 189 | .04 | | |
| BLOCKS | 1.23 | 7 | .18 | 4.99 | .000 |
| STRESS BY BLOCKS | .24 | 7 | .03 | .98 | .449 |
| SHIFT BY BLOCKS | .70 | 7 | .10 | 2.85 | .008 |
| STRESS BY SHIFT BY BLOCKS | .28 | 7 | .04 | 1.13 | .349 |

## Simple-effects of Shift Condition over Post-shift Blocks

Test Day = Baseline

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | .43 | 27 | .02 | | |
| SHIFT | .00 | 1 | .00 | .01 | .904 |
| STRESS | .00 | 1 | .00 | .30 | .585 |
| SHIFT BY STRESS | .00 | 1 | .00 | .16 | .688 |

Test Day = Block 1

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 2.14 | 27 | .08 | | |
| SHIFT | .36 | 1 | .36 | 4.50 | .043 |
| STRESS | .01 | 1 | .01 | .18 | .677 |
| SHIFT BY STRESS | .01 | 1 | .01 | .14 | .716 |

Test Day = Block 2

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1.76 | 27 | .07 | | |
| MWITHIN BLOCKS(3) | 19.06 | 1 | 19.06 | 291.59 | .000 |
| SHIFT | .79 | 1 | .79 | 12.02 | .002 |
| STRESS | .00 | 1 | .00 | .05 | .830 |
| SHIFT BY STRESS | .09 | 1 | .09 | 1.45 | .239 |

Test Day = Block 3

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1.11 | 27 | .04 | | |
| SHIFT | .62 | 1 | .62 | 15.05 | .001 |
| STRESS | .02 | 1 | .02 | .59 | .448 |
| SHIFT BY STRESS | .03 | 1 | .03 | .80 | .379 |

Test Day = Block 4

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | .71 | 27 | .03 | | |
| SHIFT | .96 | 1 | .96 | 36.38 | .000 |
| STRESS | .20 | 1 | .20 | 7.68 | .010 |
| SHIFT BY STRESS | .38 | 1 | .38 | 14.61 | .001 |

Test Day = Block 5

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1.42 | 27 | .05 | | |
| SHIFT | .64 | 1 | .64 | 12.15 | .002 |
| STRESS | .00 | 1 | .00 | .05 | .829 |
| SHIFT BY STRESS | .27 | 1 | .27 | 5.19 | .031 |

Test Day = Block 6

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | .92 | 27 | .03 | | |
| SHIFT | .23 | 1 | .23 | 6.89 | .014 |
| STRESS | .01 | 1 | .01 | .43 | .520 |
| SHIFT BY STRESS | .07 | 1 | .07 | 2.03 | .166 |

Test Day = Block 7

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1.16 | 27 | .04 | | |
| SHIFT | .16 | 1 | .16 | 3.74 | .064 |
| STRESS | .00 | 1 | .00 | .08 | .780 |
| SHIFT BY STRESS | .15 | 1 | .15 | 3.59 | .069 |

## Simple-simple Effects of Shift with Shock and No-Shock Groups

Test Day = Baseline

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | .43 | 27 | .02 | | |
| MWITHIN BLOCKS(1) | 11.27 | 1 | 11.27 | 710.44 | .000 |
| SHIFT:No-Shock | .00 | 1 | .00 | .05 | .827 |
| SHIFT:Shock | .00 | 1 | .00 | .15 | .705 |

Test Day = Block 1

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 2.14 | 27 | .08 | | |
| MWITHIN BLOCKS(2) | 18.77 | 1 | 18.77 | 237.32 | .000 |
| SHIFT:No-Shock | .12 | 1 | .12 | 1.49 | .233 |
| SHIFT:Shock | .25 | 1 | .25 | 3.13 | .088 |

Test Day = Block 2

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1.76 | 27 | .07 | | |
| MWITHIN BLOCKS(3) | 19.06 | 1 | 19.06 | 291.59 | .000 |
| SHIFT:No-Shock | .16 | 1 | .16 | 2.37 | .135 |
| SHIFT:Shock | .73 | 1 | .73 | 11.12 | .002 |

Test Day = Block 3

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1.11 | 27 | .04 | | |
| MWITHIN BLOCKS(4) | 17.57 | 1 | 17.57 | 425.82 | .000 |
| SHIFT:No-Shock | .18 | 1 | .18 | 4.30 | .048 |
| SHIFT:Shock | .47 | 1 | .47 | 11.50 | .002 |

Test Day = Block 4

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | .71 | 27 | .03 | | |
| MWITHIN BLOCKS(5) | 15.73 | 1 | 15.73 | 597.80 | .000 |
| SHIFT:No-Shock | .05 | 1 | .05 | 1.90 | .179 |
| SHIFT:Shock | 1.31 | 1 | 1.31 | 49.82 | .000 |

Test Day = Block 5

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1.42 | 27 | .05 | | |
| MWITHIN BLOCKS(6) | 16.95 | 1 | 16.95 | 321.89 | .000 |
| SHIFT:No-Shock | .03 | 1 | .03 | .61 | .442 |
| SHIFT:Shock | .88 | 1 | .88 | 16.77 | .000 |

Test Day = Block 6

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | .92 | 27 | .03 | | |
| MWITHIN BLOCKS(7) | 14.59 | 1 | 14.59 | 428.67 | .000 |
| SHIFT:No-Shock | .02 | 1 | .02 | .62 | .439 |
| SHIFT:Shock | .28 | 1 | .28 | 8.36 | .007 |

Test Day = Block 7

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1.16 | 27 | .04 | | |
| MWITHIN BLOCKS(8) | 10.72 | 1 | 10.72 | 248.83 | .000 |
| SHIFT:No-Shock | .00 | 1 | .00 | .00 | .993 |
| SHIFT:Shock | .31 | 1 | .31 | 7.29 | .012 |

Simple-simple Effects of Shock Within Unshifted and Shifted Groups

Test Day = Baseline

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | .43 | 27 | .02 | | |
| MWITHIN BLOCKS(1) | 11.27 | 1 | 11.27 | 710.44 | .000 |
| STRESS:UNSHIFT | .00 | 1 | .00 | .01 | .932 |
| STRESS:SHIFT | .01 | 1 | .01 | .46 | .503 |

Test Day = Block 1

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 2.14 | 27 | .08 | | |
| MWITHIN BLOCKS(2) | 18.77 | 1 | 18.77 | 237.32 | .000 |
| STRESS:UNSHIFT | .03 | 1 | .03 | .43 | .516 |
| STRESS:SHIFT | .00 | 1 | .00 | .00 | .963 |

Test Day = Block 2

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1.76 | 27 | .07 | | |
| MWITHIN BLOCKS(3) | 19.06 | 1 | 19.06 | 291.59 | .000 |
| STRESS:UNSHIFT | .05 | 1 | .05 | .77 | .386 |
| STRESS:SHIFT | .06 | 1 | .06 | .99 | .330 |

Test Day = Block 3

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1.11 | 27 | .04 | | |
| MWITHIN BLOCKS(4) | 17.57 | 1 | 17.57 | 425.82 | .000 |
| STRESS:UNSHIFT | .08 | 1 | .08 | 1.86 | .184 |
| STRESS:SHIFT | .00 | 1 | .00 | .00 | .947 |

Test Day = Block 4

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | .71 | 27 | .03 | | |
| MWITHIN BLOCKS(5) | 15.73 | 1 | 15.73 | 597.80 | .000 |
| STRESS:UNSHIFT | .03 | 1 | .03 | 1.24 | .276 |
| STRESS:SHIFT | .57 | 1 | .57 | 21.61 | .000 |

Test Day = Block 5

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1.42 | 27 | .05 | | |
| MWITHIN BLOCKS(6) | 16.95 | 1 | 16.95 | 321.89 | .000 |
| STRESS:UNSHIFT | .14 | 1 | .14 | 2.73 | .110 |
| STRESS:SHIFT | .16 | 1 | .16 | 3.03 | .093 |

Test Day = Block 6

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | .92 | 27 | .03 | | |
| MWITHIN BLOCKS(7) | 14.59 | 1 | 14.59 | 428.67 | .000 |
| STRESS:UNSHIFT | .02 | 1 | .02 | .48 | .492 |
| STRESS:SHIFT | .07 | 1 | .07 | 2.13 | .156 |

Test Day = Block 7

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1.16 | 27 | .04 | | |
| MWITHIN BLOCKS(8) | 10.72 | 1 | 10.72 | 248.83 | .000 |
| STRESS:UNSHIFT | .12 | 1 | .12 | 2.72 | .111 |
| STRESS:SHIFT | .05 | 1 | .05 | 1.24 | .275 |

## Analysis of Variance on Open-Field Locomotion

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 4731.91 | 27 | 175.26 | | |
| CONSTANT | 98241.28 | 1 | 98241.28 | 560.56 | .000 |
| STRESS | 268.55 | 1 | 268.55 | 1.53 | .226 |
| SHIFT | 11.86 | 1 | 11.86 | .07 | .797 |
| STRESS BY SHIFT | .33 | 1 | .33 | .00 | .966 |

Diagnostic Statistics
Tests involving 'TIME' Within-Subject Effect.

| | |
|---|---|
| Mauchly sphericity test, W = | .28319 |
| Chi-square approx. = | 32.06701 with 9 D. F. |
| Significance = | .000 |
| Greenhouse-Geisser Epsilon = | .66547 |
| Huynh-Feldt Epsilon = | .82708 |
| Lower-bound Epsilon = | .25000 |

EFFECT .. STRESS BY SHIFT BY TIME
Multivariate Tests of Significance (S = 1, M = 1 , N = 11 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .83808 | 1.15919 | 4.00 | 24.00 | .353 |

EFFECT .. SHIFT BY TIME
Multivariate Tests of Significance (S = 1, M = 1 , N = 11 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .73822 | 2.12765 | 4.00 | 24.00 | .108 |

EFFECT .. STRESS BY TIME
Multivariate Tests of Significance (S = 1, M = 1 , N = 11 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .50470 | 5.88821 | 4.00 | 24.00 | .002 |

EFFECT .. TIME
Multivariate Tests of Significance (S = 1, M = 1 , N = 11 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .18352 | 26.69433 | 4.00 | 24.00 | .000 |

Tests involving 'TIME' Within-Subject Effect.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 6210.23 | 108 | 57.50 | | |
| TIME | 4923.43 | 4 | 1230.86 | 21.41 | .000 |
| STRESS BY TIME | 1760.55 | 4 | 440.14 | 7.65 | .000 |
| SHIFT BY TIME | 498.56 | 4 | 124.64 | 2.17 | .077 |
| STRESS BY SHIFT BY TIME | 412.02 | 4 | 103.00 | 1.79 | .136 |

## Simple-effects of Shock at each Time Block

Time = 2 Min

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 3679.02 | 27 | 136.26 | | |
| MWITHIN TIME(1) | 24113.42 | 1 | 24113.42 | 176.97 | .000 |
| STRESS | 639.13 | 1 | 1639.13 | 12.03 | .002 |
| SHIFT | 238.04 | 1 | 238.04 | 1.75 | .197 |

Time = 5 Min

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 2699.24 | 27 | 99.97 | | |
| MWITHIN TIME(2) | 28016.52 | 1 | 28016.52 | 280.24 | .000 |
| STRESS | 104.14 | 1 | 104.14 | 1.04 | .316 |
| SHIFT | 53.42 | 1 | 53.42 | .53 | .471 |

Time = 10 min

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1844.26 | 27 | 68.31 | | |
| MWITHIN TIME(3) | 28819.45 | 1 | 28819.45 | 421.92 | .000 |
| STRESS | 256.41 | 1 | 256.41 | 3.75 | .063 |
| SHIFT | 8.19 | 1 | 8.19 | .12 | .732 |

Time = 20 Min

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 994.86 | 27 | 36.85 | | |
| MWITHIN TIME(4) | 14381.40 | 1 | 14381.40 | 390.30 | .000 |
| STRESS | 7.42 | 1 | 7.42 | .20 | .657 |
| SHIFT | 25.83 | 1 | 25.83 | .70 | .410 |

Time = 30 Min

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1724.77 | 27 | 63.88 | | |
| MWITHIN TIME(5) | 7833.93 | 1 | 7833.93 | 122.63 | .000 |
| STRESS | 21.99 | 1 | 21.99 | .34 | .562 |
| SHIFT | 184.93 | 1 | 184.93 | 2.89 | .100 |

Contrast Interaction Tests of Shift Effect in Shocked or No-Shock groups

Time = Min

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 3679.02 | 27 | 136.26 | | |
| MWITHIN TIME(1) | 24113.42 | 1 | 24113.42 | 176.97 | .000 |
| STRESS:UNSHIFT | 285.67 | 1 | 285.67 | 2.10 | .159 |
| STRESS:SHIFT | 1598.20 | 1 | 1598.20 | 11.73 | .002 |

Time = 5 Min

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 2699.24 | 27 | 99.97 | | |
| MWITHIN TIME(2) | 28016.52 | 1 | 28016.52 | 280.24 | .000 |
| STRESS:UNSHIFT | 12.59 | 1 | 12.59 | .13 | .725 |
| STRESS:SHIFT | 115.89 | 1 | 115.89 | 1.16 | .291 |

Time = 10 Min

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1844.26 | 27 | 68.31 | | |
| MWITHIN TIME(3) | 28819.45 | 1 | 28819.45 | 421.92 | .000 |
| STRESS:UNSHIFT | 34.46 | 1 | 34.46 | .50 | .484 |
| STRESS:SHIFT | 275.56 | 1 | 275.56 | 4.03 | .055 |

Time = 20 Min

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 994.86 | 27 | 36.85 | | |
| MWITHIN TIME(4) | 14381.40 | 1 | 14381.40 | 390.30 | .000 |
| STRESS:UNSHIFT | 15.31 | 1 | 15.31 | .42 | .525 |
| STRESS:SHIFT | 57.38 | 1 | 57.38 | 1.56 | .223 |

Time = 30 Min

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1724.77 | 27 | 63.88 | | |
| MWITHIN TIME(5) | 7833.93 | 1 | 7833.93 | 122.63 | .000 |
| STRESS:UNSHIFT | 65.44 | 1 | 65.44 | 1.02 | .320 |
| STRESS:SHIFT | 1.69 | 1 | 1.69 | .03 | .872 |

# APPENDIX E: Analysis Tables for Experiment 2B

## Analysis of Variance on Transformed Acquistion Latencies

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 9.71 | 28 | .35 | | |
| CONSTANT | 449.28 | 1 | 449.28 | 1295.96 | .000 |
| SHIFT | .01 | 1 | .01 | .03 | .875 |
| STRESS | .01 | 1 | .01 | .02 | .888 |
| SHIFT BY STRESS | .23 | 1 | .23 | .65 | .425 |

## Diagnostic Statistics

Tests involving 'BLOCKS' Within-Subject Effect.
Mauchly sphericity test, W = .04361
Chi-square approx. = 77.67279 with 44 D. F.
Significance = .001
Greenhouse-Geisser Epsilon = .55376
Huynh-Feldt Epsilon = .76025
Lower-bound Epsilon = .11111

EFFECT .. SHIFT BY STRESS BY BLOCKS
Multivariate Tests of Significance (S = 1, M = 3 1/2, N = 9 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .57123 | 1.66801 | 9.00 | 20.00 | .163 |

EFFECT .. STRESS BY BLOCKS
Multivariate Tests of Significance (S = 1, M = 3 1/2, N = 9 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .78243 | .61793 | 9.00 | 20.00 | .768 |

EFFECT .. SHIFT BY BLOCKS
Multivariate Tests of Significance (S = 1, M = 3 1/2, N = 9 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .70638 | .92370 | 9.00 | 20.00 | .526 |

EFFECT .. BLOCKS
Multivariate Tests of Significance (S = 1, M = 3 1/2, N = 9 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .17845 | 10.23067 | 9.00 | 20.00 | .000 |

Tests involving 'BLOCKS' Within-Subject Effect.
AVERAGED Tests of Significance for T_BAS using UNIQUE sums of squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 15.12 | 252 | .06 | | |
| BLOCKS | 15.18 | 9 | 1.69 | 28.11 | .000 |
| SHIFT BY BLOCKS | .37 | 9 | .04 | .69 | .719 |
| STRESS BY BLOCKS | .27 | 9 | .03 | .50 | .876 |
| SHIFT BY STRESS BY BLOCKS | .54 | 9 | .06 | 1.00 | .438 |

## Analysis of Variance on $Log_{10}$ Transformed Post-shift Latencies

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 4.09 | 28 | .15 | | |
| CONSTANT | 165.45 | 1 | 165.45 | 1133.12 | .000 |
| SHIFT | 1.09 | 1 | 1.09 | 7.49 | .011 |
| STRESS | .23 | 1 | .23 | 1.54 | .225 |
| SHIFT BY STRESS | .03 | 1 | .03 | .23 | .634 |

## Diagnostic Statistics

Tests involving 'BLOCKS' Within-Subject Effect.
Mauchly sphericity test, W = .17979
Chi-square approx. = 43.67582 with 27 D. F.
Significance = .022
Greenhouse-Geisser Epsilon = .67855
Huynh-Feldt Epsilon = .92162
Lower-bound Epsilon = .14286

EFFECT .. SHIFT BY STRESS BY BLOCKS
Multivariate Tests of Significance (S = 1, M = 2 1/2, N = 10 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .79691 | .80093 | 7.00 | 22.00 | .595 |

EFFECT .. STRESS BY BLOCKS
Multivariate Tests of Significance (S = 1, M = 2 1/2, N = 10 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .57903 | 2.28492 | 7.00 | 22.00 | .066 |

EFFECT .. SHIFT BY BLOCKS
Multivariate Tests of Significance (S = 1, M = 2 1/2, N = 10 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .68488 | 1.44604 | 7.00 | 22.00 | .238 |

EFFECT .. BLOCKS
Multivariate Tests of Significance (S = 1, M = 2 1/2, N = 10 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .16686 | 15.69230 | 7.00 | 22.00 | .000 |

Tests involving 'BLOCKS' Within-Subject Effect.
AVERAGED Tests of Significance for MEAS.1 using UNIQUE sums of squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 5.91 | 196 | .03 | | |
| BLOCKS | 4.79 | 7 | .68 | 22.71 | .000 |
| SHIFT BY BLOCKS | .46 | 7 | .07 | 2.18 | .037 |
| STRESS BY BLOCKS | .46 | 7 | .07 | 2.16 | .039 |
| SHIFT BY STRESS BY BLOCKS | .13 | 7 | .02 | .64 | .726 |

## Simple-effects Analysis of Shift Effect and Shock Effect at each Post-Shift Trial Block

Test Day =Baseline

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1.07 | 28 | .04 | | |
| MWITHIN BLOCKS(1) | 36.23 | 1 | 36.23 | 949.36 | .000 |
| SHIFT | .00 | 1 | .00 | .01 | .921 |
| STRESS | .00 | 1 | .00 | .06 | .816 |

Test Day = Block 1

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1.65 | 28 | .06 | | |
| MWITHIN BLOCKS(2) | 30.87 | 1 | 30.87 | 522.38 | .000 |
| SHIFT | .00 | 1 | .00 | .07 | .800 |
| STRESS | .14 | 1 | .14 | 2.37 | .135 |

Test Day = Block 2

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1.12 | 28 | .04 | | |
| MWITHIN BLOCKS(3) | 17.96 | 1 | 17.96 | 449.06 | .000 |
| SHIFT | .07 | 1 | .07 | 1.86 | .184 |
| STRESS | .02 | 1 | .02 | .57 | .458 |

Test Day = Block 3

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | .92 | 28 | .03 | | |
| MWITHIN BLOCKS(4) | 19.28 | 1 | 19.28 | 583.77 | .000 |
| SHIFT | .09 | 1 | .09 | 2.76 | .108 |
| STRESS | .07 | 1 | .07 | 2.01 | .167 |

Test Day = Block 4

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1.89 | 28 | .07 | | |
| MWITHIN BLOCKS(5) | 20.79 | 1 | 20.79 | 307.47 | .000 |
| SHIFT | .32 | 1 | .32 | 4.77 | .037 |
| STRESS | .13 | 1 | .13 | 1.99 | .170 |

Test Day = Block 5

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1.33 | 28 | .05 | | |
| MWITHIN BLOCKS(6) | 16.85 | 1 | 16.85 | 353.49 | .000 |
| SHIFT | .46 | 1 | .46 | 9.65 | .004 |
| STRESS | .19 | 1 | .19 | 4.00 | .055 |

Test Day = Block 6

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1.14 | 28 | .04 | | |
| MWITHIN BLOCKS(7) | 13.09 | 1 | 13.09 | 320.20 | .000 |
| SHIFT | .26 | 1 | .26 | 6.37 | .018 |
| STRESS | .11 | 1 | .11 | 2.63 | .116 |

Test Day = Block 7

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | .85 | 28 | .03 | | |
| MWITHIN BLOCKS(8) | 15.16 | 1 | 15.16 | 497.49 | .000 |
| SHIFT | .34 | 1 | .34 | 11.21 | .002 |
| STRESS | .02 | 1 | .02 | .56 | .460 |

## Analysis of Variance on Locomotor Scores

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 3720.53 | 28 | 132.88 | | |
| CONSTANT | 89968.74 | 1 | 89968.74 | 677.09 | .000 |
| STRESS | 25.28 | 1 | 25.28 | .19 | .666 |
| SHIFT | 304.85 | 1 | 304.85 | 2.29 | .141 |
| STRESS BY SHIFT | 29.30 | 1 | 29.30 | .22 | .642 |

## Diagnostic Statistics

Tests involving 'TIME' Within-Subject Effect.

```
Mauchly sphericity test, W =          .21968
Chi-square approx. =                39.55694 with 14 D. F.
Significance =                          .000
Greenhouse-Geisser Epsilon =          .61552
Huynh-Feldt Epsilon =                 .77427
Lower-bound Epsilon =                 .20000
```

EFFECT .. STRESS BY SHIFT BY TIME
Multivariate Tests of Significance (S = 1, M = 1 1/2, N = 11 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .92322 | .39922 | 5.00 | 24.00 | .844 |

EFFECT .. SHIFT BY TIME
Multivariate Tests of Significance (S = 1, M = 1 1/2, N = 11 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .89958 | .53581 | 5.00 | 24.00 | .747 |

EFFECT .. STRESS BY TIME
Multivariate Tests of Significance (S = 1, M = 1 1/2, N = 11 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .81859 | 1.06373 | 5.00 | 24.00 | .405 |

EFFECT .. TIME
Multivariate Tests of Significance (S = 1, M = 1 1/2, N = 11 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .08414 | 52.24876 | 5.00 | 24.00 | .000 |

Tests involving 'TIME' Within-Subject Effect.
AVERAGED Tests of Significance for MEAS.1 using UNIQUE sums of squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 7415.59 | 140 | 52.97 | | |
| TIME | 13467.86 | 5 | 2693.57 | 50.85 | .000 |
| STRESS BY TIME | 224.12 | 5 | 44.82 | .85 | .519 |
| SHIFT BY TIME | 184.41 | 5 | 36.88 | .70 | .627 |
| STRESS BY SHIFT BY TIME | 61.95 | 5 | 12.39 | .23 | .947 |

## APPENDIX F: Analysis Tables for Experiment 3A

### Analysis of Variance on Active Lever Response Rates Blocked over 2 Days

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 397978.49 | 24 | 16582.44 | | |
| CONSTANT | 1295933.60 | 1 | 1295933.6 | 78.15 | .000 |
| TREAT | 694.91 | 1 | 694.91 | .04 | .840 |

Diagnostic Statistics
Tests involving 'BLOCKS' Within-Subject Effect.

| | |
|---|---|
| Mauchly sphericity test, W = | .00040 |
| Chi-square approx. = | 162.79799 with 44 D. F. |
| Significance = | .000 |
| Greenhouse-Geisser Epsilon = | .41931 |
| Huynh-Feldt Epsilon = | .52803 |
| Lower-bound Epsilon = | .11111 |

EFFECT .. TREAT BY BLOCKS
Multivariate Tests of Significance (S = 1, M = 3 1/2, N = 7 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .76198 | .55531 | 9.00 | 16.00 | .813 |

EFFECT .. BLOCKS
Multivariate Tests of Significance (S = 1, M = 3 1/2, N = 7 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .18852 | 7.65229 | 9.00 | 16.00 | .000 |

Tests involving 'BLOCKS' Within-Subject Effect.
AVERAGED Tests of Significance for MEAS.1 using SEQUENTIAL Sums of Squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 294979.45 | 216 | 1365.65 | | |
| BLOCKS | 208749.69 | 9 | 23194.41 | 16.98 | .000 |
| TREAT BY BLOCKS | 2989.36 | 9 | 332.15 | .24 | .988 |

### Analysis of Variance on Inactive Lever Response Rates Blocked over 2 Days

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 75982.33 | 24 | 3165.93 | | |
| CONSTANT | 99255.38 | 1 | 99255.38 | 31.35 | .000 |
| Restraint | 14500.08 | 1 | 14500.08 | 4.58 | .043 |

### Diagnostic Statistics

Tests involving 'Days' Within-Subject Effect.

| | |
|---|---|
| Mauchly sphericity test, W = | .00001 |
| Chi-square approx. = | 235.20099 with 44 D. F. |
| Significance = | .000 |
| Greenhouse-Geisser Epsilon = | .22729 |
| Huynh-Feldt Epsilon = | .25905 |
| Lower-bound Epsilon = | .11111 |

EFFECT .. Restraint BY Days
Multivariate Tests of Significance (S = 1, M = 3 1/2, N = 7 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .57983 | 1.28825 | 9.00 | 16.00 | .315 |

EFFECT .. Days
Multivariate Tests of Significance (S = 1, M = 3 1/2, N = 7 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .55453 | 1.42811 | 9.00 | 16.00 | .256 |

Tests involving 'BLOCKS' Within-Subject Effect.
AVERAGED Tests of Significance for MEAS.1 using SEQUENTIAL Sums of Squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 147796.64 | 216 | 684.24 | | |
| Days | 4519.73 | 9 | 502.19 | .73 | .678 |
| Restraint By Days | 9421.33 | 9 | 1046.81 | 1.53 | .139 |

# APPENDIX G: Analysis Tables for Experiment 3B

## Analysis of Variance on Body Weight During Restraint Period

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 63349.24 | 73 | 867.80 | | |
| CONSTANT | 30702278.32 | 1 | 30702278 | 35379.53 | .000 |
| STRESS | .61 | 1 | .61 | .00 | .979 |

## Diagnostic Statistics

Tests involving 'DAYS' Within-Subject Effect.

| | |
|---|---|
| Mauchly sphericity test, W = | .27739 |
| Chi-square approx. = | 92.32893 with 2 D. F. |
| Significance = | .000 |
| Greenhouse-Geisser Epsilon = | .58051 |
| Huynh-Feldt Epsilon = | .59214 |
| Lower-bound Epsilon = | .50000 |

EFFECT .. STRESS BY DAYS
Multivariate Tests of Significance (S = 1, M = 0, N = 35 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .98348 | .60488 | 2.00 | 72.00 | .549 |

EFFECT .. DAYS
Multivariate Tests of Significance (S = 1, M = 0, N = 35 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .02569 | 1365.32627 | 2.00 | 72.00 | .000 |

Tests involving 'DAYS' Within-Subject Effect.
AVERAGED Tests of Significance for MEAS.1 using UNIQUE sums of squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 5062.72 | 146 | 34.68 | | |
| DAYS | 177332.16 | 2 | 88666.08 | 2556.98 | .000 |
| STRESS BY DAYS | 74.29 | 2 | 37.14 | 1.07 | .345 |

## Analysis of Variance on Locomotion

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 37529.17 | 67 | 560.14 | | |
| CONSTANT | 438786.02 | 1 | 438786.02 | 783.35 | .000 |
| STRESS | 1816.79 | 1 | 1816.79 | 3.24 | .076 |
| DRUG | 12542.60 | 3 | 4180.87 | 7.46 | .000 |
| STRESS BY DRUG | 2553.00 | 3 | 851.00 | 1.52 | .218 |

## Diagnostic Statistics

Tests involving 'TIME' Within-Subject Effect.

| | |
|---|---|
| Mauchly sphericity test, W = | .16581 |
| Chi-square approx. = | 117.54891 with 9 D. F. |
| Significance = | .000 |
| Greenhouse-Geisser Epsilon = | .59390 |
| Huynh-Feldt Epsilon = | .68151 |
| Lower-bound Epsilon = | .25000 |

EFFECT .. STRESS BY DRUG BY TIME
Multivariate Tests of Significance (S = 3, M = 0, N = 31 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .74609 | 1.65474 | 12.00 | 169.62 | .081 |

EFFECT .. DRUG BY TIME
Multivariate Tests of Significance (S = 3, M = 0, N = 31 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .83156 | 1.02060 | 12.00 | 169.62 | .432 |

EFFECT .. STRESS BY TIME
Multivariate Tests of Significance (S = 1, M = 1 , N = 31 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .98217 | .29046 | 4.00 | 64.00 | .883 |

EFFECT .. TIME
Multivariate Tests of Significance (S = 1, M = 1 , N = 31 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .27837 | 41.47704 | 4.00 | 64.00 | .000 |

Tests involving 'TIME' Within-Subject Effect.
AVERAGED Tests of Significance for OF1_PM using SEQUENTIAL Sums of Squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 15061.99 | 268 | 56.20 | | |
| TIME | 20758.50 | 4 | 5189.62 | 92.34 | .000 |
| STRESS BY TIME | 45.70 | 4 | 11.43 | .20 | .936 |
| DRUG BY TIME | 1040.84 | 12 | 86.74 | 1.54 | .109 |
| STRESS BY DRUG BY TIME | 826.32 | 12 | 68.86 | 1.23 | .265 |

## Contrast-Interactions Tests of Cocaine Effect Within each Level of Restraint at each Time

Time = 2 Min

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 9554.58 | 67 | 142.61 | | |
| 5 mg/kg: No-Restraint | 1076.09 | 1 | 1076.09 | 7.55 | .008 |
| 5 mg/kg: Restraint | .72 | 1 | .72 | .01 | .944 |
| 10 mg/kg: No-Restraint | 376.91 | 1 | 376.91 | 2.64 | .109 |
| 10 mg/kg: Restraint | 249.39 | 1 | 249.39 | 1.75 | .191 |
| 20 mg/kg: No-Restraint | 2473.39 | 1 | 2473.39 | 17.34 | .000 |
| 20 mg/kg: Restraint | .89 | 1 | .89 | .01 | .937 |

Time = 5 Min

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 9193.62 | 67 | 137.22 | | |
| 5 mg/kg: No-Restraint | 388.50 | 1 | 388.50 | 2.83 | .097 |
| 5 mg/kg: Restraint | 140.05 | 1 | 140.05 | 1.02 | .316 |
| 10 mg/kg:No-Restraint | 618.18 | 1 | 618.18 | 4.51 | .037 |
| 10 mg/kg:Restraint | 826.89 | 1 | 826.89 | 6.03 | .017 |
| 20 mg/kg:No-Restraint | 1747.06 | 1 | 1747.06 | 12.73 | .001 |
| 20 mg/kg:Restraint | 152.15 | 1 | 152.15 | 1.11 | .296 |

Time = 10 Min

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 10460.96 | 67 | 156.13 | | |
| 5 mg/kg: No-Restraint | 261.06 | 1 | 261.06 | 1.67 | .200 |
| 5 mg/kg: Restraint | 292.25 | 1 | 292.25 | 1.87 | .176 |
| 10 mg/kg:No-Restraint | 262.47 | 1 | 262.47 | 1.68 | .199 |
| 10 mg/kg:Restraint | 800.00 | 1 | 800.00 | 5.12 | .027 |
| 20 mg/kg:No-Restraint | 1497.87 | 1 | 1497.87 | 9.59 | .003 |
| 20 mg/kg:Restraint | 686.97 | 1 | 686.97 | 4.40 | .040 |

Time = 20 Min

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 11742.06 | 67 | 175.25 | | |
| 5 mg/kg: No-Restraint | 359.73 | 1 | 359.73 | 2.05 | .157 |
| 5 mg/kg: Restraint | 129.08 | 1 | 129.08 | .74 | .394 |
| 10 mg/kg:No-Restraint | 378.13 | 1 | 378.13 | 2.16 | .147 |
| 10 mg/kg:Restraint | 1104.50 | 1 | 1104.50 | 6.30 | .014 |
| 20 mg/kg:No-Restraint | 2792.54 | 1 | 2792.54 | 15.93 | .000 |
| 20 mg/kg:Restraint | 1144.01 | 1 | 1144.01 | 6.53 | .013 |

Time = 30 Min

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 11639.95 | 67 | 173.73 | | |
| 5 mg/kg: No-Restraint | 284.98 | 1 | 284.98 | 1.64 | .205 |
| 5 mg/kg: Restraint | 159.98 | 1 | 159.98 | .92 | .341 |
| 10 mg/kg:No-Restraint | 416.51 | 1 | 416.51 | 2.40 | .126 |
| 10 mg/kg:Restraint | 891.83 | 1 | 891.83 | 5.13 | .027 |
| 20 mg/kg:No-Restraint | 1978.21 | 1 | 1978.21 | 11.39 | .001 |
| 20 mg/kg:Restraint | 1806.01 | 1 | 1806.01 | 10.40 | .002 |

# APPENDIX H: Analysis Tables for Experiment 3C

## Analysis of Variance on Saccharin Intake Including Open-field Cocaine Dose as a Factor

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 3746.00 | 59 | 63.49 | | |
| CONSTANT | 67824.88 | 1 | 67824.88 | 1068.25 | .000 |
| Restraint | 7.56 | 1 | 7.56 | .12 | .731 |
| Amphet | 14747.72 | 1 | 14747.72 | 232.28 | .000 |
| Cocaine | 56.03 | 3 | 18.68 | .29 | .829 |
| Restraint BY Amphet | 32.96 | 1 | 32.96 | .52 | .474 |
| Restraint BY Cocaine | 68.58 | 3 | 22.86 | .36 | .782 |
| Amphet BY Cocaine | 207.28 | 3 | 69.09 | 1.09 | .361 |
| Restraint BY Amphet BY Cocaine | 7.38 | 2 | 3.69 | .06 | .944 |

## Diagnostic Statistics

Tests involving 'Days' Within-Subject Effect.

| | |
|---|---|
| Mauchly sphericity test, W = | .04313 |
| Chi-square approx. = | 178.48956 with 20 D. F. |
| Significance = | .000 |
| Greenhouse-Geisser Epsilon = | .45279 |
| Huynh-Feldt Epsilon = | .60006 |
| Lower-bound Epsilon = | .16667 |

EFFECT .. Restraint BY Amphet BY Cocaine BY Days
Multivariate Tests of Significance (S = 2, M = 1 1/2, N = 26 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .88286 | .57849 | 12.00 | 108.00 | .855 |

EFFECT .. Amphet BY Cocaine BY Days
Multivariate Tests of Significance (S = 3, M = 1 , N = 26 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .71163 | 1.08795 | 18.00 | 153.22 | .369 |

EFFECT .. Restraint BY Cocaine BY Days
Multivariate Tests of Significance (S = 3, M = 1 , N = 26 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .81164 | .65182 | 18.00 | 153.22 | .853 |

EFFECT .. Restraint BY Amphet BY Days
Multivariate Tests of Significance (S = 1, M = 2 , N = 26 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .87788 | 1.25199 | 6.00 | 54.00 | .295 |

EFFECT .. Cocaine BY Days
Multivariate Tests of Significance (S = 3, M = 1 , N = 26 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .80784 | .66707 | 18.00 | 153.22 | .839 |

EFFECT .. Amphet BY Days
Multivariate Tests of Significance (S = 1, M = 2 , N = 26 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .08033 | 103.03826 | 6.00 | 54.00 | .000 |

```
EFFECT .. Restraint BY Days
Multivariate Tests of Significance (S = 1, M = 2 , N = 26 )
Test Name          Value  Approx. F Hypoth. DF   Error DF  Sig. of F
Wilks             .93724     .60271       6.00      54.00       .727

EFFECT .. Days
Multivariate Tests of Significance (S = 1, M = 2 , N = 26 )
Test Name          Value  Approx. F Hypoth. DF   Error DF  Sig. of F
Wilks             .11362   70.21304       6.00      54.00       .000
```

Tests involving 'Days' Within-Subject Effect.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 4066.29 | 354 | 11.49 | | |
| Days | 3113.21 | 6 | 518.87 | 45.17 | .000 |
| Restraint BY Days | 30.64 | 6 | 5.11 | .44 | .849 |
| Amphet BY Days | 6575.20 | 6 | 1095.87 | 95.40 | .000 |
| Cocaine BY Days | 98.49 | 18 | 5.47 | .48 | .967 |
| Restraint BY Amphet BY Days | 59.29 | 6 | 9.88 | .86 | .524 |
| Restraint BY Cocaine BY Days | 162.07 | 18 | 9.00 | .78 | .720 |
| Amphet BY Cocaine BY Days | 278.22 | 18 | 15.46 | 1.35 | .157 |
| Restraint BY Amphet BY Cocaine BY Days | 83.96 | 12 | 7.00 | .61 | .835 |

## Analysis of Variance on Saccharin Intake Excluding Open-field Cocaine Factor

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 4067.02 | 70 | 58.10 | | |
| CONSTANT | 67824.88 | 1 | 67824.88 | 1167.38 | .000 |
| Restraint | 7.56 | 1 | 7.56 | .13 | .719 |
| Amphet | 14747.72 | 1 | 14747.72 | 253.83 | .000 |
| Restraint BY Amphet | 51.21 | 1 | 51.21 | .88 | .351 |

## Diagnostics Statistics

```
Tests involving 'Days' Within-Subject Effect.
Mauchly sphericity test, W =       .04278
Chi-square approx. =            213.61555 with 20 D. F.
Significance =                      .000
Greenhouse-Geisser Epsilon =       .44943
Huynh-Feldt Epsilon =              .48920
Lower-bound Epsilon =              .16667

EFFECT .. Restraint BY Amphet BY Days
Multivariate Tests of Significance (S = 1, M = 2 , N = 31 1/2)
Test Name          Value  Approx. F Hypoth. DF   Error DF  Sig. of F
Wilks             .89575    1.26084       6.00      65.00       .288

EFFECT .. Amphet BY Days
Multivariate Tests of Significance (S = 1, M = 2 , N = 31 1/2)
Test Name          Value  Approx. F Hypoth. DF   Error DF  Sig. of F
Wilks             .08740  113.11521       6.00      65.00       .000
```

EFFECT .. Restraint BY Days
Multivariate Tests of Significance (S = 1, M = 2 , N = 31 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .94674 | .60940 | 6.00 | 65.00 | .722 |

EFFECT .. Days
Multivariate Tests of Significance (S = 1, M = 2 , N = 31 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .12920 | 73.01747 | 6.00 | 65.00 | .000 |

Tests involving 'Days' Within-Subject Effect.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 4700.56 | 420 | 11.19 | | |
| Days | 3113.21 | 6 | 518.87 | 46.36 | .000 |
| Restraint BY Days | 30.64 | 6 | 5.11 | .46 | .840 |
| Amphet BY Days | 6575.20 | 6 | 1095.87 | 97.92 | .000 |
| Restraint BY Amphet BY Days | 47.76 | 6 | 7.96 | .71 | .641 |

## Simple-effect Tests of Amphetamine Effect on each Day

Test Day = Baseline

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 297.11 | 70 | 4.24 | | |
| Amphet | .53 | 1 | .53 | .13 | .724 |

Test Day = PD1

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1120.24 | 70 | 16.00 | | |
| Amphet | 2.32 | 1 | 2.32 | .14 | .705 |

Test Day = PD2

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1072.92 | 70 | 15.33 | | |
| Amphet | 3193.15 | 1 | 3193.15 | 208.33 | .000 |

Test Day = EXT1

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 666.81 | 70 | 9.53 | | |
| Amphet | 5426.70 | 1 | 5426.70 | 569.68 | .000 |

Test Day = EXT2

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 825.82 | 70 | 11.80 | | |
| Amphet | 5573.25 | 1 | 5573.25 | 472.41 | .000 |

Test Day = EXT3

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1644.63 | 70 | 23.49 | | |
| Amphet | 4224.23 | 1 | 4224.23 | 179.80 | .000 |

Test Day = EXT4

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 3140.05 | 70 | 44.86 | | |
| Amphet | 2895.63 | 1 | 2895.63 | 64.55 | .000 |

## Contrasts Comparing Saccharin Intake to Baseline Water Intake

EFFECT .. Amphetamine-Injected

Multivariate Tests of Significance (S = 1, M = 2 1/2, N = 31 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .02520 | 353.62569 | 7.00 | 64.00 | .000 |

Univariate F-tests with (1,70) D. F.

| Variable | Hypoth. SS | Error SS | Hypoth. MS | Error MS | F | Sig. of F |
|---|---|---|---|---|---|---|
| BAS-PD1 | 2080.65003 | 1192.56684 | 2080.65003 | 17.03667 | 122.12775 | .000 |
| BAS-PD2 | 6385.25193 | 1206.80290 | 6385.25193 | 17.24004 | 370.37335 | .000 |
| BAS-EXT1 | 8468.41230 | 719.58045 | 8468.41230 | 10.27972 | 823.79789 | .000 |
| BAS-EXT2 | 7200.57147 | 836.14201 | 7200.57147 | 11.94489 | 602.81626 | .000 |
| BAS-EXT3 | 5315.04781 | 1679.76538 | 5315.04781 | 23.99665 | 221.49126 | .000 |
| BAS-EXT4 | 2878.67153 | 3322.75504 | 2878.67153 | 47.46793 | 60.64456 | .000 |

EFFECT .. Saline-Injected

Multivariate Tests of Significance (S = 1, M = 2 1/2, N = 31 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .02391 | 373.26941 | 7.00 | 64.00 | .000 |

Univariate F-tests with (1,70) D. F.

| Variable | Hypoth. SS | Error SS | Hypoth. MS | Error MS | F | Sig. of F |
|---|---|---|---|---|---|---|
| BAS-PD1 | 2184.10022 | 1192.56684 | 2184.10022 | 17.03667 | 128.19995 | .000 |
| BAS-PD2 | 1.08157 | 1206.80290 | 1.08157 | 17.24004 | .06274 | .803 |
| BAS-EXT1 | 173.95162 | 719.58045 | 173.95162 | 10.27972 | 16.92182 | .000 |
| BAS-EXT2 | 473.24783 | 836.14201 | 473.24783 | 11.94489 | 39.61928 | .000 |
| BAS-EXT3 | 401.78243 | 1679.76538 | 401.78243 | 23.99665 | 16.74327 | .000 |
| BAS-EXT4 | 551.33148 | 3322.75504 | 551.33148 | 47.46793 | 11.61482 | .001 |

## Analysis of Variance on Water Intake on Days Between Sacharin Tests

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1941.95 | 59 | 32.91 | | |
| Restraint | 71.02 | 1 | 71.02 | 2.16 | .147 |
| Cocaine | 43.90 | 3 | 14.63 | .44 | .722 |
| Amphet | 1324.71 | 1 | 1324.71 | 40.25 | .000 |
| Restraint BY Cocaine | 19.22 | 3 | 6.41 | .19 | .900 |
| Restraint BY Amphet | 4.12 | 1 | 4.12 | .13 | .725 |
| Cocaine BY Amphet | 126.18 | 3 | 42.06 | 1.28 | .290 |
| Restraint BY Cocaine Amphet | 56.55 | 3 | 18.85 | .57 | .635 |

## Diagnostic Statistics

```
Tests involving 'Day' Within-Subject Effect.
Mauchly sphericity test, W =        .61238
Chi-square approx. =              28.00194 with 14 D. F.
Significance =                        .014
Greenhouse-Geisser Epsilon =        .87006
Huynh-Feldt Epsilon =              1.00000
Lower-bound Epsilon =               .20000

EFFECT .. Restraint BY Cocaine BY Amphet BY Day
Multivariate Tests of Significance (S = 3, M = 1/2, N = 26 1/2)
Test Name          Value  Approx. F Hypoth. DF   Error DF  Sig. of F
Wilks             .66458    1.61901      15.00     152.23       .075

EFFECT .. Cocaine BY Amphet BY Day
Multivariate Tests of Significance (S = 3, M = 1/2, N = 26 1/2)
Test Name          Value  Approx. F Hypoth. DF   Error DF  Sig. of F
Wilks             .58600    2.16783      15.00     152.23       .010

EFFECT .. Restraint BY Amphet BY Day
Multivariate Tests of Significance (S = 1, M = 1 1/2, N = 26 1/2)
Test Name          Value  Approx. F Hypoth. DF   Error DF  Sig. of F
Wilks             .95158     .55975       5.00      55.00       .730

EFFECT .. Restraint BY Cocaine BY Day
Multivariate Tests of Significance (S = 3, M = 1/2, N = 26 1/2)
Test Name          Value  Approx. F Hypoth. DF   Error DF  Sig. of F
Wilks             .57099    2.28416      15.00     152.23       .006

EFFECT .. Amphet BY Day
Multivariate Tests of Significance (S = 1, M = 1 1/2, N = 26 1/2)
Test Name          Value  Approx. F Hypoth. DF   Error DF  Sig. of F
Wilks             .28308   27.85777       5.00      55.00       .000

EFFECT .. Cocaine BY Day
Multivariate Tests of Significance (S = 3, M = 1/2, N = 26 1/2)
Test Name          Value  Approx. F Hypoth. DF   Error DF  Sig. of F
Wilks             .64695    1.73420      15.00     152.23       .050

EFFECT .. Restraint BY Day
Multivariate Tests of Significance (S = 1, M = 1 1/2, N = 26 1/2)
Test Name          Value  Approx. F Hypoth. DF   Error DF  Sig. of F
Wilks             .96655     .38074       5.00      55.00       .860
```

EFFECT .. Day
Multivariate Tests of Significance (S = 1, M = 1 1/2, N = 26 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .18685 | 47.87146 | 5.00 | 55.00 | .000 |

Tests involving 'Day' Within-Subject Effect.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1167.68 | 295 | 3.96 | | |
| Day | 733.02 | 5 | 146.60 | 37.04 | .000 |
| Restraint BY Day | 8.79 | 5 | 1.76 | .44 | .817 |
| Cocaine BY Day | 84.68 | 15 | 5.65 | 1.43 | .134 |
| Amphet BY Day | 413.67 | 5 | 82.73 | 20.90 | .000 |
| Restraint BY Cocaine BY Day | 99.35 | 15 | 6.62 | 1.67 | .055 |
| Restraint BY Amphet BY Day | 9.75 | 5 | 1.95 | .49 | .782 |
| Cocaine BY Amphet BY Day | 97.03 | 15 | 6.47 | 1.63 | .064 |
| Restraint BY Cocaine BY Amphet BY Day | 70.74 | 15 | 4.72 | 1.19 | .277 |

## Simple-effect Tests of the Cocaine by Restraint by Day Interaction

Test Day = Baseline

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 247.11 | 59 | 4.19 | | |
| Cocaine BY Amphet | 9.95 | 3 | 3.32 | .79 | .503 |
| Restraint BY Cocaine | 4.40 | 3 | 1.47 | .35 | .789 |
| Amphet | 1.01 | 1 | 1.01 | .24 | .624 |

Test Day = Day 13

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 636.20 | 59 | 10.78 | | |
| Cocaine BY Amphet | 21.06 | 3 | 7.02 | .65 | .586 |
| Restraint BY Cocaine | 22.09 | 3 | 7.36 | .68 | .566 |
| Amphet | 38.22 | 1 | 38.22 | 3.54 | .065 |

Test Day = Day 15

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 393.39 | 59 | 6.67 | | |
| Cocaine BY Amphet BY | 31.21 | 3 | 10.40 | 1.56 | .209 |
| Restraint BY Cocaine | 26.11 | 3 | 8.70 | 1.31 | .281 |
| Amphet | 298.88 | 1 | 298.88 | 44.83 | .000 |

Test Day = Day 17

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 544.52 | 59 | 9.23 | | |
| Cocaine BY Amphet | 76.63 | 3 | 25.54 | 2.77 | .050 |
| Restraint BY Cocaine | 47.54 | 3 | 15.85 | 1.72 | .173 |
| Amphet DAY(4) | 447.16 | 1 | 447.16 | 48.45 | .000 |

Test Day = Day 19

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 504.60 | 59 | 8.55 | | |
| Cocaine BY Amphet | 28.49 | 3 | 9.50 | 1.11 | .352 |
| Restraint BY Cocaine | 56.53 | 3 | 18.84 | 2.20 | .097 |
| Amphet | 400.19 | 1 | 400.19 | 46.79 | .000 |

Test Day = Day 21

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 783.81 | 59 | 13.28 | | |
| Cocaine BY Amphet Y | 22.17 | 3 | 7.39 | .56 | .646 |
| Restraint BY Cocaine | 93.21 | 3 | 31.07 | 2.34 | .083 |
| Amphet | 432.75 | 1 | 432.75 | 32.57 | .000 |

# APPENDIX I: Analysis Tables for Experiment 4

## Anova on Body Weights During Restraint Period

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 398354.25 | 45 | 8852.32 | | |
| CONSTANT | 62595376.83 | 1 | 62595377 | 7071.07 | .000 |
| Restraint | 12.78 | 1 | 12.78 | .00 | .970 |
| ETOH-Avail | 3074.44 | 1 | 3074.44 | .35 | .559 |
| Restraint BY ETOH-Avail | 3454.06 | 1 | 3454.06 | .39 | .535 |

## Diagnostic Statistics

Tests involving 'Day' Within-Subject Effect.

Mauchly sphericity test, W = .00070
Chi-square approx. = 308.59529 with 27 D. F.
Significance = .000
Greenhouse-Geisser Epsilon = .33999
Huynh-Feldt Epsilon = .38418
Lower-bound Epsilon = .14286

EFFECT .. Restraint BY ETOH-Avail BY Day
Multivariate Tests of Significance (S = 1, M = 2 1/2, N = 18 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .88323 | .73658 | 7.00 | 39.00 | .642 |

EFFECT .. ETOH-Avail BY Day
Multivariate Tests of Significance (S = 1, M = 2 1/2, N = 18 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .90101 | .61212 | 7.00 | 39.00 | .742 |

EFFECT .. Restraint BY Day
Multivariate Tests of Significance (S = 1, M = 2 1/2, N = 18 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .89445 | .65743 | 7.00 | 39.00 | .706 |

EFFECT .. Day
Multivariate Tests of Significance (S = 1, M = 2 1/2, N = 18 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .03531 | 152.19620 | 7.00 | 39.00 | .000 |

Tests involving 'Day' Within-Subject Effect.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 29867.94 | 315 | 94.82 | | |
| Day | 72125.88 | 7 | 10303.70 | 108.67 | .000 |
| Restraint BY Day | 331.61 | 7 | 47.37 | .50 | .835 |
| ETOH-Avail BY Day | 322.77 | 7 | 46.11 | .49 | .844 |
| Restraint BY ETOH-Avail BY Day | 922.00 | 7 | 131.71 | 1.39 | .209 |

## Analysis of Covariance on ETOH Intake on Post-Restraint Tests

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 599.64 | 45 | 13.33 | | |
| CONSTANT | 2053.31 | 1 | 2053.31 | 154.09 | .000 |
| Restraint | 16.82 | 1 | 16.82 | 1.26 | .267 |
| ETOH-Avail | 4.75 | 1 | 4.75 | .36 | .554 |
| Restraint BY ETOH-Avail | 17.83 | 1 | 17.83 | 1.34 | .253 |

### Diagnostic Statistics

Tests involving 'Days' Within-Subject Effect.

| | |
|---|---|
| Mauchly sphericity test, W = | .69034 |
| Chi-square approx. = | 16.08882 with 9 D. F. |
| Significance = | .065 |
| Greenhouse-Geisser Epsilon = | .83485 |
| Huynh-Feldt Epsilon = | .96992 |
| Lower-bound Epsilon = | .25000 |

EFFECT .. Restraint BY ETOH-Avail BY Days
Multivariate Tests of Significance (S = 1, M = 1 , N = 20 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .80704 | 2.51054 | 4.00 | 42.00 | .056 |

EFFECT .. ETOH-Avail BY Days
Multivariate Tests of Significance (S = 1, M = 1 , N = 20 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .88658 | 1.34321 | 4.00 | 42.00 | .270 |

EFFECT .. Restraint BY Days
Multivariate Tests of Significance (S = 1, M = 1 , N = 20 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .76123 | 3.29339 | 4.00 | 42.00 | .020 |

EFFECT .. Days
Multivariate Tests of Significance (S = 1, M = 1 , N = 20 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .71067 | 4.27479 | 4.00 | 42.00 | .005 |

Tests involving 'Days' Within-Subject Effect.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 166.84 | 180 | .93 | | |
| Days | 14.06 | 4 | 3.51 | 3.79 | .006 |
| Restraint BY Days | 8.72 | 4 | 2.18 | 2.35 | .056 |
| ETOH-Avail BY Days | 4.86 | 4 | 1.21 | 1.31 | .268 |
| Restraint BY ETOH-Avail BY Days | 8.44 | 4 | 2.11 | 2.28 | .063 |

## Simple-effect Tests for Restraint for both ETOH-Availability Groups on each Test Day

Test Day = DAY 1

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 167.23 | 45 | 3.72 | | |
| ETOH-Avail | 2.96 | 1 | 2.96 | .80 | .377 |
| ETOH-NotAvail | 3.52 | 1 | 3.52 | .95 | .335 |

Test Day = DAY 2

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 151.64 | 45 | 3.37 | | |
| ETOH-Avail | .58 | 1 | .58 | .17 | .680 |
| ETOH-NotAvail | 25.10 | 1 | 25.10 | 7.45 | .009 |

Test Day = DAY 3

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 145.86 | 45 | 3.24 | | |
| ETOH-AvailN | .19 | 1 | .19 | .06 | .811 |
| ETOH-NotAvail | 2.41 | 1 | 2.41 | .74 | .393 |

Test Day = DAY 4

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 132.59 | 45 | 2.95 | | |
| ETOH-Avail | .26 | 1 | .26 | .09 | .768 |
| ETOH-NotAvail | 3.15 | 1 | 3.15 | 1.07 | .306 |

Test Day = DAY 5

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 169.16 | 45 | 3.76 | | |
| ETOH-Avail | 4.38 | 1 | 4.38 | 1.16 | .286 |
| ETOH-NotAvail | 9.86 | 1 | 9.86 | 2.62 | .112 |

**Analysis of Variance on ETOH Intake during Restraint Period (Includes ETOH-Available Animals Only)**

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 204.30 | 22 | 9.29 | | |
| CONSTANT | 615.66 | 1 | 615.66 | 66.30 | .000 |
| Restraint | .42 | 1 | .42 | .04 | .834 |

**Diagnostic Statistics**

Tests involving 'Days' Within-Subject Effect.

| | |
|---|---|
| Mauchly sphericity test, W = | .45806 |
| Chi-square approx. = | 16.17908 with 5 D. F. |
| Significance = | .006 |
| Greenhouse-Geisser Epsilon = | .77053 |
| Huynh-Feldt Epsilon = | .90541 |
| Lower-bound Epsilon = | .33333 |

EFFECT .. Restraint BY Days
Multivariate Tests of Significance (S = 1, M = 1/2, N = 9 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .71635 | 2.63982 | 3.00 | 20.00 | .077 |

EFFECT .. Days
Multivariate Tests of Significance (S = 1, M = 1/2, N = 9 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .79270 | 1.74337 | 3.00 | 20.00 | .190 |

Tests involving 'Days' Within-Subject Effect.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 62.39 | 66 | .95 | | |
| Days | 5.07 | 3 | 1.69 | 1.79 | .158 |
| Restraint BY Days | 5.34 | 3 | 1.78 | 1.88 | .141 |

## Simple-effects of Restraint on ETOH Intake for each Restraint Day

Test Day = Day 1

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 70.01 | 22 | 3.18 | | |
| Restraint | .77 | 1 | .77 | .24 | .627 |

Test Day = Day 2

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 48.91 | 22 | 2.22 | | |
| Restraint | .51 | 1 | .51 | .23 | .638 |

Test Day = Day 3

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 72.81 | 22 | 3.31 | | |
| Restraint | 1.07 | 1 | 1.07 | .32 | .575 |

Test Day = Days 4

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 74.95 | 22 | 3.41 | | |
| Restraint | 3.40 | 1 | 3.40 | 1.00 | .328 |

## Analysis of Variance on Total Fluid Consumption During Restraint Period

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 14596.58 | 43 | 339.46 | | |
| CONSTANT | 299022.63 | 1 | 299022.63 | 880.89 | .000 |
| Restraint | 551.22 | 1 | 551.22 | 1.62 | .209 |
| ETOH-Avail | 878.83 | 1 | 878.83 | 2.59 | .115 |
| Restraint BY ETOH-Avail | 172.11 | 1 | 172.11 | .51 | .480 |

## Diagnostic Statistics

Tests involving 'Days' Within-Subject Effect.
Mauchly sphericity test, W = .84882
Chi-square approx. = 6.83855 with 5 D. F.
Significance = .233
Greenhouse-Geisser Epsilon = .90385
Huynh-Feldt Epsilon = 1.00000
Lower-bound Epsilon = .33333

EFFECT .. Restraint BY ETOH-Avail BY Days
Multivariate Tests of Significance (S = 1, M = 1/2, N = 19 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .90958 | 1.35853 | 3.00 | 41.00 | .269 |

EFFECT .. ETOH-Avail BY Days
Multivariate Tests of Significance (S = 1, M = 1/2, N = 19 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .88209 | 1.82686 | 3.00 | 41.00 | .157 |

EFFECT .. Restraint BY Days
Multivariate Tests of Significance (S = 1, M = 1/2, N = 19 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .96179 | .54293 | 3.00 | 41.00 | .656 |

EFFECT .. Days
Multivariate Tests of Significance (S = 1, M = 1/2, N = 19 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .92361 | 1.13034 | 3.00 | 41.00 | .348 |

Tests involving 'Days' Within-Subject Effect.
AVERAGED Tests of Significance for MEAS.1 using SEQUENTIAL Sums of Squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 8185.59 | 129 | 63.45 | | |
| Days | 213.60 | 3 | 71.20 | 1.12 | .343 |
| Restraint BY Days | 109.58 | 3 | 36.53 | .58 | .632 |
| ETOH-Avail BY Days | 305.58 | 3 | 101.86 | 1.61 | .191 |
| Restraint BY ETOH-Avail BY Days | 224.85 | 3 | 74.95 | 1.18 | .320 |

## Analysis of Variance on Total Fluid Consumption in Post-Restraint Period

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 19723.55 | 40 | 493.09 | | |
| CONSTANT | 321327.89 | 1 | 321327.89 | 651.66 | .000 |
| Restraint | 182.37 | 1 | 182.37 | .37 | .547 |
| ETOH-Avail | 453.59 | 1 | 453.59 | .92 | .343 |
| Restraint BY ETOH-Avail | .02 | 1 | .02 | .00 | .995 |

## Diagnostic Statistics

Tests involving 'Days' Within-Subject Effect.

| | |
|---|---|
| Mauchly sphericity test, W = | .89714 |
| Chi-square approx. = | 4.20324 with 5 D. F. |
| Significance = | .521 |
| Greenhouse-Geisser Epsilon = | .93528 |
| Huynh-Feldt Epsilon = | 1.00000 |
| Lower-bound Epsilon = | .33333 |

EFFECT .. Restraint BY ETOH-Avail BY Days
Multivariate Tests of Significance (S = 1, M = 1/2, N = 18 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .91949 | 1.10912 | 3.00 | 38.00 | .357 |

EFFECT .. ETOH-Avail BY Days
Multivariate Tests of Significance (S = 1, M = 1/2, N = 18 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .94541 | .73134 | 3.00 | 38.00 | .540 |

```
EFFECT .. Restraint BY Days
Multivariate Tests of Significance (S = 1, M = 1/2, N = 18 )
Test Name          Value  Approx. F Hypoth. DF   Error DF  Sig. of F
Wilks            .96823     .41563       3.00      38.00       .743

EFFECT .. Days
Multivariate Tests of Significance (S = 1, M = 1/2, N = 18 )
Test Name          Value  Approx. F Hypoth. DF   Error DF  Sig. of F
Wilks            .38210   20.48383       3.00      38.00       .000
```

Tests involving 'Days' Within-Subject Effect.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 8421.73 | 120 | 70.18 | | |
| Days | 3098.72 | 3 | 1032.91 | 14.72 | .000 |
| Restraint BY Days | 103.22 | 3 | 34.41 | .49 | .690 |
| ETOH-Avail BY Days | 125.87 | 3 | 41.96 | .60 | .618 |
| Restraint BY ETOH-Avail BY Days | 253.72 | 3 | 84.57 | 1.21 | .311 |

## Analysis of Variance on Open-Field Locomotion

Tests of Between-Subjects Effects.
Tests of Significance for T1 using SEQUENTIAL Sums of Squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 6933.80 | 34 | 203.94 | | |
| CONSTANT | 154759.10 | 1 | 154759.10 | 758.86 | .000 |
| Restraint | 23.57 | 1 | 23.57 | .12 | .736 |
| Amphet | 4153.48 | 1 | 4153.48 | 20.37 | .000 |
| Restraint BY Amphet | 5.62 | 1 | 5.62 | .03 | .869 |

## Diagnostic Statistics

```
Tests involving 'Time' Within-Subject Effect.
Mauchly sphericity test, W =       .25293
Chi-square approx. =             44.56123 with 9 D. F.
Significance =                      .000
Greenhouse-Geisser Epsilon =       .59533
Huynh-Feldt Epsilon =              .69966
Lower-bound Epsilon =              .25000

EFFECT .. Restraint BY Amphet BY Time
Multivariate Tests of Significance (S = 1, M = 1 , N = 14 1/2)
Test Name          Value  Approx. F Hypoth. DF   Error DF  Sig. of F
Wilks            .84378    1.43482       4.00      31.00       .246

EFFECT .. Amphet BY Time
Multivariate Tests of Significance (S = 1, M = 1 , N = 14 1/2)
Test Name          Value  Approx. F Hypoth. DF   Error DF  Sig. of F
Wilks            .62811    4.58867       4.00      31.00       .005

EFFECT .. Restraint BY Time
Multivariate Tests of Significance (S = 1, M = 1 , N = 14 1/2)
Test Name          Value  Approx. F Hypoth. DF   Error DF  Sig. of F
Wilks            .96758     .25970       4.00      31.00       .901
```

EFFECT .. Time
Multivariate Tests of Significance (S = 1, M = 1 , N = 14 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .08699 | 81.34254 | 4.00 | 31.00 | .000 |

Tests involving 'Time' Within-Subject Effect.
AVERAGED Tests of Significance for MEAS.1 using SEQUENTIAL Sums of Squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 4621.75 | 136 | 33.98 | | |
| Time | 15219.61 | 4 | 3804.90 | 111.96 | .000 |
| Restraint BY Time | 29.41 | 4 | 7.35 | .22 | .929 |
| Amphet BY Time | 479.02 | 4 | 119.76 | 3.52 | .009 |
| Restraint BY Amphet BY Time | 418.13 | 4 | 104.53 | 3.08 | .018 |

## Linear Regression of Restraint, Post-Restraint ETOH Intake, Amphetamine, and their two-way interactions on Locomotion in the last first 2 Min of the 30 min Open-Field Test

**Dependent Variable.. MIN2_PM Min 2 Locomotion**

```
Block Number  3.  Method:  Enter      DRXPS2   STRXPS2
Variable(s) Entered on Step Number  5..   STRXPS2
                                    6..   DRXPS2

Multiple R            .52938                                       Analysis of Variance
R Square              .28024     R Square Change    .07475                        DF    Sum of Squares    Mean Square
Adjusted R Square     .13629     F Change          1.55778      Regression         6        1195.95879      199.32646
Standard Error      10.11867     Signif F Change    .2272       Residual          30        3071.62229      102.38741
                                                                    F =      1.94679        Signif F =  .1054

------------------------------ Variables in the Equation ------------------------------
Variable            B         SE B       Beta    SE Beta    Correl  Part Cor   Partial        F   Sig F
STRXDPG     12.556558     7.530152    .534394    .320476   .282214   .258285   .291245    2.781   .1058
DRUGX        -.760582     4.813623   -.035085    .222050   .272177  -.024474  -.028836     .025   .8755
STRESSX     -9.256122     5.600091   -.430775    .260625  -.016534  -.256016  -.288900    2.732   .1088
PS2ETOHX     8.842166     3.914214    .789797    .349624   .066337   .349902   .381278    5.103   .0313
STRXPS2     -6.397979     4.063902   -.413569    .262693  -.210022  -.243855  -.276249    2.479   .1259
DRXPS2      -5.055726     4.105801   -.336374    .273173   .021985  -.190730  -.219340    1.516   .2278
(Constant)  44.906521     3.591620                                                       156.328   .0000
End Block Number   3   All requested variables entered.
```

**Linear Regression of Restraint, Post-Restraint ETOH Intake, Amphetamine, and their Two-way Interactions on Locomotion in the last 10 Min of the 30 min Open-Field Test**

**Dependent Variable.. MIN30 Min 30 locomotion**

**Block Number 3. Method: Enter DRXPS2 STRXPS2**

Variable(s) Entered on Step Number 5.. STRXPS2
6.. DRXPS2

| | | | |
|---|---|---|---|
| Multiple R | .80122 | | |
| R Square | .64196 | R Square Change | .09792 |
| Adjusted R Square | .57035 | F Change | 4.10239 |
| Standard Error | 153.82687 | Signif F Change | .0266 |

Analysis of Variance

| | DF | Sum of Squares | Mean Square |
|---|---|---|---|
| Regression | 6 | 1272794.09856 | 212132.34976 |
| Residual | 30 | 709881.14468 | 23662.70482 |

F = 8.96484 Signif F = .0000

------------------ Variables in the Equation ------------------

| Variable | B | SE B | Beta | SE Beta | Correl | Part Cor | Partial | F | Sig F |
|---|---|---|---|---|---|---|---|---|---|
| STRXDRG | -96.527746 | 114.475524 | -.190594 | .226032 | .315050 | -.092118 | -.152157 | .711 | .4058 |
| DRUGX | 343.006143 | 73.178078 | .734083 | .156612 | .670298 | .512068 | .650193 | 21.971 | .0001 |
| STRESSX | 50.741914 | 85.134185 | .109560 | .183819 | -.004615 | .065113 | .108180 | .355 | .5556 |
| PS2ETOHX | 131.421097 | 59.505005 | .544612 | .246590 | .113940 | .241278 | .373970 | 4.878 | .0350 |
| STRXPS2 | -160.726136 | 61.780596 | -.482011 | .185277 | -.277868 | -.284211 | -.429041 | 6.768 | .0143 |
| DRXPS2 | 22.975986 | 62.417565 | .070922 | .192669 | .203991 | .040214 | .067055 | .135 | .7154 |
| (Constant) | 536.311806 | 54.600842 | | | | | | 96.480 | .0000 |

End Block Number 3 All requested variables entered.

# APPENDIX J: Analysis Tables for Experiment 5

## Analysis of Variance on Body Weights

Tests of Between-Subjects Effects.
Tests of Significance for T1 using SEQUENTIAL Sums of Squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 77580.94 | 38 | 2041.60 | | |
| CONSTANT | 22803518.01 | 1 | 22803518 | 11169.41 | .000 |
| Strain | 39836.72 | 1 | 39836.72 | 19.51 | .000 |
| Amphet | 9387.19 | 1 | 9387.19 | 4.60 | .038 |
| Strain BY Amphet | 4808.89 | 1 | 4808.89 | 2.36 | .133 |

## Diagnostic Statistics

Tests involving 'Day' Within-Subject Effect.

| | |
|---|---|
| Mauchly sphericity test, W = | .15161 |
| Chi-square approx. = | 69.27738 with 5 D. F. |
| Significance = | .000 |
| Greenhouse-Geisser Epsilon = | .52142 |
| Huynh-Feldt Epsilon = | .58275 |
| Lower-bound Epsilon = | .33333 |

Tests involving 'Day' Within-Subject Effect.
AVERAGED Tests of Significance for MEAS.1 using SEQUENTIAL Sums of Squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 8947.16 | 114 | 78.48 | | |
| Day | 164153.35 | 3 | 54717.78 | 697.19 | .000 |
| Strain BY Day | 516.64 | 3 | 172.21 | 2.19 | .093 |
| Amphet BY Day | 3370.79 | 3 | 1123.60 | 14.32 | .000 |
| Strain BY Amphet BY Day | 151.32 | 3 | 50.44 | .64 | .589 |

## Simple-effects of Strain on Baseline Water Intake

Test Day = Baseline

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 81.03 | 38 | 2.13 | | |
| Strain | 39.58 | 1 | 39.58 | 18.56 | .000 |

## Analysis of Variance on Saccharin Intake

Tests of Between-Subjects Effects.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 52848.61 | 38 | 1390.75 | | |
| CONSTANT | 977438.21 | 1 | 977438.21 | 702.81 | .000 |
| Strain | 36.40 | 1 | 36.40 | .03 | .872 |
| Amphet | 22242.28 | 1 | 22242.28 | 15.99 | .000 |
| Strain BY Amphet | 2220.50 | 1 | 2220.50 | 1.60 | .214 |

## Diagnostic Statistics

Tests involving 'Day' Within-Subject Effect.

Mauchly sphericity test, W = .00011
Chi-square approx. = 301.86798 with 104 D. F.
Significance = .000
Greenhouse-Geisser Epsilon = .38429
Huynh-Feldt Epsilon = .49042
Lower-bound Epsilon = .07143

EFFECT .. Strain BY Amphet BY Day
Multivariate Tests of Significance (S = 1, M = 6 , N = 11 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .42757 | 2.39068 | 14.00 | 25.00 | .028 |

EFFECT .. Amphet BY Day
Multivariate Tests of Significance (S = 1, M = 6 , N = 11 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .03453 | 49.92573 | 14.00 | 25.00 | .000 |

EFFECT .. Strain BY Day
Multivariate Tests of Significance (S = 1, M = 6 , N = 11 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .35134 | 3.29692 | 14.00 | 25.00 | .005 |

EFFECT .. Day
Multivariate Tests of Significance (S = 1, M = 6 , N = 11 1/2)

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .07046 | 23.55754 | 14.00 | 25.00 | .000 |
| Roys | .92954 | | | | |

Tests involving 'Day' Within-Subject Effect.

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 28630.15 | 532 | 53.82 | | |
| Day | 15832.59 | 14 | 1130.90 | 21.01 | .000 |
| Strain BY Day | 3395.68 | 14 | 242.55 | 4.51 | .000 |
| Amphet BY Day | 24431.15 | 14 | 1745.08 | 32.43 | .000 |
| Strain BY Amphet BY Day | 2209.63 | 14 | 157.83 | 2.93 | .000 |

**Simple-effect Tests of Amphetamine and Strain Effects on Baseline Water Intake and Saccharin Intake**

Test Day = Baseline

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 503.81 | 38 | 13.26 | | |
| Amphet | 1.86 | 1 | 1.86 | .14 | .710 |
| Strain | 47.83 | 1 | 47.83 | 3.61 | .065 |
| Amphet BY Strain | 7.48 | 1 | 7.48 | .56 | .457 |

Test Day = PD1

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 4665.36 | 38 | 122.77 | | |
| Amphet | 24.69 | 1 | 24.69 | .20 | .656 |
| Strain | 1318.94 | 1 | 1318.94 | 10.74 | .002 |
| Amphet BY Strain | 120.56 | 1 | 120.56 | .98 | .328 |

Test Day = PD2

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 3113.41 | 38 | 81.93 | | |
| Amphet | 10925.89 | 1 | 10925.89 | 133.35 | .000 |
| Strain | 2.90 | 1 | 2.90 | .04 | .852 |
| Amphet BY Strain | 43.97 | 1 | 43.97 | .54 | .468 |

Test Day = Ext1

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 2439.13 | 38 | 64.19 | | |
| Amphet | 17589.36 | 1 | 17589.36 | 274.03 | .000 |
| Strain | 77.43 | 1 | 77.43 | 1.21 | .279 |
| Amphet BY Strain | 16.75 | 1 | 16.75 | .26 | .612 |

Test Day = Ext2

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 5753.54 | 38 | 151.41 | | |
| Amphet | 8270.48 | 1 | 8270.48 | 54.62 | .000 |
| Strain | 746.12 | 1 | 746.12 | 4.93 | .032 |
| Amphet BY Strain | 20.81 | 1 | 20.81 | .14 | .713 |

Test Day = Ext3

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 7797.46 | 38 | 205.20 | | |
| Amphet | 4524.56 | 1 | 4524.56 | 22.05 | .000 |
| Strain | 422.88 | 1 | 422.88 | 2.06 | .159 |
| Amphet BY Strain | 5.44 | 1 | 5.44 | .03 | .871 |

Test Day = Ext4

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 8710.06 | 38 | 229.21 | | |
| Amphet | 2278.09 | 1 | 2278.09 | 9.94 | .003 |
| Strain | 11.68 | 1 | 11.68 | .05 | .823 |
| Amphet BY Strain | 254.68 | 1 | 254.68 | 1.11 | .298 |

Test Day = Ext5

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 6995.36 | 38 | 184.09 | | |
| Amphet | 1037.97 | 1 | 1037.97 | 5.64 | .023 |
| Strain | 3.15 | 1 | 3.15 | .02 | .897 |
| Amphet BY Strain | 362.82 | 1 | 362.82 | 1.97 | .168 |

Test Day = Ext6

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 6678.18 | 38 | 175.74 | | |
| Amphet | 896.77 | 1 | 896.77 | 5.10 | .030 |
| Strain | 4.58 | 1 | 4.58 | .03 | .873 |
| Amphet BY Strain | 982.21 | 1 | 982.21 | 5.59 | .023 |

Test Day = Ext7

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 6670.91 | 38 | 175.55 | | |
| Amphet | 322.00 | 1 | 322.00 | 1.83 | .184 |
| Strain | 304.75 | 1 | 304.75 | 1.74 | .196 |
| Amphet BY Strain | 525.92 | 1 | 525.92 | 3.00 | .092 |

Test Day = Ext8

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 6127.48 | 38 | 161.25 | | |
| Amphet | 166.09 | 1 | 166.09 | 1.03 | .317 |
| Strain | 252.89 | 1 | 252.89 | 1.57 | .218 |
| Amphet BY Strain | 789.32 | 1 | 789.32 | 4.89 | .033 |

Test Day = Ext9

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 6953.07 | 38 | 182.98 | | |
| Amphet | 250.47 | 1 | 250.47 | 1.37 | .249 |
| Strain | 164.95 | 1 | 164.95 | .90 | .348 |
| Amphet BY Strain | 280.43 | 1 | 280.43 | 1.53 | .223 |

Test Day = Ext10

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 5299.78 | 38 | 139.47 | | |
| Amphet | 210.01 | 1 | 210.01 | 1.51 | .227 |
| Strain | 42.31 | 1 | 42.31 | .30 | .585 |
| Amphet BY Strain | 335.72 | 1 | 335.72 | 2.41 | .129 |

Test Day = Ext11

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 4523.33 | 38 | 119.04 | | |
| Amphet | 144.87 | 1 | 144.87 | 1.22 | .277 |
| Strain | 30.17 | 1 | 30.17 | .25 | .618 |
| Amphet BY Strain | 668.35 | 1 | 668.35 | 5.61 | .023 |

Test Day = Ext12

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 5247.89 | 38 | 138.10 | | |
| Amphet | 30.33 | 1 | 30.33 | .22 | .642 |
| Strain | 1.52 | 1 | 1.52 | .01 | .917 |
| Amphet BY Strain | 15.65 | 1 | 15.65 | .11 | .738 |

## Simple-simple Effect Tests for Amphetamine Effect for each Strain at each Test Day

Test Day = Baseline

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 503.81 | 38 | 13.26 | | |
| Amphet: Long-Evans | 7.10 | 1 | 7.10 | .54 | .469 |
| Amphet: Sprague-Dawley | .54 | 1 | .54 | .04 | .842 |

Test Day = PD1

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 4665.36 | 38 | 122.77 | | |
| Amphet: Long-Evans | 9.15 | 1 | 9.15 | .07 | .786 |
| Amphet: Sprague-Dawley | 100.88 | 1 | 100.88 | .82 | .370 |

Test Day = PD2

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 3113.41 | 38 | 81.93 | | |
| Amphet:Long-Evans | 4778.45 | 1 | 4778.45 | 58.32 | .000 |
| Amphet:Sprague-Dawley | 6192.38 | 1 | 6192.38 | 75.58 | .000 |

Test Day = Ext1

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 2439.13 | 38 | 64.19 | | |
| Amphet: Long-Evans | 8304.77 | 1 | 8304.77 | 129.38 | .000 |
| Amphet: Sprague-Dawley | 9298.05 | 1 | 9298.05 | 144.86 | .000 |

Test Day = Ext2

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 5753.54 | 38 | 151.41 | | |
| Amphet: Long-Evans | 4680.40 | 1 | 4680.40 | 30.91 | .000 |
| Amphet: Sprague-Dawley | 3624.38 | 1 | 3624.38 | 23.94 | .000 |

Test Day = Ext3

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 7797.46 | 38 | 205.20 | | |
| Amphet: Long-Evans | 2169.75 | 1 | 2169.75 | 10.57 | .002 |
| Amphet: Sprague-Dawley | 2356.63 | 1 | 2356.63 | 11.48 | .002 |

Test Day = Ext4

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 8710.06 | 38 | 229.21 | | |
| Amphet: Long-Evans | 509.30 | 1 | 509.30 | 2.22 | .144 |
| Amphet: Sprague-Dawley | 2017.73 | 1 | 2017.73 | 8.80 | .005 |

Test Day = Ext5

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 6995.36 | 38 | 184.09 | | |
| Amphet: Long-Evans | 85.51 | 1 | 85.51 | .46 | .500 |
| Amphet: Sprague-Dawley | 1317.68 | 1 | 1317.68 | 7.16 | .011 |

Test Day = Ext6

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 6678.18 | 38 | 175.74 | | |
| Amphet: Long-Evans | 1.12 | 1 | 1.12 | .01 | .937 |
| Amphet: Sprague-Dawley | 1882.02 | 1 | 1882.02 | 10.71 | .002 |

Test Day = Ext7

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 6670.91 | 38 | 175.55 | | |
| Amphet: Long-Evans | 16.92 | 1 | 16.92 | .10 | .758 |
| Amphet: Sprague-Dawley | 868.59 | 1 | 868.59 | 4.95 | .032 |

Test Day = Ext8

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 6127.48 | 38 | 161.25 | | |
| Amphet: Long-Evans | 127.30 | 1 | 127.30 | .79 | .380 |
| Amphet: Sprague-Dawley | 869.40 | 1 | 869.40 | 5.39 | .026 |

Test Day = Ext9

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 6953.07 | 38 | 182.98 | | |
| Amphet: Long-Evans | 1.17 | 1 | 1.17 | .01 | .937 |
| Amphet: Sprague-Dawley | 549.93 | 1 | 549.93 | 3.01 | .091 |

Test Day = Ext10

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 5299.78 | 38 | 139.47 | | |
| Amphet: Long-Evans | 8.56 | 1 | 8.56 | .06 | .806 |
| Amphet: Sprague-Dawley | 547.84 | 1 | 547.84 | 3.93 | .055 |

Test Day = Ext11

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 4523.33 | 38 | 119.04 | | |
| Amphet: Long-Evans | 91.76 | 1 | 91.76 | .77 | .385 |
| Amphet: Sprague-Dawley | 706.52 | 1 | 706.52 | 5.94 | .020 |

Test Day = Ext12

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 5247.89 | 38 | 138.10 | | |
| Amphet: Long-Evans | 1.11 | 1 | 1.11 | .01 | .929 |
| Amphet: Sprague-Dawley | 45.30 | 1 | 45.30 | .33 | .570 |

## Analysis of Variance on Open-Field Locomotion

Tests of Between-Subjects Effects.
Tests of Significance for T1 using SEQUENTIAL Sums of Squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 3028.47 | 38 | 79.70 | | |
| CONSTANT | 83242.11 | 1 | 83242.11 | 1044.49 | .000 |
| Strain | 1111.88 | 1 | 1111.88 | 13.95 | .001 |
| Amphet | 43.65 | 1 | 43.65 | .55 | .464 |
| Strain BY Amphet | 15.52 | 1 | 15.52 | .19 | .661 |

## Diagnostic Statistics

Tests involving 'Day' Within-Subject Effect.

| | |
|---|---|
| Mauchly sphericity test, W = | .22681 |
| Chi-square approx. = | 53.55967 with 14 D. F. |
| Significance = | .000 |
| Greenhouse-Geisser Epsilon = | .65085 |
| Huynh-Feldt Epsilon = | .77522 |
| Lower-bound Epsilon = | .20000 |

Tests involving 'TIME' Within-Subject Effect.
AVERAGED Tests of Significance for MEAS.1 using SEQUENTIAL Sums of Squares

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 5346.03 | 190 | 53.82 | | |
| TIME | 31164.00 | 5 | 6232.80 | 221.52 | .000 |
| Strain BY TIME | 183.28 | 5 | 36.66 | 1.30 | .264 |
| Amphet BY TIME | 85.00 | 5 | 17.00 | .60 | .697 |
| Strain BY Amphet BY TIME | 108.02 | 5 | 21.60 | .77 | .574 |

## Simple-effect Tests of Strain Effect at each Time in Open-field

Time = Min 2

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 2953.76 | 38 | 77.73 | | |
| Strain | 325.93 | 1 | 325.93 | 4.19 | .048 |

Time = Min 5

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 2077.02 | 38 | 54.66 | | |
| Strain | 7.15 | 1 | 7.15 | .13 | .720 |

Time = Min 10

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 1009.84 | 38 | 26.57 | | |
| Strain | 156.99 | 1 | 156.99 | 5.91 | .020 |

Time = Min 20

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 852.59 | 38 | 22.44 | | |
| Strain | 338.87 | 1 | 338.87 | 15.10 | .000 |

Time = Min 30

| Source of Variation | SS | DF | MS | F | Sig of F |
|---|---|---|---|---|---|
| WITHIN CELLS | 558.84 | 38 | 14.71 | | |
| Strain | 317.62 | 1 | 317.62 | 21.60 | .000 |

## Analysis of Variance on Emergence Latencies in Light/Dark Emergence Test

### Latency to Enter Dark Chamber

| Source of Variation | Sum of Squares | DF | Mean Square | F | Signif of F |
|---|---|---|---|---|---|
| Main Effects | 319.108 | 2 | 159.554 | 2.172 | .128 |
| Strain | 117.000 | 1 | 117.000 | 1.593 | .215 |
| Amphet | 202.107 | 1 | 202.107 | 2.751 | .105 |
| 2-way Interactions | 153.638 | 1 | 153.638 | 2.092 | .156 |
| Strain Amphet | 153.638 | 1 | 153.638 | 2.092 | .156 |
| Explained | 472.745 | 3 | 157.582 | 2.145 | .111 |
| Residual | 2791.311 | 38 | 73.456 | | |
| Total | 3264.056 | 41 | 79.611 | | |

### Latency to Enter Light Chamber

| Source of Variation | Sum of Squares | DF | Mean Square | F | Signif of F |
|---|---|---|---|---|---|
| Main Effects | 46491.068 | 2 | 23245.534 | 1.640 | .207 |
| Strain | 42249.772 | 1 | 42249.772 | 2.981 | .092 |
| Amphet | 4241.296 | 1 | 4241.296 | .299 | .588 |
| 2-way Interactions | 21706.537 | 1 | 21706.537 | 1.532 | .223 |
| Strain Amphet | 21706.537 | 1 | 21706.537 | 1.532 | .223 |
| Explained | 68197.605 | 3 | 22732.535 | 1.604 | .204 |
| Residual | 538541.516 | 38 | 14172.145 | | |
| Total | 606739.121 | 41 | 14798.515 | | |

**Multivariate Analysis of Variance on Saccharin Intake, Open-Field Locomotion and Emergence Latencies**

EFFECT .. Strain BY Amphet
Multivariate Tests of Significance (S = 1, M = 2 1/2, N = 15 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .58982 | 3.17909 | 7.00 | 32.00 | .011 |

**Roy-Bargmann Stepdown F - tests For Strain by Amphetamine Interaction**

| Variable | Hypoth. MS | Error MS | StepDown F | Hypoth. DF | Error DF | Sig of F |
|---|---|---|---|---|---|---|
| Min2 | 30.19529 | 77.73056 | .38846 | 1 | 38 | .537 |
| Min30 | 10.85335 | 14.62143 | .74229 | 1 | 37 | .394 |
| Dark | 155.02334 | 76.89014 | 2.01617 | 1 | 36 | .164 |
| Light | 26879.3942 | 13525.8160 | 1.98727 | 1 | 35 | .167 |
| Neophobia | 1057.00213 | 640.77900 | 1.64956 | 1 | 34 | .208 |
| E1-E3 | .25709 | 4.23056 | .06077 | 1 | 33 | .807 |
| E4-E6 | 215.80037 | 16.71335 | 12.91186 | 1 | 32 | .001 |

EFFECT .. Amphet
Multivariate Tests of Significance (S = 1, M = 2 1/2, N = 15 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .17297 | 21.85687 | 7.00 | 32.00 | .000 |

**Roy-Bargmann Stepdown F - tests for Amphetamine Effect**

| Variable | Hypoth. MS | Error MS | StepDown F | Hypoth. DF | Error DF | Sig of F |
|---|---|---|---|---|---|---|
| Min2 | 113.61477 | 77.73056 | 1.46165 | 1 | 38 | .234 |
| Min30 | .09352 | 14.62143 | .00640 | 1 | 37 | .937 |
| Dark | 171.33552 | 76.89014 | 2.22832 | 1 | 36 | .144 |
| Light | 22.76298 | 13525.8160 | .00168 | 1 | 35 | .968 |
| Neophobia | 55.77725 | 640.77900 | .08705 | 1 | 34 | .770 |
| E1-E3 | 356.54417 | 4.23056 | 84.27829 | 1 | 33 | .000 |
| E4-E6 | 251.94015 | 16.71335 | 15.07419 | 1 | 32 | .000 |

EFFECT .. Strain
Multivariate Tests of Significance (S = 1, M = 2 1/2, N = 15 )

| Test Name | Value | Approx. F | Hypoth. DF | Error DF | Sig. of F |
|---|---|---|---|---|---|
| Wilks | .33799 | 8.95401 | 7.00 | 32.00 | .000 |

**Roy-Bargmann Stepdown F - tests for Strain Effect**

| Variable | Hypoth. MS | Error MS | StepDown F | Hypoth. DF | Error DF | Sig of F |
|---|---|---|---|---|---|---|
| Min2 | 334.69529 | 77.73056 | 4.30584 | 1 | 38 | .045 |
| Min30 | 246.25521 | 14.62143 | 16.84208 | 1 | 37 | .000 |
| Dark | 86.57063 | 76.89014 | 1.12590 | 1 | 36 | .296 |
| Light | 69260.8628 | 13525.8160 | 5.12064 | 1 | 35 | .030 |
| Neophobia | 6448.67795 | 640.77900 | 10.06381 | 1 | 34 | .003 |
| E1-E3 | 16.51658 | 4.23056 | 3.90411 | 1 | 33 | .057 |
| E4-E6 | 35.25550 | 16.71335 | 2.10942 | 1 | 32 | .156 |

**Legend**:

E1-E3 = [(Ext1 + Ext2 + Ext3)/baseline ]/3; Phobia = [PD1/(Baseline Water)]*(100)

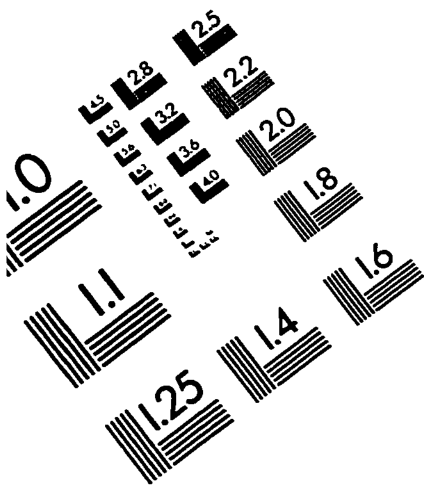
E4-E6 = [(Ext4 + Ext5 +Ext6)/baseline]/3 Min2 = Locomotion/min at Min 2

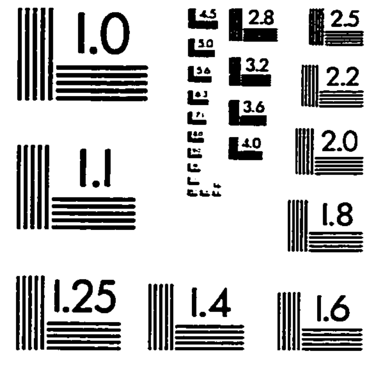
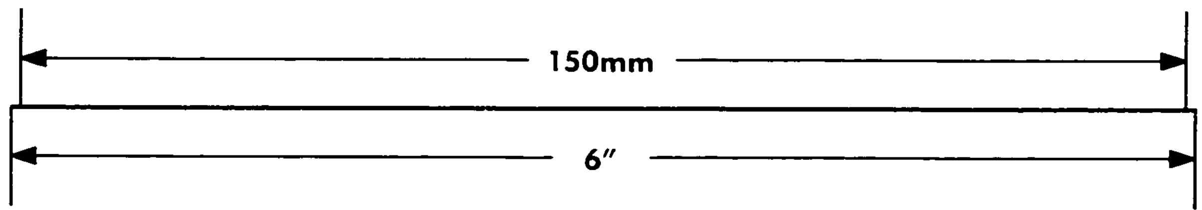
Min30 = Locomotion/ min at Min 30

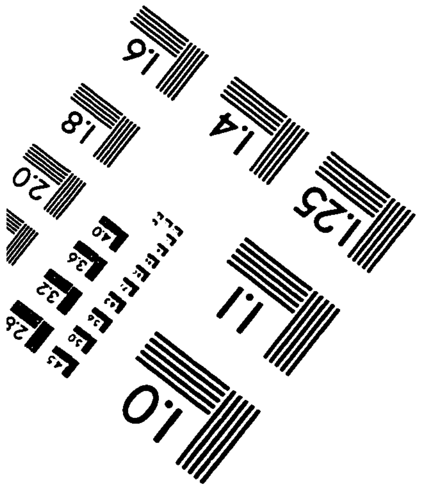
Dark = Latency to Enter Dark Chamber in Light/dark Emergence Test

Light = Latency to Enter Light Chamber in Light/dark Emergence Test

IMAGE EVALUATION
TEST TARGET (QA-3)





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