INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

U·M·I

University Microfilms International
A Bell & Howell Information Company
300 North Zeeb Road Ann Arbor MI 48106-1346 USA
313 761-4700 800 521-0600

Order Number 9218249

The development of tolerance to caffeine's alerting effects: A learning model

Lipschutz-Broch, Lauren, Ph.D.

City University of New York, 1992

Copyright ©1992 by Lipschutz-Broch, Lauren. All rights reserved.

U·M·I

300 N. Zeeb Rd.
Ann Arbor, MI 48106

PLEASE NOTE

Pages 97-106 have very light print.
Best copy available from
author or university.
Filmed as received.

University Microfilms International

THE DEVELOPMENT OF TOLERANCE TO CAFFEINE'S ALERTING EFFECTS: A LEARNING MODEL

BY

LAUREN LIPSCHUTZ-BROCH

A dissertation submitted to the Graduate Faculty in Psychology
in partial fulfillment of the requirements for the degree
of Doctor of Philosophy,
the City University of New York.
1992.

Copyright by
Lauren Lipschutz-Broch
1992
All rights reserved

This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

1/28/92
Date

Chair of Examining Committee

1/28/92
Date

Executive Officer

Dr. Arthur J. Spielman
Dr. Nancy Hemmes
Dr. Paul Glovinsky

Supervisory Committee

The City University of New York

Abstract

The Development of Tolerance to Caffeine's Alerting Effects:
A Learning Model
by
Lauren Lipschutz-Broch

Advisor: Professor Arthur Spielman

Traditional theories view the development of drug tolerance, purely in terms of drug exposure (e.g. dose, interdrug interval). Alternative approaches study the influence of such nonpharmacological factors as the environmental cues present at the time of drug administration and the recipient's experiences and expectations. The contribution of stimuli that become associated with drug delivery has been incorporated in a Pavlovian classical conditioning model of drug tolerance. Unlike the traditional model, however, drug studies have demonstrated that the conditioned response (CR) elicited in anticipation of some drugs are opposite in direction to the unconditioned response (UR). The net result of CR and UR results in drug tolerance.

The present research focused on caffeine and tested three hypotheses: Caffeine initially alerts subjects; over repeated administrations, tolerance develops to caffeine's alerting effects; and lastly, caffeine tolerance is influence by conditioning principles. Nineteen normal-sleeping, healthy, male subjects, were studied over 15 days of controlled coffee administration in the morning. After 250 mg caffeine, objective (Multiple Sleep Latency Test, MSLT) and subjective alertness were significantly increased throughout the day relative to baseline day (no caffeine). After 12 days of a morning coffee beverage (six caffeinated and six decaffeinated), the same dose of caffeine on Day 14 did not

objectively alert subjects as much as on Day 1, thus tolerance develops.

To test the possible influences of conditioning, all subjects received 250 mg caffeine on Day 15, but eleven subjects were told they had received decaffeinated coffee and the remaining eight subjects were told they received caffeinated coffee. It was hypothesized that the subjects who expected decaffeinated would not elicit an opposite de-alerting response and would be more alerted by the caffeine than the group that expected caffeinated coffee. Statistical analysis revealed no difference in alertness between these two conditions. While the present data does not support a Pavlovian analysis of drug tolerance, problems with the time limit of the MSLT, small sample size, the caffeine vehicle and the population tested, as well as the theoretical model used to design the experiment, might have impacted adversely on the results.

Acknowledgements

It is fitting that I begin my acknowledgements with my mentor Dr. Arthur J. Spielman, for it is his work in sleep research and his ability to teach and inspire creative thought in others, that first attracted me to the field of sleep. I thank him for his unfaltering support and belief in me through the years, as well as for his knowledge, wisdom, and humorous perspective.

I express my gratitude to the other members of my committee; Dr. Nancy Hemmes from Queens College of the City University of New York and Dr. Paul Glovinsky from City College of the City University of New York. Their gentle but surehanded support and criticism helped make this work intelligible and clear. I also thank Dr. Mark R. Pressman from the Sleep Disorders Center in the Department of Medicine at Lankenau Hospital, and Dr. William Redd from Memorial Sloan-Kettering Institute for serving as outside readers.

A more general thanks goes to all the professors, researchers, and clinicians who have served as mentors to me during my graduate career. While negotiating the arduous task of setting up my defense date with my committee members and outside readers, it suddenly occurred to me that the reason these people were getting together, was for me and my future. At that time, I realized the selfless role that mentors willingly play, and I thank them all for it.

With respect to running my study, I would very much like to acknowledge Jessica Mitchell and Peggy Spier, both psychology graduate students at City College of the City University of New York, for their invaluable assistance and multidimensional support. Their

ability to learn quickly, act decisively, and work well with others, suggests to me that they are already professionals, in every sense of the word.

Thanks to all my friends and to Daniel's parents; Herman and Rose for their willingness to listen and support me. And to Elana, a special thanks for the use of her computer; it was definitely the kick I needed.

To my non-coffee drinking and extremely patient husband Daniel, I am particularly grateful for his broad perspective, emotional support, and sometimes late night trips to the sleep lab bearing such gifts as clean sheets, extra blankets, sleep records, and encouraging words.

Finally, I wish to thank my parents, Madeline and Victor, and my sisters, Misia and Ricki, for their unshakeable patience, faith and love.

Table of contents

Page

List of tables

Page

List of Figures

Page

List of Appendices

REVIEW OF LITERATURE

Traditional Theories of Drug Tolerance

Many drugs are associated with the well known phenomenon of tolerance. Tolerance refers to the diminished effect of a fixed drug dose as the result of repeated exposure and can be operationally measured by a shift to the right in the dose-response curve. (Fernandes, Kluwe, & Coper, 1977). The study of tolerance has wide-ranging importance given its significant relationship to the consumption of drugs. In particular, an understanding of why addicts require and self-administer increasing amounts of drug in order to obtain desired effects (tolerance), may help explain the processes of addiction and relapse after drug abstinence.

Traditional theories view the development of drug tolerance as a function of drug exposure (e.g., dose, interval between drug administrations). Thus, attempts to account for the underlying physiological mechanisms that occur in concert with tolerance, involves research on pharmacokinetic and pharmacodynamic changes associated with chronic drug use. Pharmacokinetic or dispositional research of drug tolerance involves the study of changes in the distribution, uptake, and metabolism of a drug that cause a net decrease in the amount of drug at the receptor site. Pharmacodynamic or functional research of drug tolerance involves the study of neurochemical changes that result in a decrease in receptor sensitivity to the drug.

Unfortunately, results of studies reporting on pharmacokinetic and pharmacodynamic changes that occur in parallel with the development of

tolerance are equivocal (Demellweek & Goudie, 1983; File, 1985; Kalant, Le Blanc, & Gibbins, 1971). While some studies report physiological changes that are consistent with the development of drug tolerance (e.g., decreases in distribution, increases in metabolism, decreases in receptor sensitivity), other studies have demonstrated physiological changes that are incompatible with pharmacological theories of drug tolerance (e.g., increases in distribution, decreases in metabolism, enhanced receptor sensitivity, increases in distribution).

What's more, there is an abundance of research supporting the hypothesis that tolerance is not only influenced by drug dose and interdose interval, but also by such nonpharmacological factors as the recipient's prior experiences and expectations, and the environmental cues present at the time of drug administration. These findings are inconsistent with the notion that drug tolerance is simply a function of drug exposure. The notion that a drug may become associated with drug-predictive cues (e.g., expectations, environment, drug administration rituals) has been incorporated into several different types of learning models of drug tolerance (Schull, 1979; Siegel, 1975, 1976, 1977; Solomon & Corbit, 1974; Tiffany & Baker, 1981).

In the present dissertation, the development of tolerance to caffeine's alerting effects is studied using a learning model. In the first section, I briefly review basic principles of the classical conditioning model in an effort to provide the reader with some fundamental knowledge of learning theory. I then present a brief history of the data supporting Siegel's conditioning analysis of drug tolerance and some of the unresolved issues and alternative ways of interpreting the data. Next, the decision to study the alerting effects of caffeine and the

dependent measure used to assess changes in alertness are examined. After presentation of my experiment, the discussion section summarizes the results and expands on the issues associated with the interpretation of the experimental results.

Pavlovian Classical Conditioning Model

Classical conditioning is a model or paradigm that stipulates the essential conditions for the acquisition of associations. The first stipulation is that some stimulus reliably elicits a characteristic response. The connection between the stimulus and response is unlearned (innate) and thus, the pair are termed unconditioned stimulus (US) and unconditioned response (UR), respectively. The third and fourth elements of the classical conditioning paradigm are the conditioned stimulus (CS) and the conditioned response (CR). The CS is an originally neutral cue that acquires the ability to elicit a learned response, the CR, after being repeatedly paired with the US.

Pavlov asserted that the most important feature of the classical conditioning procedure was the contiguity or close presentation of CS and US in time. Figure 1 diagrams Pavlov's original classical conditioning experiment (1927) involving the presentation of the CS (bell) followed by the US (meat powder). On the first trial, the presentation of the bell, a neutral stimulus, is followed by the presentation of the food. Initially, only the US will elicit salivation, however, after repeated pairings both the bell (the CS) and the food (the US) will elicit salivation.

Thus, the significant outcome of the classical conditioning paradigm is that the CS is now capable of eliciting a CR. The importance of this

CR is that the animal has learned to anticipate the presentation of food and elicit the necessary response (salivation) that will enhance digestion of the food.

A control group used in these procedures, would have the CS explicitly unpaired with the US (bell only). It is hypothesized that in this group, no association is formed between the CS and US and thus, this group serves as a control for the conditioning that takes place in the experimental group, which reliably pairs the CS with the US. While it may be advantageous for the CR to closely resemble the UR in Pavlov's original experiment, it has become increasingly apparent and relevant to the present thesis that in some types of classical conditioning, it is advantageous for the CR to be different or opposite in direction from the UR.

There are generally two phases in a typical Pavlovian classical conditioning procedure; acquisition and extinction. On the first few trials of the acquisition phase, there will be little or no conditioning to the CS. After repeated pairings, the CR gradually increases and gains strength. The association between CS and US and the development of strength of the CR is referred to as the acquisition phase. Figure 2 shows a hypothetical diagram of the acquisition phase, in which the rate of conditioned responding increases to the conditioned stimulus over trials or days. The pattern of results suggest that learning is greatest during the first several conditioning days and that after this point, the stable maximum level of conditioned responding or asymptote is approached.

Once a conditioned response is acquired, the mere passage of time will have relatively little effect on the strength of a conditioned response.

However, following an acquisition phase, extinction is a procedure which reduces and eventually eliminates the strength of the CR. The extinction procedure involves repeated presentations of the CS without the US. Like the acquisition phase, Figure 2 shows that during the initial trials or days of the extinction phase, there are large reductions in the acquired behavior. During the last few days, the decreases in conditioned responding is more gradual but eventually the CR will disappear altogether.

Stimulus substitution theory

In an attempt to explain how CRs are acquired and what function the CS serves in conditioning, Pavlov proposed a theory of classical conditioning referred to as the stimulus substitution theory. According to this theory, the CS becomes a substitute for the US through repeated pairings. Despite apparent support in some of the research, the stimulus substitution theory has been criticized for several reasons. First of all, it is widely accepted that the CR is rarely an exact replica of the UR and instead, differs from the UR in terms of the temporal pattern and magnitude. Second, the CS generally does not elicit all of the same responses as the US and instead may elicit some responses of its own.

Possibly the most difficult finding to explain in terms of a stimulus substitution theory, is that in some cases the direction of the CR is opposite to that of the UR. For example, in experiments where morphine has been paired with a CS (e.g., environment A), the CR is sometimes an increase in body temperature but in other cases, a decrease in body temperature (Siegel, 1978b). Conditioned responses that are opposite to the UR were originally referred to as examples of paradoxical conditioning (Finch, 1938), and more recently termed

conditioned compensatory responses (Siegel, 1975, 1988). Regardless of their label, it can be seen that there are significant difficulties with the stimulus substitution theory as a general theory of classical conditioning.

Information processing theory

An information processing theory by Rescorla (1967) has provided a new perspective on classical conditioning. Simply stated, a CS acquires meaning concerning whatever event follows it in time. If a CS reliably predicts the presence or absence of a US, the CS will gain considerable "information value" regarding the likelihood of the occurrence or absence of the US. The emphasis is placed on CS-US contingency rather than CS-US contiguity.

According to the information processing theory, a CS will not acquire information value when it is equally likely to predict the occurrence or the absence of a US. However, as the CS increasingly predicts the presence or absence of the US, the probability or associative strength of the CS-US will increase in either a positive or negative direction.

Using a conditioned suppression technique with rats, Rescorla (1978) assessed the strength of conditioning when the CS-US probability was manipulated. In the first part of the experiment, four groups were trained to press a lever for food. After this behavior was stabilized, the lever was removed from the cage and in the second phase, a classical conditioning paradigm was initiated. In this phase, the probability of receiving a shock (US) in the presence of a tone (CS) was .4 for all four groups. The probability of receiving the US in the absence of the CS was .4, .2, .1 and 0 for the four groups, respectively. In the third phase, the lever was reintroduced and lever pressing behavior was again

stabilized. In the final test phase, the tone CS was presented without the shock US and suppression of lever pressing was measured.

Since it has been shown that a shock US will suppress lever pressing, assessment of the CS-US associative strength was measured in terms of a suppression of lever pressing rate ratio. The suppression ratio equals B/A+B, where A is the number of responses just prior to the CS and B is the number of responses during the CS. As depicted in Figure 3, in the final phase of the experiment responding was greatest for the .4 group, where CS equally predicted the presence or absence of the US.

In contrast, significant suppression of lever pressing was noted in the other groups and the initial degree of suppression was inversely related to the probability of the US in the absence of the CS. Rescorla concluded that the CS's ability to elicit the same response as the US (excitatory conditioning) occurs when the probability of the CS predicting the presence of the US (CS-US presence) outweighs the probability of the CS predicting the absence of the US (CS-US absence). Conversely, a CS's ability to inhibit a CR (inhibitory conditioning) will increase when the probability of the CS-US absence is greater than the probability of the CS-US presence.

Rescorla's findings that the disparity of the probabilities between CS-US presence and CS-US absence directly influences the outcome or response, has important implications for learning theory. These data suggest that during classical conditioning procedures, the CS will acquire information or "meaning" with respect to the US when the CS either predicts the presence or absence of the US. As a result of these findings, Rescorla asserts, that the most appropriate control condition in Pavlovian experiments, is when a truly random relationship exists

between the CS and its outcome, for this is the only case where the CS will remain neutral.

While Rescorla's own work supports the information processing theory, more recent investigations have shown that a truly random control group may result in conditioning. For example, Kremer (1971) and Kremer and Kamin (1971) have reported differential responding to random CS-US training procedures and Furedy and Schiffman (1973) have failed to find any differences in responding between random control groups and explicitly unpaired CS-US groups. More recently, Papini and Bitterman (1990) have asserted that "CS-US contingency is neither necessary nor sufficient for conditioning and that the concept has long outlived any usefulness it may once have had in the analysis of conditioning".

Despite opposition, Rescorla maintains that the strength of the CS is found in the consistency of the CS-US contingency or correlation rather than in terms of CS-US pairings alone. In a recent paper, Rescorla (1988) stated that "conditioning is now described as the learning of relations among events so as to allow the organism to represent its environment". Although the controversy between the contingency and contiguity theories remains very much alive and is far from resolved, Rescorla's information processing theory reminds us that an important goal of learning research must be to characterize how animals come to expect and anticipate future events.

Classical Conditioning Analysis of Drug Tolerance

Pavlov was the first to suggest that the drug administration procedure can serve as a CS because the injection ritual cues and

environment in which the drug is injected reliably precede the effects of the drug. He showed that a tone, reliably paired with the administration of apomorphine, came to elicit some of the same behavioral symptoms of the drug.

As mentioned earlier, CRs do not always mimic URs but are sometimes opposite in direction. In an early demonstration of such a CR, Subkov and Zilov (1937) found that dogs exhibited a decrease in heart rate when in the presence of cues which were repeatedly paired with administrations of epinephrine (which causes increases in heart rate). Since this demonstration of pharmacological conditioning, numerous studies have shown that CRs can be opposite to the drug effect and that CRs that are opposite to URs play an integral role in the development of drug tolerance (see Siegel, 1988 for review).

One of the first studies to demonstrate that environmental stimuli present at the time of drug administration may have profound effects on the development of drug tolerance was unwittingly done by Adams, Yeh, Wood and Mitchell (1969). In this study, morphine's analgesic effect was assessed using a common measure of pain sensitivity, the hot plate procedure. During this procedure, the rat was placed on the surface container for one minute and the time elapsed until it first licks a paw (hereafter referred to as the paw-lick latency) was measured. Analgesic responses were indicated by relatively long paw-lick latencies and hyperalgesic responses by relatively short paw-lick latencies.

During baseline assessment, all animals were found to be analgesic in response to morphine administration. In the tolerance development phase, rats were separated into two groups: morphine administration reliably paired with home cage environment (M-CAGE), and morphine

reliably paired with the hot-plate test environment (M-HP). To test for development of tolerance, both groups received morphine in the test-environment and latency of paw lick to the hot-plate was measured. The data showed that Group M-HP was significantly less analgesic than baseline; thus, the rats in this group developed tolerance to morphine's analgesic effects. The data also showed that Group M-HP was significantly less analgesic than Group M-CAGE. Thus, Group M-CAGE was less tolerant than Group M-HP to morphine's analgesic effects.

Since both groups received the same drug exposure schedule, Mitchell and colleagues were unable to explain differences in tolerance levels between the M-CAGE and M-HP groups in terms of traditional pharmacological theories which assert that tolerance depends on drug exposure parameters (e.g., dose, interdrug dose interval). To determine if practice making the analgesic response was responsible for the decrease in analgesia in the M-HP group, a third group was added. In this control group, morphine was repeatedly paired with the hot-plate test environment at an ambient (cold-C) temperature (M-CP) (Adams et al., 1969).

The data supported the initial findings of enhanced tolerance when tolerance acquisition and testing were done in the same environment. Thus, practice effects could not account for differential enhancement of tolerance in the two environments. Although these findings were quite unexpected and difficult to explain in terms of traditional physiological models, Mitchell and colleagues suggested that the test environment might produce stress and that tolerance may be enhanced by the co-occurrence of drug effects and stress.

Siegel's conditioning model

Several years later, Siegel did a series of sophisticated experiments which supported Mitchell's findings of enhancement of tolerance when tolerance development and tolerance testing phase were conducted in the same environment. Unlike Mitchell's interpretation, Siegel asserted that contextual enhancement of tolerance can be attributed to Pavlovian conditioning (1975).

According to Siegel's Pavlovian conditioning model of drug tolerance, the US is the drug and the UR is the physiological effect of the drug. The CS is any environmental cue that reliably predicts the occurrence of the US. Unlike the traditional Pavlovian conditioning model, Siegel hypothesized that the CR is a homeostatic mechanism that opposes and thereby minimizes the drug's effect. Thus, it is the summation of the UR and "compensatory" CR which results in decreased drug effect (tolerance) and restoration of homeostasis in the organism.

In an early experiment, Siegel (1975) studied the effects of the environment on the development of tolerance to morphine's analgesic effects. Morphine-naive rats were divided into four groups: morphine paired with hot plate (M-HP); morphine paired with hot plate at ambient temperature (M-CP); morphine paired with home cage (M-CAGE); and saline paired with hot plate (S-HP). On each of the four sessions of the study, Groups M-HP, M-CP and M-CAGE received equivalent morphine injections and Group S-HP received saline. On the first three sessions, each group received drug in its respective environment and analgesic effects were assessed in Groups M-HP and S-HP only, using the hot plate procedure described above. On session 4, analgesic effects

were assessed in all four groups.

The mean paw-lick latency results and design are shown in Figure 4. On session 1, Group M-HP was significantly more analgesic than Group S-HP. These results demonstrate the significant analgesic effects of morphine when compared to saline in morphine-naive rats. On sessions 2-4, Group M-HP had progressively shorter paw-lick latencies than on session 1 and there was no difference in paw-lick latencies on session 4 between groups M-HP and S-HP. These findings indicate that the analgesic effects of morphine were significantly less pronounced on successive drug administration sessions; tolerance develops.

Since there was no significant difference in analgesia between Groups M-HP and M-CP on session 4, practice effects could not account for the development of tolerance in Group M-HP. Finally, Group M-CAGE was significantly more analgesic than the other groups on session 4 and not significantly different from Group M-HP on session 1.

These results suggest that analgesic tolerance is not an inevitable consequence of repeated morphine administration because equivalent opiate exposure did not lead to equivalent levels of tolerance in the three groups that received morphine. Instead, the data demonstrate that tolerance is more pronounced when the drug is administered in the context of the usual predrug cues than in the context of alternative cues. It appears then, that a viable explanation for the development of tolerance must include associational mechanisms.

If it is true that tolerance involves some form of learning, then perhaps it is understandable that results of studies attempting to relate pharmacological changes to the development of tolerance have been equivocal; for the pharmacology of drug tolerance may be analogous to

unraveling the pharmacology of learning- a formidable task at best.

What's more, there are problems with the interpretation that the development of tolerance is caused by pharmacological changes since correlational findings do not necessarily imply causality between the two phenomena being correlated. As Kalant (1973) suggested in a paper on ethanol tolerance: "It is true that tolerance has been shown to be accompanied by certain definable metabolic changes.. But until we know how this relates to neuronal firing rate, to modulatory influences from other neurones, to level of behavioural arousal.. we are not really explaining very much." With this in mind, I will now return to studies which support and extend the potential role that Pavlovian conditioning plays in the development of tolerance.

According to a conditioning analysis of tolerance, the compensatory CR may be directly observed by presenting the previously associated drug cues without administering the drug. In Siegel's study mentioned above, sessions 5-8 were added where Group M-HP then received placebo (saline) injections and analgesic levels were measured.

As shown in Figure 5, the mean paw-lick latencies for Group M-HP were significantly shorter during the successive morphine injections (tolerance developed) and after the fourth session of morphine injections, were equivalent to baseline levels of analgesia. However, when placebo was then administered during sessions 5-8, in the presence of the usual predrug cues, analgesia levels dropped significantly below baseline levels, indicating that the animals were more analgesic or hypersensitive relative to baseline. Siegel concluded that ".. in response to a ritual that had been associated with morphine administration but now not followed by the central effects of the drug, morphine-tolerant Group M-HP rats

displayed hyperalgesia."

In the same paper, Siegel studied the effects of an extinction procedure on tolerance using the following design: In sessions 1-3, morphine was reliably paired with the test environment in two groups and the development of analgesic tolerance was assessed; then one group received nine sessions of CS paired with saline (placebo, Group M-P-M) and a control group (Group M-REST-M) was left undisturbed in its home cage; In sessions 4-6, morphine was paired with predrug cues in both groups and tolerance was assessed.

Figure 6 shows the results of the six sessions. Both groups evidenced analgesic tolerance over the course of the first three administrations of the drug. On session 1, Group M-P-M was more analgesic (less tolerant) than Group M-REST-M. Thus, the repeated administration of predrug cues alone in Group M-P-M extinguished the compensatory CR, but the mere passage of time did not affect tolerance levels in Group M-REST-M. This finding is a unique prediction of classical conditioning theory and can not be explained in terms of traditional theories of tolerance.

Other conditioning principles applied to drug tolerance research

Since these early experiments, there has been an abundance of literature on research that applies other conditioning principles to the problem of drug tolerance development. For example, conditioning theory states that the more salient or distinctive a CS is, the better it will be at predicting the occurrence of a US. Krank, Hinson, and Siegel (1981) demonstrated that tolerance develops more rapidly and is more resistant to extinction in a more distinctive environment (e.g., potent olfactory, auditory, and visual cues) when compared to a nondistinctive

environment. The acquisition of tolerance has also been shown to be influenced by other environmental manipulations known to be effective in retarding the acquisition of CRs. Two such manipulations which retard acquisition of CRs are partial reinforcement and latent inhibition.

In a partial reinforcement procedure, CS-alone presentations are interspersed among CS-US pairings and the acquisition of CR is shown to be substantially attenuated. Latent inhibition involves conditioning of the CS prior to CS-US pairings. The result of the CS preconditioning is a decrease in the effectiveness of that stimulus when it is subsequently paired with the US. Several studies have shown that partial reinforcement and latent inhibition procedures are effective in retarding the development of tolerance (Dyck, Greenberg, & Osachuk, 1986; Krank, Hinson, & Siegel, 1984; Siegel, 1977, 1978; Siegel, Sherman, & Mitchell, 1980; Tiffany & Baker, 1981).

Tolerance may also be affected by "unauthorized CS's" which disrupt the association between the intended CS and the US. For example, Dafters and Bach (1985) demonstrated that injection-ritual cues tend to "overshadow" less distinctive environmental cues suggesting that the injection procedures may be a potent CS and that less distinctive environments may be ineffective CSs. Once tolerance is established, a novel and salient stimulus may disrupt a CS from eliciting a CR. This type of classical conditioning procedure termed external inhibition has also been shown to be effective in the disruption of the display of tolerance (Siegel & Sdao-Jarvie, 1986).

Prediction of the conditioned response

At present the conditions that favor the expression of a drug-mimicking) CR or a drug-opposite (drug-compensatory) CR are unclear.

A related unresolved issue is how to account for both mimicking and opposing CRs within a single response system. Eikelboom and Stewart (1982) have proposed a model that attempts to answer both questions in terms of Pavlov's stimulus substitution theory. According to their theory, the CR always mimics the UR. It is important, however, to correctly define the US and the UR. While conditioning studies generally consider a drug, the US, and the observed drug effects, the UR, Eikelboom and Stewart offer a more restrictive definition; one which defines stimulus and response in terms of the drug's relationship to the central nervous system (CNS).

Eikelboom and Stewart state that the stimulus always acts on the afferent arm of the CNS and the response is the CNS-mediated response. Thus, a drug is considered a US only when it acts on the afferent arm of the CNS because the drug acts directly on the CNS. In this situation, the UR is the CNS-mediated observed drug effect (Figure 7). In contrast, when a drug acts peripheral or efferent to the CNS, it is the effects of the drug that act on the CNS and thus, the observed drug effects are considered the US. Such drug effects cause a disequilibrium which is counteracted by a CNS-mediated compensatory response, the UR (Figure 7).

Once the site of action of a drug relative to the CNS is specified according to its relationship to the CNS, it becomes possible to predict the direction of the CR in terms of stimulus substitution theory; as stated earlier, the CR always mimics the UR. For example, it has been shown that morphine receptor sites involved in analgesia may be efferent to the CNS. According to Eikelboom and Stewart's model, it is the observed analgesic effect of morphine, the US, that acts on the CNS and it is the

CNS-mediated hyperalgesic response, the UR, that serves to counteract the US. Through successive pairings of the predrug cues (CS) and morphine, the CS becomes capable of substituting for the US and elicits a hyperalgesic CR, like the UR. Although the terms used may be somewhat different than Siegel's classical conditioning model, tolerance is still viewed as a summation of the systemic effects of the drug and a compensatory hyperalgesic response.

To explain how tolerance develops to some but not other drug effects, it is posited that a drug may have both afferent and efferent sites of action. For example, it is possible to explain why analgesic tolerance is observed more often than thermic tolerance with chronic morphine administration in terms of morphine's different sites of action. Since analgesic sites of morphine are efferent to the CNS, the UR will counteract the US and so will the CR, thus the summation of the systemic effects (US and UR) and the CR results in analgesic tolerance. However, since thermic sites of morphine are both afferent and efferent to the CNS, the summation of the drug and the CR may or may not result in thermic tolerance. Although the simplicity of this explanation is quite appealing, it should be noted that the data are incomplete and that the issue of CR topography is far from resolved.

Criticism of Siegel's conditioning model

While most learning theorists agree that the data suggest that tolerance development conforms to a traditional model of learning, Siegel's classical conditioning analysis of tolerance has been criticized for several reasons. Some investigators have had difficulty finding a consistent and robust compensatory CR. In particular, some

investigators have not observed the hyperalgesic CR that Siegel hypothesizes mediates morphine analgesic tolerance (Fanselow & German, 1982; King, Bouton, & Musty, 1987; Siegel, 1988; Tiffany, Petrie, Baker, & Dahl, 1983).

The conditioned response and Siegel's rebuttal

Although some suggest that the failure to demonstrate the compensatory CR is "clearly embarrassing for Siegel's account of tolerance" (Goudie & Griffiths, 1986), Siegel presents several explanations to account for the elusive nature of the compensatory CR, that are consistent with a Pavlovian analysis of drug tolerance.

As King et al. (1987) first suggested, environmental specificity of tolerance may be easier to measure than the compensatory CR. Also, the compensatory CR may be particularly sensitive to the method used to measure the drug effect. For example, Krank (1987) showed that a hyperalgesic CR was found using the hot-plate technique but was not found using the tail-flick technique. Since the hot-plate technique has a much higher baseline response latency than the tail-flick technique, one might expect that the hot-plate technique would be more sensitive in measuring decreases in response latency (hyperalgesia).

It is also possible that the compensatory CR is counteracted by regulatory, homeostatic influences, in the absence of the systemic drug effects the CR normally attenuates. Thus, the compensatory CR is observable only if the response system is pharmacologically primed or "challenged".

A clever example of such a challenge is the presentation of drug-associated cues and then, administration of a drug that has opposite effects on that response system (DRUG-OPP) to the drug normally

associated with the cues. If there is an enhancement of DRUG-OPP's effects, it may be explained in terms of a summation of the CR and UR in the same direction. Hinson and Siegel (1982) showed that when cocaine (behaviorally stimulating) was administered in the presence of cues normally associated with pentobarbital (behaviorally sedating), the convulsive effect of cocaine was exaggerated. Hinson and colleagues have also demonstrated the enhancement of other drugs when paired with drug-opposite cues (Poulos & Hinson, 1984; Hinson & Rhijnsburger, 1984).

Another explanation for why the compensatory CR may not always be detectable may involve external inhibition, however, in the case of compensatory CR testing it may be the absence of the usual drug-onset cues that acts as a novel event and hence, disrupts the CR. Thus, failure to demonstrate the compensatory CR in these procedures may support the environmental specificity of tolerance. That is, the absence of the early effects of the drug may disrupt the compensatory CR because these early drug effects are an integral part of the drug-predictive cues.

Several investigators have provided evidence demonstrating the importance of the drug onset cues in the expression of the compensatory CR (Greeley, Le, Poulos, & Cappell, 1984; King et al., 1987; Mackintosh, 1987; Walter & Riccio, 1983).

Nonassociational tolerance and habituation theory

A second criticism of the conditioning analysis of drug tolerance which has been more difficult to account for using Pavlovian principles is, that in some instances, tolerance develops when there are no reliable environmental cues (Tiffany & Baker, 1981, 1983).

There is considerable evidence that, in the absence of reliable drug-

predictive environmental cues, the development of tolerance varies as a direct function of dose and as an inverse function of the interdose interval (IDI) (Davis, 1970; Fernandes et al., 1977; Kalant et al., 1971; Mucha, Kalant, & Linesman, 1979). For example, it has been demonstrated that in the absence of reliable drug-predictive cues, morphine analgesic tolerance develops rapidly with large doses of morphine and brief IDIs (Tiffany & Baker, 1983).

This finding is opposite to the commonly accepted observation of stronger associative tolerance with lower doses and longer IDIs. Thus, Tiffany and Baker have suggested that situations where tolerance develops without drug-cue contingencies are not associational in nature and should be referred to as nonassociational tolerance.

To explain both associational and nonassociational tolerance, Baker and Tiffany (1985) have proposed a learning model that borrows from Wagner's more general information-processing habituation model (1977).

According to Wagner's model, an incoming stimulus is compared with a representation of the stimulus in short term memory (STM). A surprising or novel stimulus will not be represented or "primed" in STM and consequently will be processed more effectively than an expected stimulus, which will be primed in STM. The more a stimulus is processed, the more likely it is that the stimulus will evoke a response to the stimulus event. Conversely, repeated presentation of the stimuli results in an increase in priming, which leads to less stimulus processing and a decrease in the likelihood of a response. Habituation refers to the decreased responding to a stimulus event over repeated presentation.

Wagner's "comparator theory" of habituation posits that there are

two ways in which a stimulus representation is primed in STM; associatively and self-generatively. Associative priming occurs when stimuli previously associated with the stimulus are presented, and self-generated priming is a result of recent exposure to the corresponding stimulus itself.

Applying this model to drug tolerance, Baker and Tiffany (1985) suggest that the drug is the stimulus or US, and the diminution of the drug's effects over repeated administrations (tolerance) is the UR. In this view, tolerance may be a result of associative priming (presentation of reliable drug-predictive cues) and/or self-generated priming (pharmacological factors- dose and IDI). Although a detailed analysis of how the habituation model predicts drug tolerance is beyond the scope of this dissertation, it is important to highlight the similarities and differences between this model and Siegel's classical conditioning model.

Siegel's model vs. habituation model

Both models predict that associative phenomena such as environmental specificity and extinction procedures will have profound effects on the development of tolerance. As elaborated earlier, Siegel's model explains tolerance in terms of a summation of the UR and compensatory CR. Baker and Tiffany (1985) account for the development of associative tolerance in terms of Wagner's concept of associative priming, thus, repeated pairings of an environment and a drug causes a diminution of the UR; the observed drug effect. In both models then, reliable pairing of a drug with drug-predictive environmental cues results in tolerance.

An important difference between these two models lie in their

ability to explain drug tolerance phenomena. While Siegel's model can account for drug tolerance that occurs when a drug is reliably preceded by drug delivery cues, his model can not account for the development of drug tolerance in the absence of drug-predictive cues. Baker and Tiffany's habituation model can account for both associational and nonassociational tolerance. As mentioned earlier, numerous studies have shown that, in the absence of environmental drug-predictive cues, both dose and IDI influence the development of tolerance in a manner contrary to learning principles.

In a study by Tiffany and Baker (1981), analgesic tolerance developed in two types of groups; one group had morphine explicitly paired with the test apparatus (M-TEST) and the other group had morphine explicitly unpaired with the test apparatus (M-CAGE). Although it should be noted that Group M-TEST was less analgesic (more tolerant) than Group M-CAGE, it is difficult to explain the tolerance observed in Group M-CAGE by associative mechanisms.

Furthermore, this study also demonstrated that in the absence of drug predictive cues (unsignaled situation), tolerance was a direct function of dose (higher doses of morphine, more tolerance). Another study showed that in the absence of reliable environmental cues, drug tolerance develops quicker with shorter IDIs (Tiffany & Maude-Griffin, 1988).

Since the habituation model also predicts that the development of tolerance through nonassociative mechanisms will attenuate the acquisition of associative tolerance, a recent study by Tiffany, Maude-Griffin, & Drobes (1991) evaluated the interaction between associative and nonassociative tolerance.

During the tolerance development phase, there were three different IDIs (12-, 24-, or 96-hr) and two different environments (distinctive environment, DC, or home cage, HC) giving a total of six different drug delivery conditions. Rats reliably received eight injections of 20 mg/kg morphine sulfate in one of these six different conditions. To reduce the salience of the home-cage injection procedures, animals in these six conditions were injected with saline in the home cage, in between each morphine injection. A seventh control condition was included where rats received saline injections in both the distinctive environment and the home cage.

At the end of the tolerance development phase, all rats were assessed for analgesic sensitivity in the distinctive environment using dose-response methodology (DRC). DRC methodology involves giving several different test doses (e.g., 2.5, 5, 7.5, 20 mg/kg) to the subgroups within a condition. DRC methodology was used to assess tolerance because Dafters and Odber (1989) showed that the evaluation of tolerance development using single test doses may produce misleading results regarding tolerance magnitude. Using the DRC methodology, tolerance is indexed by a shift to the right in the dose-response curve relative to the control condition.

The results depicted in Figure 8 show that rats in all three DC conditions developed more tolerance than rats in the three HC conditions, but that both DC and HC conditions produced more tolerance than the saline control condition. Within the three DC conditions, the 12-hr IDI condition developed significantly less tolerance than the 24- or 96-hr IDIs but there were no systematic differences in the DRC shift between the three HC conditions. The authors stated that the

findings of tolerance in the distinctive environment conditions provide clear evidence of "robust associative tolerance" and the results of tolerance in the HC conditions suggest that nonassociative tolerance may also develop. The authors also suggested that the attenuated tolerance found in the 12-hr DC condition relative to the 24- and 96-hr DC conditions possibly represents a disruption in associative tolerance caused by nonassociative mechanisms.

To test whether the tolerance found in the 12-hr DC condition was an interaction of associative and nonassociative tolerance and the tolerance in the three HC conditions might be produced primarily by nonassociative tolerance, a second experiment studied the retention of tolerance over time. According to the habituation model, nonassociative tolerance will decay over time after drug abstinence. The six different conditions for the tolerance development phase in experiment two were as follows: 12- or 96-hr IDIs, distinctive or home cage environment injections, and morphine or saline administrations. Like experiment 1, there were eight injections of morphine or saline. During a 30-day retention interval, home cage injections of saline were administered to reduce the salience of the injection ritual cues. After 30 days, analgesic sensitivity was assessed using DRC methodology and tolerance magnitude was indexed by a shift to the right in the dose-response curve relative to the two saline control conditions.

Results from experiment 2, depicted in Figure 9, demonstrate that associative tolerance in both the 12- and 96-hr DC conditions was retained over a 30-day interval but tolerance was not retained over 30 days in either of the HC conditions. These findings are not consistent with the hypothesis that nonassociative mechanisms produced the

disruption of associative tolerance in the 12-hr DC condition. The absence of tolerance in the two HC conditions after 30 days, could be due to nonassociative mechanisms or alternatively, the administration of saline injections during the 30-day retention interval may have extinguished the association between injection ritual cues and drug.

These results, however, weaken another associative interpretation of the data that is usually given to account for the tolerance exhibited in unsignaled drug delivery. That is, that an association is formed between early drug onset cues and later drug effects and that these initial drug cues act as "interoceptive" CSs which elicit compensatory CRs (Greeley et al., 1984; Taukulis, 1982). If the tolerance originally displayed in the HC tolerance conditions was due to the associative control of tolerance by drug interoceptive CSs, tolerance should have persisted over the 30 days.

In sum, the review of tolerance research provides clear evidence that associative mechanisms play a significant role in the development of tolerance, however, it has become increasingly evident that nonassociative mechanisms are also involved. In particular, conditioning models have had difficulty explaining the findings of tolerance in unsignaled drug delivery paradigms. Thus, it appears that at this time, Siegel's model is at a loss for explaining how in explicitly unpaired or unsignaled situations, dose and IDI impact on the development of tolerance in a manner opposite to that generally observed with associative tolerance.

Although Baker and Tiffany's habituation model can account for associative and nonassociative findings of tolerance, their model has its shortcomings as well. Since memory mechanisms are integral to their

theory of habituation, their model cannot explain demonstrations of nonassociative tolerance that occur in vitro; that tissues that are bathed in a drug solution become insensitive to effects of the drug (Ehrenpreis, Light, & Schonbuch, 1972; Schulz, Seidl, Wuster, & Herz, 1982).

Also, the habituation model does not attempt to explain underlying mediating mechanisms and can not predict how different classical conditioning procedures (e.g., external inhibition, partial reinforcement) impact on the development of tolerance and or explain how tolerance can develop to some behaviors (e.g., analgesia) but not to other behavior (e.g., thermia) with the same drug (e.g., morphine). Perhaps the most clinically significant failing of the habituation model, is that it does not provide a unitary account of tolerance, sensitization, and drug dependence.

Tolerance, Sensitization, and Drug Dependence

According to Siegel's model, tolerance, sensitization, and drug dependence may be explained by classical conditioning principles. Drug sensitization refers to the increased effect of a fixed drug dose over repeated drug administrations. Since the conditioning model allows for both drug mimicking and drug compensatory responses, it is hypothesized that sensitization involves a CR which mimics the UR. Like the compensatory CR, the drug-like CR modulates the observed drug effect. In this case, however, the net result of the drug-like CR and UR leads to an augmentation of the drug effect over the course of repeated administrations. Several recent studies have provided evidence that supports Siegel's conditioning model of drug sensitization (Post, Contel, & Gold, 1980; Bennet & Krank, 1985).

Drug dependence refers to the establishment of a CNS state caused by chronic drug exposure. Although drug dependence is inferred from evidence which demonstrates that withdrawal symptoms occur when the drug is withdrawn, it is hypothesized that physical dependence continues even during drug exposure. Siegel suggests that once tolerance or sensitization has developed, environmental cues continue to elicit anticipatory CRs whether drug is administered or not. Thus, withdrawal symptoms are drug-preparatory CRs elicited in the absence of drug administration.

According to Siegel's conditioning interpretation, all three phenomena associated with chronic drug exposure (tolerance, sensitization, and dependence) are a result of a single homeostatic mechanism which serves to modulate a drug's effects. While tolerance may be viewed as an adaptive process, the underlying compensatory CR (the withdrawal symptoms) may be the less than perfect means through which homeostasis is achieved. Cappell and Le Blanc (1981) eloquently characterize the relationship between tolerance and dependence in the following quote: "Tolerance represents an ideal window through which to examine the adaptations of units ranging in size from individual cells to intact organisms. Similarly, physical dependence appears to represent a biological "price" for this adaptation with physiological and behavioral consequences of its own."

While there is much controversy over the relationship between tolerance and dependence and over the model that best accounts for the drug tolerance research, it has become apparent that associational mechanisms are involved in the development of tolerance. Thus, the central issue of the present dissertation is that Pavlovian conditioning is

integrally involved in the development of tolerance in a nonopiate drug; caffeine.

Rationale for the Present Study

In a review article, Siegel (1988) reports on drug tolerance research in which compensatory CRs were observed in behaviorally sedating drugs (e.g., barbiturates, benzodiazepines, alcohol), as well as in behaviorally stimulating drugs (e.g., amphetamines and caffeine). I have chosen to study caffeine for several reasons: it is the most widely used drug in today's society (Griffiths & Woodson, 1988); studies of the reinforcing effects of caffeine and the withdrawal syndrome associated with abstinence from caffeine suggest that caffeine has some of the cardinal features of a prototypic drug of abuse and; although subjective reports suggest that caffeine is often consumed for its alerting effects, the objective alerting effects of acute and chronic caffeine consumption are poorly characterized.

Eighty percent of the adult population in the U.S. are estimated to consume caffeine in some form (Dews, 1982). Caffeine has mild central stimulatory actions, which may be manifested under the right circumstances, as enhanced alertness, wakefulness, increased energy, and elevated mood. Ninety-nine percent of ingested caffeine is readily absorbed by the gastrointestinal tract and within minutes is distributed into the CNS and into various tissues in approximate proportion to their water content. Peak plasma levels are generally reached within 15 to 45 minutes after ingestion and caffeine's average plasma half-life, though quite variable, is 3.5 hours (Axelrod & Reichenthal, 1953; Dews, 1982; Stephenson, 1977).

Caffeine as a drug of abuse

In an effort to understand why there is such a high prevalence of caffeine use, the reinforcing effects of caffeine has more recently been investigated. In a study by Griffiths, Bigelow, & Liebson (1986), nine heavy caffeine users (mean: 14 cups of coffee/day) were allowed to freely self-administer only caffeinated coffee for ten days (caffeinated background). During this ten day period, subjects did not significantly increase the number of cups of coffee but in a choice test immediately following this period, subjects reliably chose caffeinated coffee over decaffeinated coffee and rated decaffeinated coffee as being aversive relative to caffeinated coffee. In contrast, after ten days of freely self-administering only decaffeinated coffee (decaffeinated background), the same nine subjects did not reliably choose caffeinated coffee or rate it as being better liked than decaffeinated coffee.

To the extent that choice tests and rating scales predict reinforcing effects, the authors interpreted these findings as evidence that caffeine can serve as a reinforcer when subjects are caffeine tolerant/dependent (caffeine background condition). However, under conditions in which subjects are nontolerant/ nondependent (decaffeinated background condition), the reinforcing effects of caffeine are equivocal.

While tolerance and dependence are presumed to influence consumption of caffeine, there are problems with the authors' interpretation of the results. One can not infer that these subjects were dependent or tolerant simply because they chose caffeinated coffee or rated decaffeinated coffee as being aversive relative to caffeinated coffee. As Cappell and Le Blanc (1981) have pointed out, the assumed link between tolerance, dependence and drug self-administration remains

controversial.

Perhaps the most convincing piece of evidence against the authors' hypothesis is that the subjects did not significantly increase the number of cups of coffee consumed over time. Thus, there is no evidence that tolerance developed in the caffeine background condition. Nevertheless, this study is important because it suggests that prior caffeine use influences present caffeine consumption and plays a role in determining caffeine's reinforcing effects. Several other human studies and one animal experiment have replicated and extended this observation to include subjects with histories of moderate caffeine use and to caffeine in capsule form (Griffiths & Woodson, 1987b, 1988b; Stern, Chait, & Johanson, 1989).

Griffiths et al. (1986) also suggested that the aversive subjective effects that were associated with decaffeinated coffee in the caffeinated background condition may reflect withdrawal symptoms from caffeine. To characterize the extent and course of the caffeine withdrawal syndrome, seven subjects from the first study were switched abruptly from caffeinated to decaffeinated coffee for 10 or more days. The most sensitive and reliable subject-rated symptom related to caffeine withdrawal was headache, however, increased sleepiness and laziness and decreased alertness and activeness were also reported. Other studies have also shown that there are significant aversive effects associated with abstinence from caffeine use (Goldstein, Warren, & Kaizer, 1965, Goldstein, Kaizer, & Whitby, 1969; Vitiello & Woods, 1977; Stern et al., 1989).

While the findings that caffeine can serve as reinforcer and produce withdrawal symptoms appear to implicate caffeine as a drug of abuse, it

should be noted that there are some important distinctions between caffeine and other classic drugs of abuse. For example, cocaine and d-amphetamine maintain high levels of self-administration but caffeine tends to maintain lower levels of self-administration (Griffiths & Woodson, 1988b). Thus, it appears that further research is needed to delineate the precise conditions under which caffeine does and does not control behavior.

Caffeine's reinforcing effects have been summarized by Ritchie (1975) in the following terms: "Caffeine results in a more rapid and clearer flow of thought, and allaying of drowsiness and fatigue." Since many other anecdotal reports suggest that caffeine is often consumed for it's alerting effects, much research has focused on the subjective and objective alerting effects of caffeine on nighttime sleep and daytime wakefulness.

Caffeine's alerting effects

In 1965, Goldstein et al. found that 300 mg caffeine dissolved in decaffeinated coffee given before bedtime, caused distinctly less subjective wakefulness in subjects who habitually drank >3 cups of coffee/day than in nonconsumers (>1 cup coffee/day). They also found that on subjective rating scales, nonconsumers tended to report more negative effects (e.g., headaches, jitteriness) and habitual caffeine users consistently reported positive effects (e.g., alertness and an increase in performance), after repeated morning caffeine administrations (300 mg/day). As a result of these findings, Goldstein et al. concluded that there were both qualitative and quantitative differences in response to caffeine that are related to the degree of habitual caffeine consumption.

In a later study (1969), Goldstein et al. confirmed earlier findings of

subjective disruption of nighttime sleep in nonconsumers when 300 mg caffeine was given before bedtime but also found that all subjects reported sleeping significantly more soundly on nights when placebo (decaffeinated coffee alone) was given before bedtime than when caffeine was administered. Goldstein concluded that "despite their [habitual users] high caffeine consumption, they are apparently not tolerant to the sleep-disturbing effects. Indeed, we can find no convincing published evidence that tolerance develops to any action of caffeine in man."

Using an objective measure of nighttime sleep (polysomnographic recording), Colton (1968) demonstrated that a lower dose of caffeine (100 mg) given before bedtime did not modify sleep parameters in consumers but significantly increased sleep latency and number of awakenings during the night in nonconsumers. Contrary to Goldstein's interpretation, Colton concluded that tolerance to caffeine's sleep disrupting effects may develop with lower doses of caffeine.

The discrepancy between Goldstein and Colton's findings may partially be resolved by Karacan, Thornby, Anch, Booth Williams, & Salis's (1976) study which demonstrated that in habitual consumers, approximately 100 mg caffeine given before bedtime, had little or no effect on objectively measured nighttime sleep parameters. However, 150 mg caffeine had significant effects, and 300 mg caffeine had the most significant effects on sleep parameters.

This study also demonstrated that, although subjective measures of sleep parameters were not as sensitive as objective measures, there was a similar positive relationship between caffeine dose and subjective levels of sleep disruption. Thus, this study suggests that in habitual consumers,

caffeine produces dose-related changes in objective and subjective sleep parameters and emphasizes the importance of the dose used to assess tolerance to caffeine's alerting effects.

Lipschutz, Roehrs, Spielman, Zwyghuizen, Lamphere, & Roth (1988) showed that 250 mg caffeine given twice a day, improved objective daytime alertness, as measured by the Multiple Sleep Latency Test (MSLT), in sleepy normal males who consumed <3 cups coffee/day. The MSLT has been shown to be an objective measure of sleepiness/alertness (see METHOD section for description of MSLT procedure) (Carskadon & Dement, 1976, 1978, 1989).

In the same study, Lipschutz et al. showed that the same amount of caffeine given the next day, did not alert subjects as much as on the previous day. The conclusions drawn from this study were that caffeine is a potent stimulant that enhances daytime alertness and that tolerance to caffeine's alerting effects may develop rapidly.

While some have shown objective enhancement of daytime alertness with caffeine (Lipschutz et al., 1988; Nicholson & Stone, 1980), other investigators have failed to demonstrate enhanced alertness using other measures of alertness (Hartmann, 1968; Clubley, Bye, Henson, Peck & Riddington, 1979). Kuznicki and Turner (1986) have shown that caffeine users (>3 and <5 cups coffee/day) do not subjectively report changes in alertness with chronic use of caffeine but do report tolerance to the negative effects (e.g., jitteriness, tension) with chronic caffeine use.

The following presentation of the research suggests that much of the inconsistencies on the findings of caffeine's alerting effects largely reflect the inadequacy of proper controls in the research (e.g., population studied, dose administered, methodological assessment of

alertness/sleepiness). Drawing from this knowledge, the present analysis will attempt to control for these variables while studying the alerting effects of caffeine over repeated administrations.

Hypotheses and Predictions

I have tested three specific hypotheses in this dissertation. The first is that humans are alerted by caffeine with acute use. Using the MSLT (Carskadon & Dement, 1977) and subjective scales of sleepiness/alertness and mood, caffeine's alerting effects after an initial administration of 250 mg caffeine, were measured. The second hypothesis is that humans develop tolerance to the alerting effects of caffeine. Following the initial administration of caffeine, this hypothesis was tested by first administering 6 doses of 250 mg caffeine over a 2 week period, and then testing whether the same dose of caffeine had diminished objective and subjective alerting effects when compared to the initial administration.

The final hypothesis is that the development of tolerance to caffeine's alerting effects over repeated administrations, is a result of Pavlovian conditioning. According to Siegel's conditioning model, the US, caffeine, has a physiological UR which is alerting. The knowledge and expectation of getting caffeine is a significant CS which over repeated administrations, will come to elicit a compensatory CR which is de-alerting. The acquisition of caffeine tolerance is a result of the summation of the systemic alerting effects of caffeine and a conditioned compensatory de-alerting response elicited by the expectations that reliably predict the caffeine administration.

I indirectly tested this hypothesis by comparing two groups that

were tolerant to caffeine's alerting effects; one group expected caffeine and got caffeine and the other group expected decaffeinated and got caffeine. Note that although both groups received caffeine, only the former group expected caffeine while the latter group expected decaffeinated coffee. According to Siegel's model, it was hypothesized that the group that expected caffeine would elicit the compensatory de-alerting response but the group that did not expect caffeine would not elicit the compensatory de-alerting response. Thus, it was predicted that the group that did not expect caffeine would be more alerted, both objectively and subjectively, after receiving the same dose of caffeine as the group that expected the caffeine.

Figure 1. The events of a Pavlovian classical conditioning trials both before (top) and after (bottom) a conditioned response is established.

(Redrawn from Domjan, M. & Burkhard, B. (1982). The principles of learning and behavior. Monterey, Cal: Brooks/Cole).

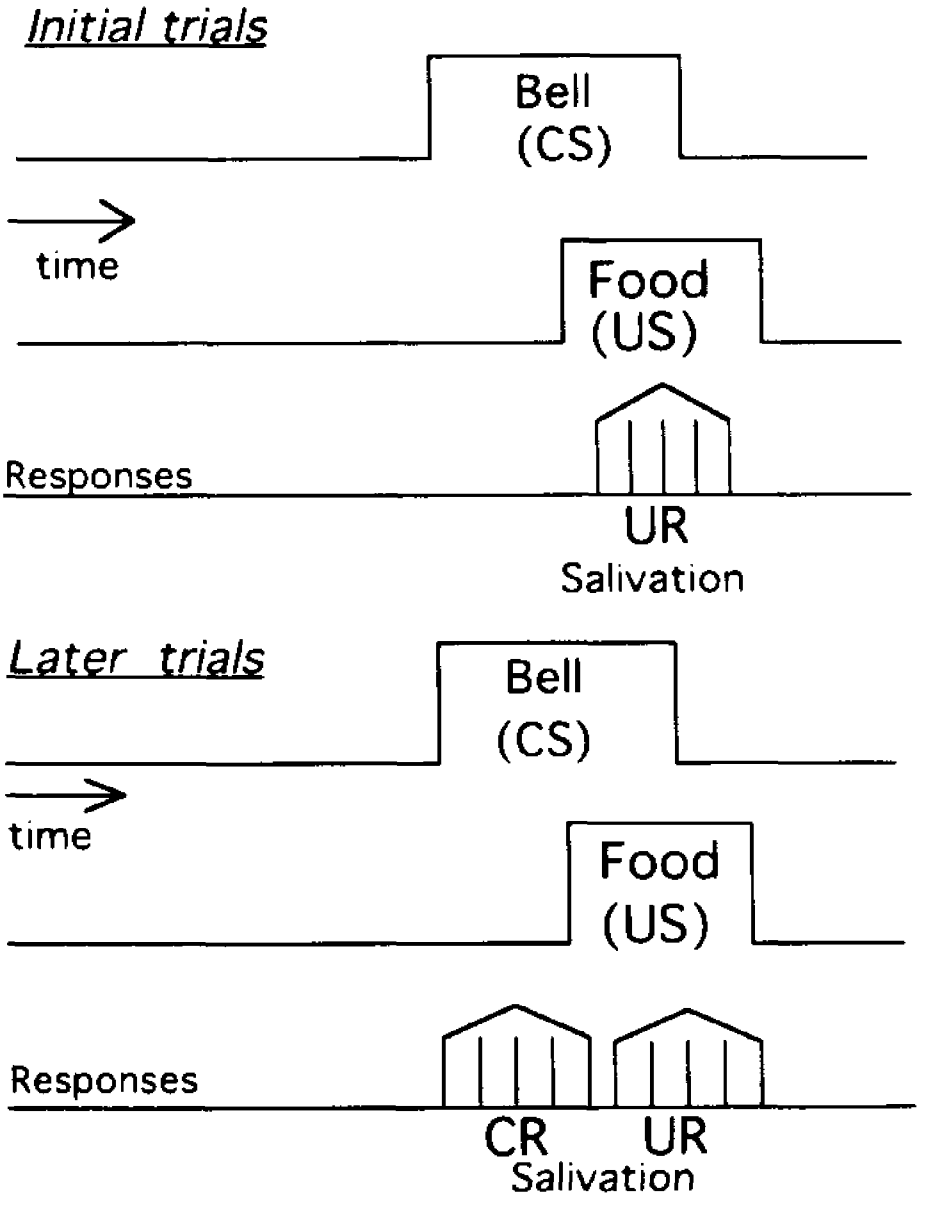


Figure 2. Idealized changes in the strength of the conditioned response during acquisition and extinction.

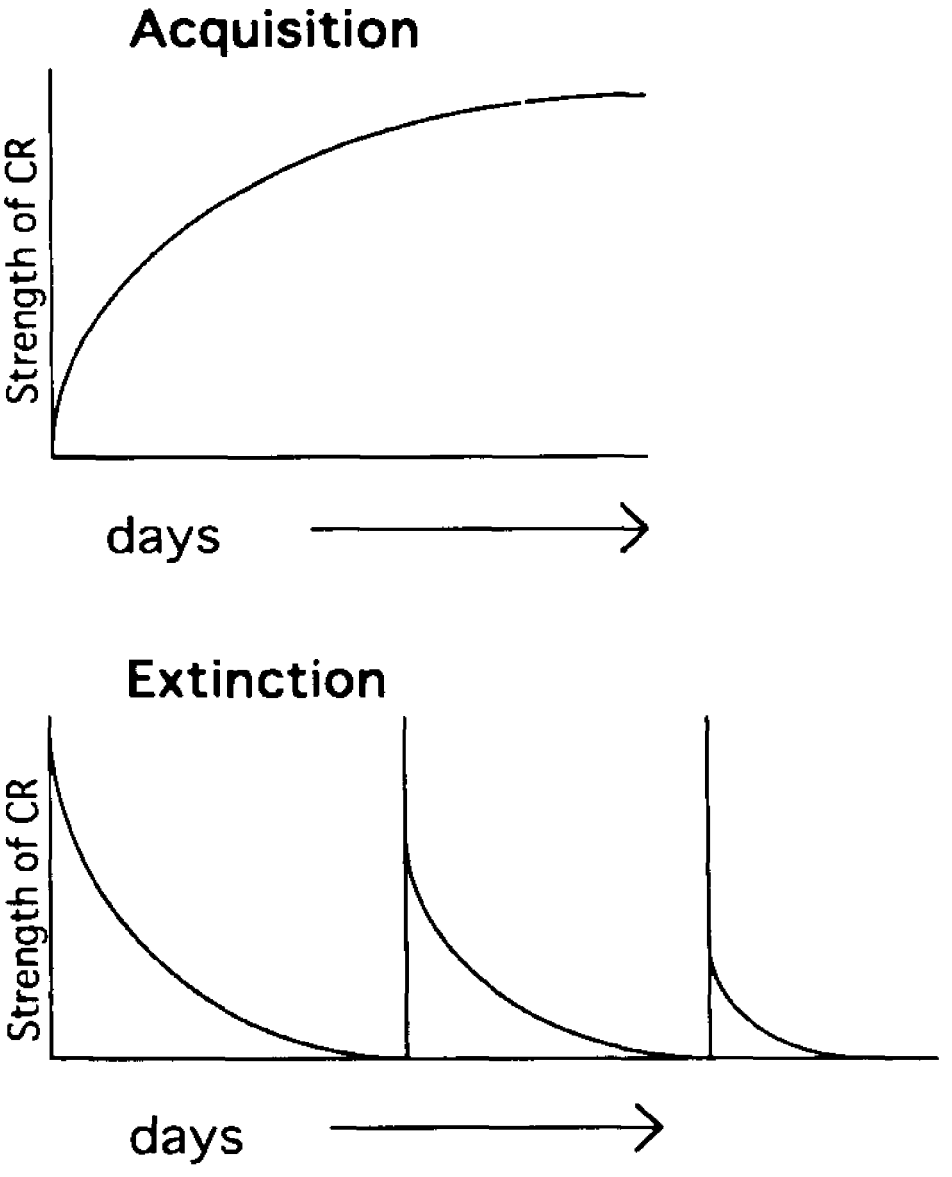


Figure 3. Median suppression ratio for the four groups as a function of test sessions. The probability of US during the CS was .4 for all subjects, the probability of US during CS absence is noted for each group.

(Redrawn from Rescorla, R. A. (1967). Pavlovian conditioning and its proper control procedures.*Psychological Review*, 74, 71-80).

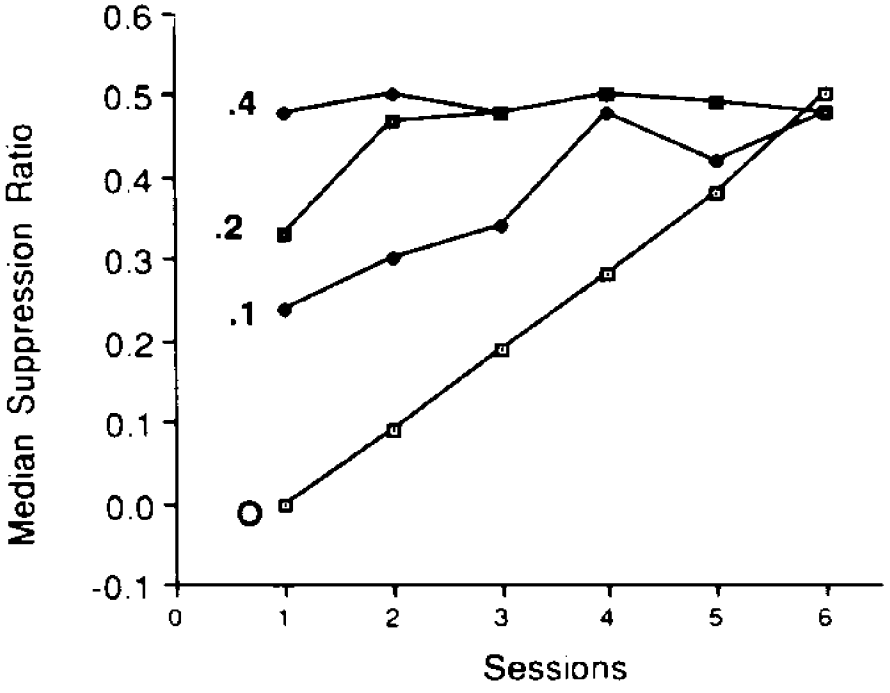
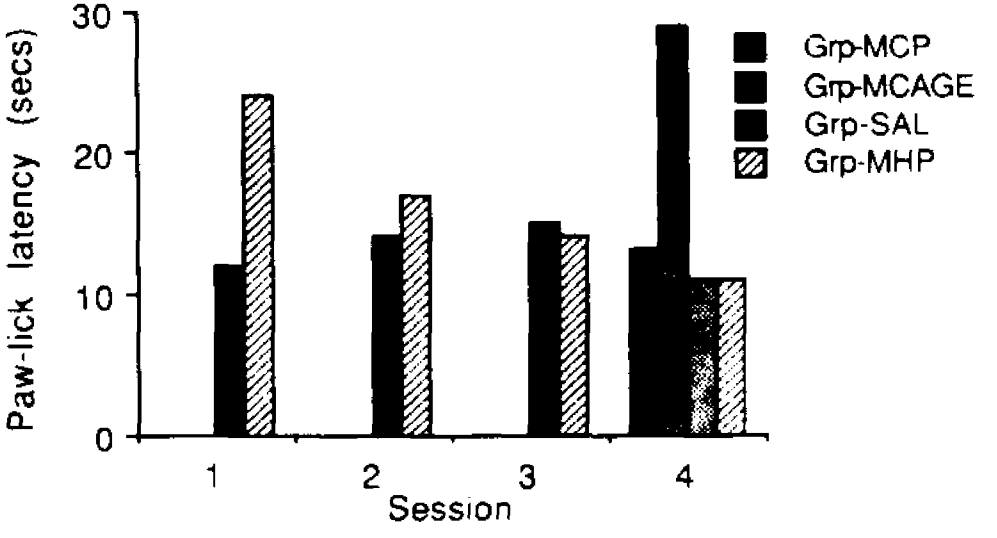


Figure 4. Mean paw-lick latencies for the four groups.

(Redrawn from Siegel, S. (1975). Evidence from rats that morphine tolerance is a learned response. *Journal of Comparative & Physiological Psychology*, 89(5): 498-506).



Design

Grp-MHP: Morphine paired with hot-plate environment and tested for analgesia on all four sessions.

Grp-SAL: Saline paired with hot-plate environment and tested for analgesia on all 4 sessions.

Grp-MCP: Morphine paired with hot-plate environment at ambient temperature (cold-C) for first three sessions: then morphine paired with hot-plate environment and tested for analgesia on fourth session.

Grp-MCAGE: Morphine paired with home cage environment for first three sessions; then morphine paired with hot-plate environment and tested for analgesia on fourth session.

Figure 5. Percent change from baseline paw-lick latency after each of four morphine injections and, 2 weeks later, after four physiological saline injections.

(Redrawn from Siegel, S. (1975). Evidence from rats that morphine tolerance is a learned response. *Journal of Comparative & Physiological Psychology*, 89(5); 498-506).

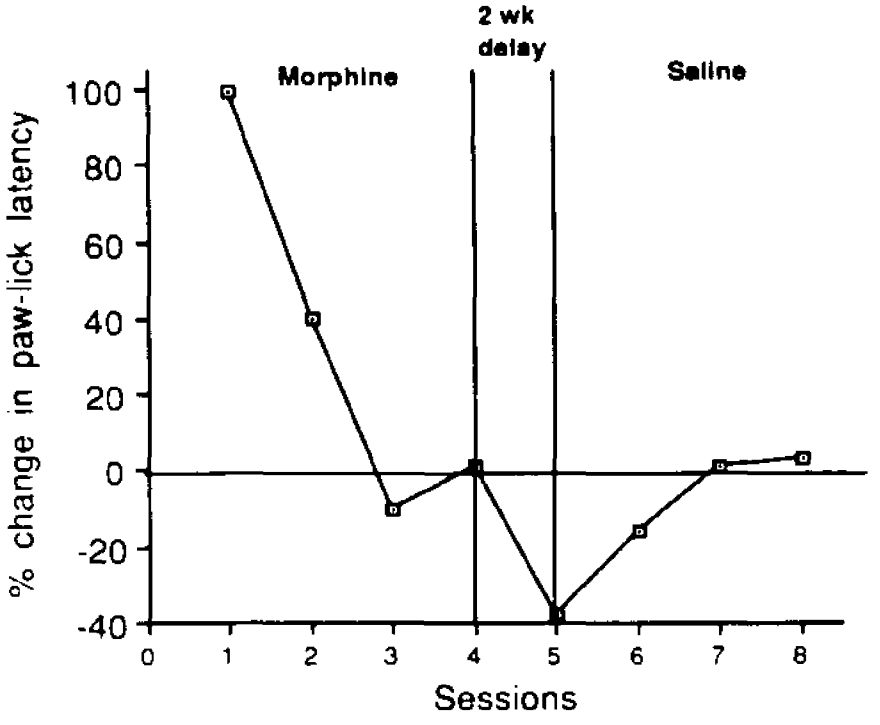


Figure 6. Mean tail-flick latencies after each of six daily morphine injections in the two groups. Group M-P-M received nine placebo sessions and Group M-REST-M received a 9-day rest interval interpolated between morphine Sessions 3 & 4.

(Redrawn from Siegel, 1975).

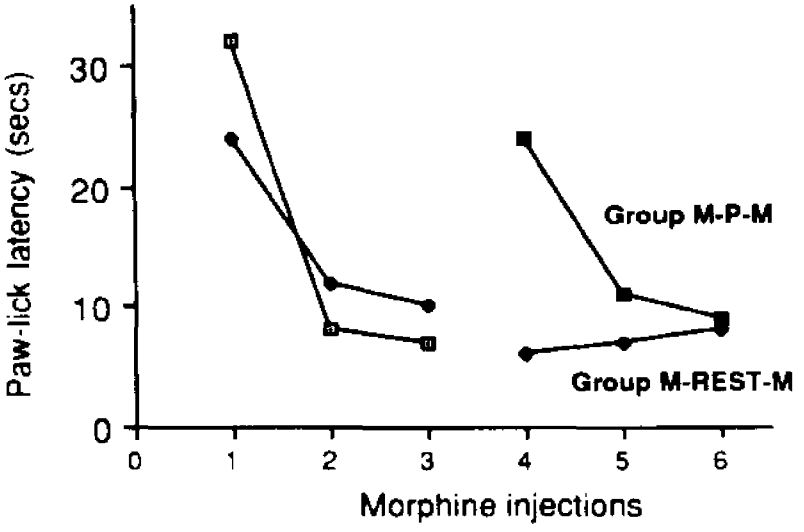


Figure 7. Eikelboom and Stewart's prediction of the conditioned response. The unconditioned stimulus (US) and unconditioned response (UR) are defined in terms of the drug's relationship to the central nervous system (CNS).

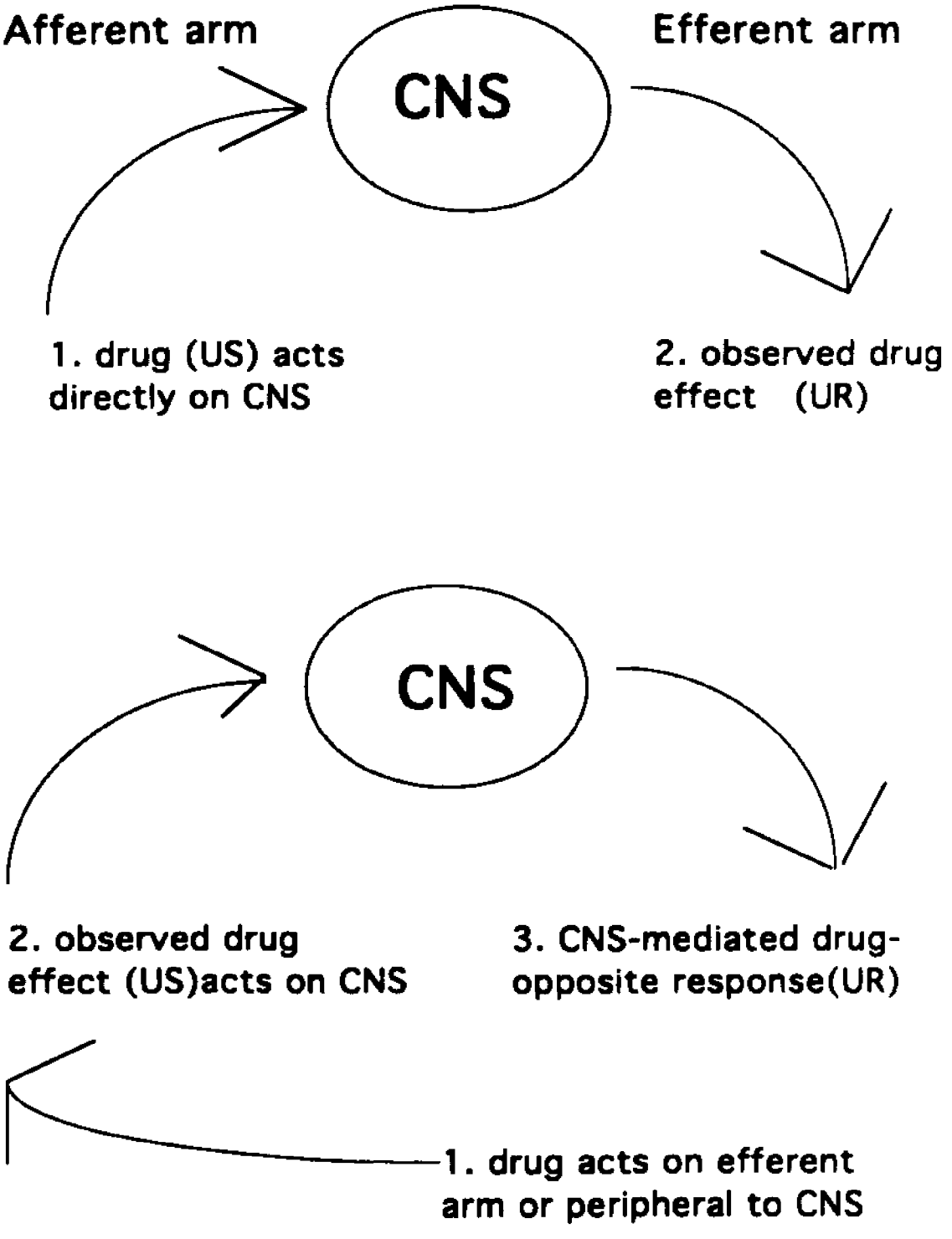


Figure 8. Mean tail-flick latency on the test session for each dose group as a function of log-morphine dose for each of the four conditions. (Distinctive condition (DC); saline condition (A); home cage condition (HC); and saline cage condition (SC) (B).

(Copied from Tiffany, S.T., Maude-Griffin, P.M., & Drobes, D.J. (1991). *Behavioral Neuroscience*, 105(1), 49-61).

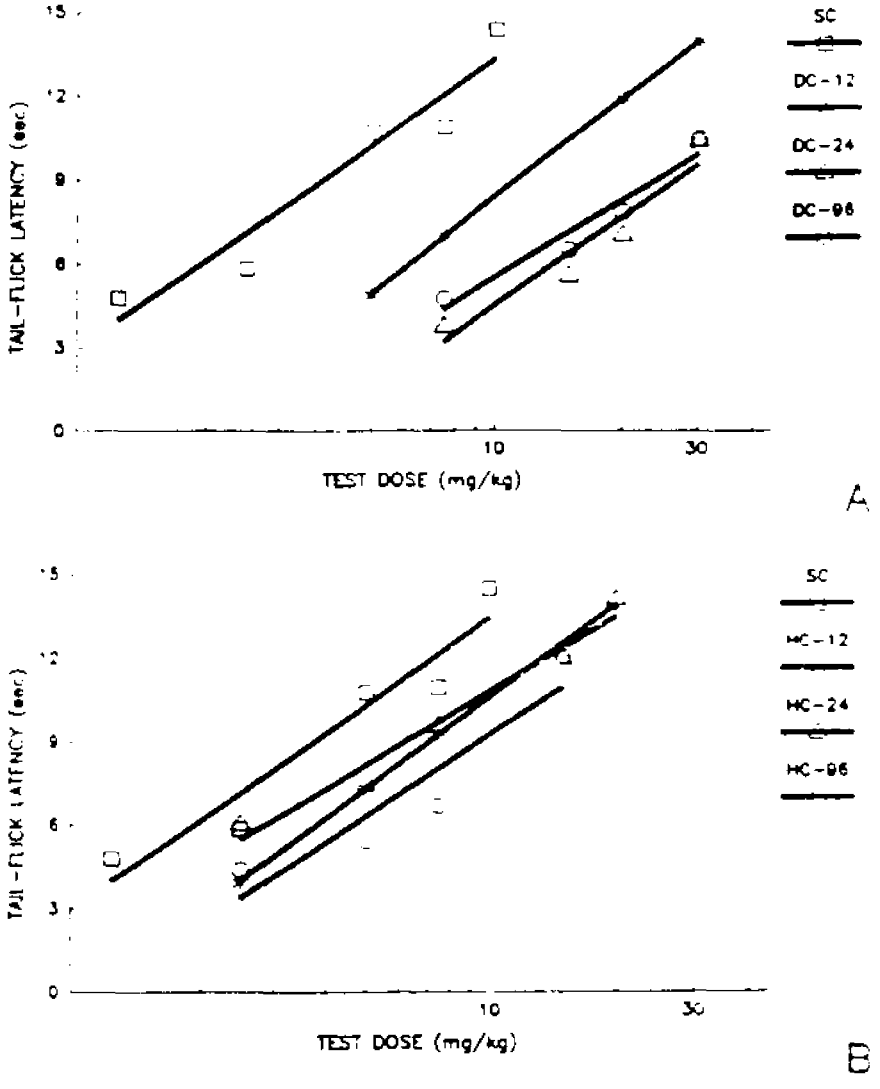
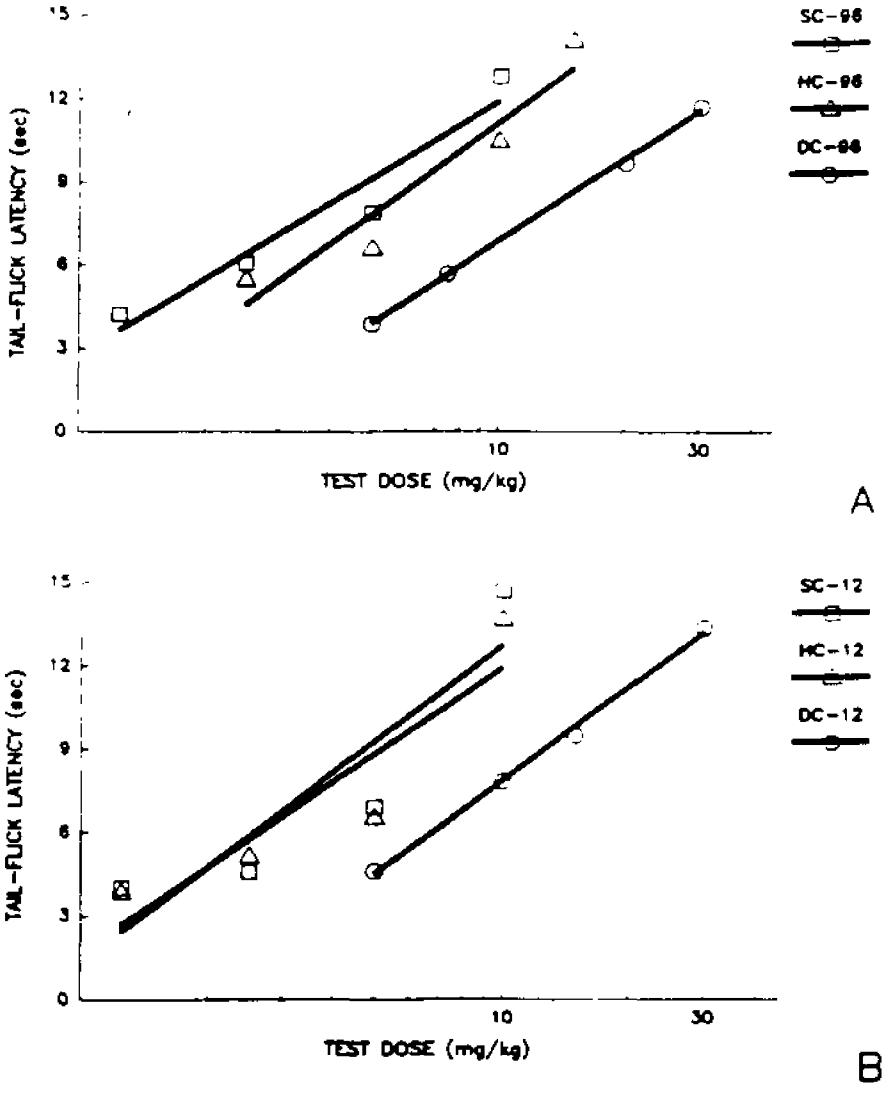


Figure 9. Mean tail-flick latency on the retention test session for each dose group as a function of log-morphine dose for each of the 96-hr IDI conditions (A) and the 12-hr IDI conditions (B).

(The straight line represents the best fitting line for each condition with tail-flick latency regressed on log dose. DC=morphine explicitly paired with distinctive context. HC=morphine explicitly unpaired with distinctive context. SC= saline control.

(Copied from Tiffany et al., 1991).



METHOD

Subjects

The subjects were 19 normal sleeping, non-smoking males, aged 19-35 years recruited from nearby colleges. Subjects were screened in a telephone interview ten days prior to the study for the following criteria: <250 mg habitual caffeine intake per day; no tobacco use; nocturnal sleep times of 7-9 hours; nighttime sleep latencies of less than 30 minutes; generally consistent bedtimes and waketimes; and an avoidance of habitual napping (Appendices 1 and 2).

To insure that subjects had no caffeine in their system before the screen and study, subjects were asked to refrain from any type of caffeine intake for ten days prior to the study and during the study (besides laboratory caffeine administrations). To insure that subjects were not sleep deprived before the screen, average bedtimes and waketimes for each subject were determined and maintained, beginning seven days prior to the study.

Constant bedtimes and waketimes were also maintained during the study, through sleep diaries (Appendix 3). Every day of the study, the subject was questioned about his previous night's sleep. If the subject reported spending $\pm$ 30 minutes of his set time in bed, he was instructed to maintain his set time in bed.

Any subject who evidenced sleep pathology or $<85\%$ sleep efficiency (time asleep $\div$ time in bed x 100) on a polysomnographic recording of nighttime sleep (see NPSG for explanation of nighttime sleep recordings) was excluded from the study. Also, any subject with excessively low or high sleep latency (<5 or >17 min) on the screen

MSLT, was excluded to avoid ceiling effects on caffeine.

As a result of the screening criteria, two prospective subjects were excluded due to nighttime sleep pathology and two subjects were excluded for excessively high MSLT sleep latencies. One other prospective subject withdrew from the study after the screening procedure. One subject was admitted into the study without going through the screening/baseline MSLT.

The average age of the sample was 22.1 years (standard deviation: ± 3.3) and the mean caffeine consumption per day was 75 mg (standard deviation: ± 76.9), which is approximately the equivalent of one cup of caffeinated coffee per day. The mean MSLT score for the screen was 11.2 min (standard deviation: ± 4.6) and mean sleep efficiency for baseline night was 93% (standard deviation: ± 3.4). The subject was remunerated for his participation and a consent form was signed (Appendix 4). After the completion of the study, the subject was debriefed. The protocol was accepted by City College's human experimental procedures committee.

Measures of nighttime sleep and daytime sleepiness

Nocturnal Polysomnographic Recording (NPSG)

Technicians calibrated the machines before each NPSG (Appendix 5) and paper was set up for a full night of recording. The subject reported to the laboratory approximately two hours prior to his average bedtime and the following montage of electrodes were applied: four referential electroencephalogram (EEG) (right and center central-C4 and CZ and right occipital-O2 and center parietal-PZ), two horizontal referential eye movement leads [right and left outer canthus electro-

oculogram (EOG)], two mental/submental electromyogram (EMG), and two electrocardiogram (EKG). On the screen night only, nasal/oral thermistors were applied to monitor air flow and four leg electrodes were applied to monitor periodic leg movements.

For each NPSG, the subject spent his average time in bed while being polygraphically recorded, using standard procedures (Rechtschaffen & Kales, 1968). Approximately 15 minutes before bedtime and after waketime, the subject filled out questionnaires to insure that the subject's subjective experience of his nighttime sleep was normal (Appendix 6).

Following an NPSG, three measures of daytime sleepiness were obtained: one objective; the Multiple Sleep Latency Test, (Carskadon & Dement, 1977) and two subjective; the Visual Analog Scale (Monk, Fookson, Moline, & Pollak, 1985) and Stanford Sleepiness Scale (Hoddes, Dement, & Zarcone, 1972).

Multiple Sleep Latency Test (MSLT)

While previous methods of categorizing sleepiness included activity, performance, and introspective measures, the MSLT was the first standardized test to objectively measure levels of sleepiness/alertness. The rationale behind the MSLT is as follows; the more sleepy/less alert a person is, the quicker he or she should fall asleep. Thus, the MSLT, whose dependent variable is latency to fall asleep in minutes, is hypothesized to measure objective sleepiness/alertness.

After many studies in both research and clinical populations, Carskadon and Dement (1982) found that the MSLT was not only sensitive to manipulations of sleepiness (e.g. sleep deprivation, sleep extension), but also effective in clinically separating diagnostic

categories of sleep disorder populations.

A standard MSLT (Carskadon, Dement, Mitler, Roth, Westbrook, & Keenan, 1986) consists of five nap opportunities, separated by two hour intervals so that changes in alertness can be studied across the day. At each nap opportunity, the amount of sleep is generally limited to 1-2 minutes so that the subject does not accumulate significant amounts of sleep. In between naps, the subject is generally allowed to read, listen to the radio or watch TV, but is not allowed to sleep or stay in bed. Besides five individual sleep latency measures for each nap, a mean sleep latency score is calculated by taking the mean of the five naps for the day.

In the present study, the first nap began approximately 2-3 hours after the subject's waketime and one hour after coffee consumption (time zero). During the time preceding each nap opportunity, loose electrodes and electrodes with high impedances were replaced. Five minutes before each nap, the subject was hooked up in bed, and calibrations were performed to test the hookup and equipment. Then lights were turned off and standard instructions to begin the test were given "Please lie quietly, keep your eyes closed, and try to get some sleep." The MSLT was terminated after three consecutive 30 second epochs (1.5 minutes) of unambiguous stage 1 sleep or the first epoch of another sleep stage or after 20 min if no sleep had ensued.

Sleep latency for each nap was calculated in minutes by measuring the elapsed time from lights out to the first epoch scored as sleep (scoring procedures-Rechtschaffen & Kales, 1968). The author scored the NPSG's and MSLT's blind to the subject, condition, and day of each record.

Visual Analog Scale (VAS)

The Visual Analog Scale (VAS) technique (Appendix 7) was first used by Folstein and Luria (1973) and later modified by Monk et al. (1985) to detect changes in mood and subjective activation. On each VAS, the subject is instructed to draw a vertical line through a 100 mm horizontal visual analog scale according to how he or she feels on that particular measure. The VAS score is measured in millimeters (mm) from 0 to 100 mm.

For example, on the "alertness" scale the very left end of the line is most alert and the right end of the line is least alert. If a subject draws a line which bisects the alertness scale, the VAS score is 50 mm. An advantage of the VAS is that the subject does not become "anchored" to a particular numerical value since the line allows for a continuum of responses (Folstein & Luria, 1973).

The VAS technique of measuring subjective alertness has been shown to be a sensitive measure of nonpathological levels of subjective sleepiness, especially when comparisons are made "within" subjects (Monk et al., 1985, 1987).

Since the present investigation was mainly interested in subjective activation levels, four of the ten scales which assessed activation levels were used; they were alertness, effort, weariness and sleepiness. In addition, a fifth VAS, which asked the subject how he felt overall, was used. While each scale can be analyzed separately, Monk et al. (1987) found that a summary score of the four vigor scales yielded a more reliable and valid measure of global activation or vigor.

Monk's formula for the summary global vigor measure was slightly

modified in the present investigation to incorporate the fifth scale. The formula used in the present analysis was:

```
Global Vigor = [(alert)+(overall)+200-(sleepy)-(effort)-(weary)]/4.
```

Stanford Sleepiness Scale

On the Stanford Sleepiness Scale (SSS) (Hoddes et al., 1973) (Appendix 7), the subject selects the single sentence from a list of seven that best characterizes his subjective level of alertness (e.g. 1- 'Alert, Wide Awake'; 7- 'Almost Asleep'). The SSS was chosen in the present analysis because some researchers have found that it is correlated with the MSLT (Carskadon & Dement,1977).

Procedure

Screen

After ten days of caffeine abstinence and seven days of fixed bedtimes and waketimes, a nighttime adaptation/screen NPSG was conducted. The following day, a screen MSLT was conducted. Prior to each nap opportunity, the VAS and the SSS were administered to assess subjective levels of alertness/sleepiness. Eighteen of the 19 subjects went through the screening procedure and the screen sleep latency test measures and subjective sleepiness scale scores for these subjects were used as baseline measures of daytime sleepiness.

Study

Table 1 presents the design for the screen and study. Days 1, 14, and 15, were spent in the lab and daytime levels of sleepiness were assessed during these days, using the standard MSLT. To assess subjective alertness, the subject also filled out the SSS and VAS questionnaires mentioned above, prior to each nap opportunity.

Unlike the baseline day, a caffeine questionnaire which asked the subject to write in what beverage he had consumed that morning (e.g. caffeinated or decaffeinated coffee) was given at the time of coffee administration (time zero, TZ) and prior to every nap opportunity (Appendix 8). The caffeine form given before each nap served to remind the subject of the beverage he had consumed in the morning. Nights preceding the daytime MSLT were spent in the lab and NPSG recordings were performed. An NPSG was also performed following Day 1.

All daytime caffeine administrations on Days 1, 14, and 15 were identical (Table 1). Two hundred and fifty milligrams of anhydrous caffeine dissolved in decaffeinated coffee was administered at TZ, which was approximately 1.5 hours after waketime and 30 minutes after a light breakfast (juice and a bagel). The subject was told to pace his coffee consumption over a 15 minute interval. The subject was allowed to eat lunch after the second nap but was told to limit his food intake between meals.

On Days 1 and 14, all subjects were told that they had received caffeine in their coffee (Table 1). On Day 15, although all subjects received caffeinated coffee, subjects were randomly assigned to one of two conditions. In condition one, eight subjects were correctly told that they had received caffeinated coffee and in condition two, eleven subjects were falsely informed that they had received decaffeinated coffee. Note that on Day 15, the only difference between the two conditions is the knowledge or expectation of receiving caffeinated or decaffeinated coffee. The experimenter administering the MSLT on this day was blind to the condition of each subject.

On Days 2-13, when no daytime testing was done, the subject reported to the lab at approximately TZ and drank either caffeinated or decaffeinated coffee. Diaries were kept to insure that the subject was maintaining his regular sleep time and consuming a light breakfast before reporting to the laboratory.

Over the course of Days 2-13, six caffeinated and six decaffeinated coffee beverages were administered in a non-alternating fashion (Table 1). Lactose was added to the decaffeinated coffee administrations since previous studies have suggested that decaffeinated plus lactose generally cannot be differentiated from caffeinated coffee (Goldstein et al., 1964).

Each day, the subject was correctly told what beverage he had received and was asked to fill in "caffeinated coffee" or "decaffeinated coffee" in the caffeine questionnaire at TZ. To remind him of what beverage he had consumed, the subject also filled in a caffeine questionnaire 45 minutes after TZ. The VAS and SSS questionnaires were also administered just prior to TZ and 45 minutes after TZ to assess changes in subjective alertness.

After establishing basal levels of sleepiness on the screen/baseline MSLT, the Day 1 MSLT assessed the alerting effects of the initial caffeine administration. According to the conditioning model, Days 2-13 were considered conditioning trials because the subject learned to associate the expectations or knowledge of caffeine or no caffeine with their respective systemic effects.

As mentioned earlier, Siegel's conditioning model of drug tolerance hypothesizes that the repeated pairing of caffeine and the expectation of caffeine results in a summing of two types of responses, that of the caffeine which is alerting and that of the expectation of caffeine which is

de-alerting. This summation results in diminished drug effect or drug tolerance. The Day 14 MSLT measured tolerance to chronic caffeine administration.

According to the conditioning model, the subjects in condition one on Day 15 (expected caffeine) should be tolerant to caffeine's alerting effects, like on Day 14. In contrast, the Day 15 subjects in condition two (expected decaffeinated coffee) should not have the expectation of caffeine and it's associated de-alerting response. So the de-alerting compensatory response would not be elicited to counteract the caffeine and subjects in condition two should be more alert/less sleepy than subjects in condition one.

Data Analysis

To assess overall changes in objective alertness, a Day x Time within subject repeated measures analysis of variance (ANOVA) (Systat software package: Wilkinson, 1990) was conducted comparing sleep latencies for the baseline, initial caffeine administration day (Day 1) and chronic caffeine administration or tolerance test day (Day 14). Day 15 was analyzed separately because a between subject factor (condition) was added to the design on this day. Since one subject was missing baseline data, average sleep latency values for each nap for the group were used for this subject in this analysis.

To study the initial objective alerting effects of caffeine relative to baseline, an apriori contrast compared the sleep latencies for the baseline and Day 1. With regard to tolerance, an apriori contrast compared the sleep latencies for Day 1 and Day 14. Since multiple comparisons were being made at one time, significance achieved on all ANOVAs was

determined by the conservative Huynh-Feldt (1982) approach and the .05 level was used for significance.

To assess the time course of the alerting effects of caffeine and the time of day effects on daytime sleep latency, an apriori contrast compared the mean of the first two latency tests versus the mean of the third and fourth latency tests for each day (baseline, Day 1 and Day 14). A mean of two sleep latency tests was used instead of a single sleep latency test since it has been shown that single latency tests have reduced reliability (Zwyghuizen-Doorenbos, Roehrs, Schaefer, & Roth, 1988).

To assess the influence of the expectation of caffeinated or decaffeinated coffee on sleep latency, a Day x Nap x Condition mixed design repeated measures ANOVA was conducted comparing days 14 and 15. Day 14 data was used in this analysis to control for differences in tolerance levels. An apriori contrast compared the mean of the first two sleep latency tests versus the mean of the third and fourth sleep latency tests, to assess caffeine's time course effects and a possible interaction with condition.

A polynomial regression analysis of the five naps over the two days was conducted, to characterize the change in objective alertness over this time. To assess within subject changes in objective alertness from Day 14 to Day 15, caffeine and "decaff" conditions were analyzed separately using a Day x Nap within subject ANOVA.

To assess the subjective alerting effects on baseline and caffeine days, the SSS, the Global Vigor summary measure and the individual VAS scales (Alertness, Effort, Weariness, Overall, Sleepiness) were analyzed in a similar manner to the MSLT data.

A Time (pre- or post-coffee administration) x Treatment

(caffeinated or decaffeinated coffee) within subject repeated measures ANOVA was performed on Days 2 through 13, to assess the subjective alerting effects of the coffee administration during the conditioning phase of the experiment. In addition, change scores were calculated by subtracting pre-coffee administration subjective scores from post-coffee administration scores. Since three subjects missed one day of decaffeinated coffee administration, sixteen subjects were used for these analyses.

Relationships among the three measures of sleepiness (MSLT, SSS, and GV) were initially assessed using Pearson Product-Moment correlations. First, a single score for each day on each of the three measures was obtained and correlations were performed. Then correlations of the three measures for each nap of each day were performed. Due to the large number of correlations being run, the .01 level of significance was used to reduce the likelihood of committing a type 1 error.

To assess the effects of morning caffeine on nighttime sleep parameters, nighttime data were analyzed using a within subject repeated measures ANOVA and two contrasts were set up: night after baseline (no morning caffeine) vs. night after initial caffeine administration; and night after initial caffeine administration vs. night after chronic caffeine administration.

Although many sleep parameters were measured, only nighttime sleep parameters known to be affected by caffeine administration were analyzed and they were; sleep efficiency, amount Stage 1, 2, slow wave, and REM, sleep latency, and wake after sleep onset and movement time.

To insure that the subject was given the same amount of time in bed

throughout the study procedure, total amount of dark time was analyzed. Since multiple comparisons were being performed, significance achieved on analyses of the night data was determined by the conservative Huynh-Feldt approach and significance level was .05.

To assess whether prior night sleep effects affected daytime MSLT data, a correlation was conducted between the prior night total sleep time and the MSLT data. If significant, prior night sleep effects were removed by a repeated measures analyses of covariance (ANCOVA).

Table 1: Design of caffeine study.

TZ= Time zero, coffee administration

			TIME				
Day	Time zero		TZ+1hr	TZ+3	TZ+5	TZ+7	TZ+9
Friday					NPSG		
Saturday	S		S, N1	S, N2	S, N3	S, N4	S, N5
					NPSG		
Sunday	S	C	S, N1	S, N2	S, N3	S, N4	S, N5
					NPSG		
Monday	S	D	S				
Tuesday	S	D	S				
Wednesday	S	C	S				
Thursday	S	C	S				
Friday	S	D	S				
Saturday	S	C	S				
Sunday		OFF					
Monday	S	D	S				
Tuesday	S	D	S				
Wednesday	S	C	S				
Thursday	S	C	S				
Friday	S	D	S		NPSG		
Saturday	S	C	S, N1	S, N2	S, N3	S, N4	S, N5
					NPSG		
Sunday		C	S, N1	S, N2	S, N3	S, N4	S, N5
					NPSG		
		"D"	S, N1	S, N2	S, N3	S, N4	S, N5
					NPSG		

C = given caffeine, 250 mg + lactose
D = given decaffeinated + lactose
"D"= given caffeine, expected decaffeinated
NPSG = nocturnal polysomnograph recording
N= nap
S= subjective alertness questionnaire

RESULTS

The MSLT, SSS, and Global Vigor data for each nap and the average for baseline, initial caffeine day (Day 1), and chronic caffeine administration or tolerance test day (Day 14) are depicted in Table 2. Table 3 displays the means for the three sleep measures on the conditioned tolerance test day (Day 15).

MSLT Findings

Figure 10 illustrates the objective alertness data for baseline, Day 1, and Day 14. Statistical analyses of the MSLT data for these three days revealed significant main effects of day ($F(2,36) = 25.04$, $p < .01$) and nap ($F(4,72) = 2.69$, $p < .03$) and no significant interactions.

Planned comparisons revealed that subjects were objectively more alert on the initial caffeine administration day (mean: 17.34 min $\pm$ 2.40) than the baseline day (mean: 11.29 min $\pm$ 4.36) ($F(1,18) = 71.81$, $p < .001$) and the chronic caffeine administration day (mean: 14.65 min $\pm$ 3.98) ($F(1,18) = 13.57$, $p < .002$). Thus, subjects were initially alerted by caffeine but after 6 administrations, subjects were not alerted as much, by the same dose of caffeine.

Planned comparisons of the time course of caffeine's objective alerting effects and time of day effects revealed no significant differences between the mean of naps 1 and 2 and mean of naps 3 and 4, for either the baseline day or the initial caffeine administration day. However, on the chronic caffeine administration day, subjects were objectively more alert on the mean of naps 1 and 2 (mean: 16.2 min $\pm$ 5.1) than on the mean of naps 3 and 4 (mean: 13.5 $\pm$ 4.3) ($F(1,18) = 8.55$, $p < .009$).

Table 2: Means and standard deviations of Multiple Sleep Latency Test (MSLT); Stanford Sleepiness Scale (SSS); Global Vigor Summary Measure (GV) on baseline, Day 1, and Day 14.

	Means (SDs in parentheses)		
Times of day	MSLT	SSS	GV
baseline (N=18)			
nap 1	12.4 (5.4)	2.3 (1.0)	66.0 (19.2)
nap 2	10.9 (6.3)	1.9 (0.8)	70.6 (18.6)
nap 3	11.3 (6.4)	1.9 (0.9)	78.1 (17.0)
nap 4	9.7 (4.7)	2.1 (0.8)	68.6 (17.7)
nap 5	12.4 (5.8)	2.0 (0.8)	66.6 (23.3)
mean	11.3 (4.5	2.0 (.69)	70.0 (15.1)
Day 1 (initial caffeine) (N=19)			
nap 1	18.9 (2.9)	1.6 (.6)	76.2 (19.1)
nap 2	17.5 (3.3)	1.6 (.6)	80.0 (17.1)
nap 3	6.3 (4.3)	1.7 (.7)	74.3 (23.1)
nap 4	16.8 (4.9)	1.7 (.8)	78.6 (20.9)
nap 5	16.9 (4.6)	1.5 (.6)	79.4 (19.7)
mean	17.3 (2.5)	1.6 (.5)	77.7 (16.9)
Day 14 (chronic caffeine) (N=19)			
nap 1	15.9 (6.2)	1.8 (.6)	76.7 (23.0)
nap 2	16.5 (5.5)	1.6 (.5)	83.0 (15.8)
nap 3	12.7 (5.5)	2.0 (.7)	84.3 (14.5)
nap 4	14.4 (5.7)	1.8 (.9)	85.4 (14.3)
nap 5	13.9 (6.6)	1.9 (.9)	81.7 (18.2)
mean	14.7 (3.9)	1.8 (.5)	82.2 (12.4)

Table 3: Means and standard deviations of Multiple Sleep Latency Test (MSLT); Stanford Sleepiness Scale (SSS); Global Vigor Summary Measure (GV) on Day 15.

	Means (SDs in parentheses)		
Times of day	MSLT	SSS	GV
Day 15			
caffeine condition (N=8)			
nap 1	18.2 (4.6)	1.9 (.8)	82.3 (17.7)
nap 2	13.3 (7.3)	1.4 (.7)	91.2 (8.2)
nap 3	11.4 (4.1)	1.4 (.5)	84.1 (15.6)
nap 4	13.3 (5.3)	1.6 (.7)	79.9 (20.1)
nap 5	14.4 (5.5)	1.9 (.8)	81.2 (17.3)
mean	14.1 (4.1)	1.6 (.4)	83.7 (12.6)
"decaff" condition (N=11)			
nap 1	17.8 (4.8)	1.8 (.6)	82.4 (17.0)
nap 2	16.9 (4.5)	1.9 (.7)	83.3 (17.0)
nap 3	13.4 (6.1)	1.9 (.7)	87.1 (12.0)
nap 4	14.9 (5.6)	1.8 (.6)	82.6 (17.1)
nap 5	18.4 (2.8)	1.6 (.5)	91.2 (6.9)
mean	16.4 (3.2)	1.8 (.4)	85.3 (13.3)

Post hoc comparisons of the corresponding naps for each day revealed that subjects were more alert on each of the five sleep latency tests on Day 1 versus the corresponding nap on the baseline day (probabilities ranging .001-.003). Comparisons of each of the sleep latency tests on Day 1 versus Day 14 revealed that sleep latencies for naps 1, 3, and 5 for Day 1 were significantly higher than the corresponding nap on Day 14 (probabilities ranging from .02 -.05).

These findings suggest that the initial caffeine administration had significant alerting effects throughout the day when compared to no caffeine (baseline). Also, the same dose of caffeine after chronic administration did not alert subjects as much, throughout the day.

The possible conditioned effects of caffeine associated with the two conditions (caffeine and "decaff") on Day 15, the conditioned tolerance test day, are illustrated in Figure 11 and the means are represented in Table 3. Statistical analyses of the MSLT data comparing the two conditions on Days 14 and 15 revealed a significant main effect of nap ($F(4,4,68) = 3.71$, $p < .01$) but no other main effects or interactions.

A planned polynomial regression analysis used to characterize the change over the five naps for the two days revealed a significant quadratic component ($F(1,1,17) = 11.64$, $p < .003$) indicating that for both days, latencies linearly declined and then linearly increased. Planned comparisons of the mean of naps 1 and 2 and the mean of naps

3 and 4 on Day 15 by condition revealed no significant main effects or interactions.

Analysis of each condition separately revealed a nonsignificant increase in mean sleep latency in the "decaff" group ($F(1,10) =$, $p<.06$) from Day 14 (mean: 15.0 $\pm$ 2.9)) to Day 15 (mean: 16.4 $\pm$ 3.2). Figure 12 depicts the change in alertness from Day 14 to Day 15 in the "decaff"group. Post hoc analysis of these findings revealed that subjects in the "decaff" group were significantly more alert on nap 5 on the conditioned tolerance day (Day 15) when compared to the tolerance test day (Day 14). There was no difference in mean sleep latency in the caffeine group from Day 14 (mean: 14.2 $\pm$ 5.2) to Day 15 (mean: 14.1 $\pm$ 4.1).

Subjective Sleepiness Findings

The SSS and GV measures for the 5 naps for baseline, Day 1, and Day 14 are illustrated in Figures 13 and 14, respectively. Statistical analyses of the SSS data revealed a significant main effect of day ($F(2,36) = 4.19$, $p<.02$) and no other significant main effects or interactions. Analysis of the GV data yielded similar results; a significant main effect of day ($F(2,36) = 6.09$, $p<.01$) and no other main effects or interactions.

Apriori contrasts of the SSS data revealed that subjects felt subjectively more alert after the initial caffeine administration

(mean:1.62 ± .49) than on baseline (mean:2.04 ± .69) ($F(1,18) = 8.30$, $p < .01$) and there was no significant difference in subjective alertness between initial and chronic caffeine (mean:1.81 ± .54). Apriori contrasts of the GV data revealed similar subjective results; subjects felt more activated after the initial caffeine administration (mean:77.66 ± 16.9) than on baseline (mean:69.98 ± 15.1) ($F(1,18) = 6.11$, $p < .02$) and there was no significant difference in subjective activation between initial and chronic caffeine (mean:82.21 ± 12.4).

Apriori contrasts studying the time course of caffeine's subjective alerting effects revealed no significant differences in the SSS data between the mean of naps 1 and 2 and mean of naps 3 and 4 for the baseline day or the initial or chronic caffeine administration days and no interactions. On the GV measure, subjects felt subjectively less alert on the mean of naps 1 and 2 (68.26 ± 18.8) than on the mean of naps 3 and 4 (73.28 ± 17.3) for the baseline day ($F(1,18) = 7.40$, $p < .01$) but there were no significant differences between the means of naps 1-2 and 3-4 on Day 1 or Day 14.

On Day 15, the subjective alerting effects of caffeine as measured by the SSS scale and the GV measure for the 5 naps for the two conditions are depicted in Figures 15 and 16, respectively. Comparing the SSS data for Days 14 and 15, there were no main effects of the within subject factors (day, nap) or between subject factor (condition) however, there was a day by nap by group interaction ($F(68,4,4) =$

3.36, $p < .02$).

Interestingly, similar results were found for the GV measure; no significant main effects but a day by nap by group interaction ($F(68,4,4) = 6.77$, $p < .01$). Since a three way interaction was not predicted nor can it be easily explained, further analysis was not done.

Comparisons of the mean of naps 1 and 2 and the mean of naps 3 and 4 for both the SSS and GV measures on Day 15 by condition revealed no significant main effects of interactions.

Subscales of the Global Activation Measure

The findings for the five subscale measures of the Global Vigor measure are summarized in Table 4. On the "Alertness" subscale, there were significant main effects of day and nap for the baseline, Day 1, and Day 14 comparisons but no significant interactions. The apriori contrasts comparing baseline to Day 1 and Day 1 to Day 14 were nonsignificant. On the "Effort" subscale, there was a significant main effect of day and no other significant main effects or interactions. The apriori contrasts comparing baseline to Day 1 and Day 1 to Day 14 were nonsignificant.

On the "Weariness" subscale, there was a significant main effect of day and no other main effects or interactions. Apriori contrasts revealed that subjects felt significantly wearier on baseline than on Day 1 but there were no differences in subjective weariness between Day 1 and

Day 14. On the "Sleepiness" subscale, there was a significant main effect of day and no other main effects of nap or interactions. Apriori contrasts revealed that subjects felt sleepier on the baseline day than Day 1 and there was a significant day by nap interaction. There was no difference in subjective sleepiness between Day 1 and Day 14. For the "Overall" subscale, there were no significant main effects or interactions.

When Days 14 and 15 were compared on the five subscales, there were no significant between group effects for condition, however, on the weariness subscale there was a group by day by nap interaction. Since this three way interaction was neither predicted or easily explained, no further analysis was performed.

Pre and post coffee treatment

Figures 17 and 18 depict the change scores (pretreatment minus posttreatment for SSS and GV measures, respectively) for the six administrations of caffeinated coffee and six administrations of decaffeinated coffee (Days 2-13). Analysis of the SSS and GV data pre- and post-caffeinated and pre- and post-decaffeinated treatment on Day 2 through Day 13 revealed that subjects felt significantly more alert after treatment (for SSS - $F(1,16) = 38.44$, $p < .001$) (for GV - $F(1,16) = 17.45$, $p < .001$), however, there were no significant differences between caffeinated and decaffeinated treatments and no interactions.

Relationship Among Sleep Measures

The correlations between the subjective (SSS, GV) and objective (MSLT) measures are presented in Table 5. The correlations between the mean subjective and mean objective measures for each day did not approach significance; the largest correlation was .33 between SSS and MSLT for Day 1.

Statistical analysis of the objective-subjective correlations for each of the five naps for baseline, Day 1, and Day 14 revealed generally nonsignificant findings; the only significant correlations were between SSS and MSLT and between GV and MSLT for nap 1 on Day 14 [SSS-MSLT ($r(19) = -.57$, $p < .01$) and GV-MSLT ($r(19) = .70$, $p < .001$)]. In contrast to the poor correlation between objective and subjective scales, the SSS was significantly correlated with the GV measure as well as with its five subscale measures for each nap suggesting that these two scales are measuring the same underlying construct.

Nighttime Findings

The results of the nighttime data can be found in Table 6. There was no difference in total dark time between baseline night and night after initial caffeine and between night after initial caffeine and night after chronic caffeine, thus, total amount of darktime for each subject was held constant throughout the study. However, there were significant differences between several other parameters comparing the night after baseline to the night after initial caffeine administration: sleep

latency and wake after sleep onset were significantly increased and sleep efficiency and slow wave sleep were significantly decreased on the night after initial caffeine. Comparing the night after initial caffeine to the night after chronic caffeine, sleep efficiency was significantly decreased and sleep latency was significantly increased on the night after initial caffeine.

Since the correlation between prior night total sleep time and MSLT was nonsignificant, a repeated measures ANCOVA which would remove prior night sleep effects from the objective daytime data, was not conducted.

Table 4: Means and standard deviations of the five visual analog subscales used in the Global Vigor measure. (Significant main effects and interactions are listed below).

	Alertness	Effort	Weariness	Sleepy	Overall
baseline (N=18)					
nap 1	.70(.16)	.25(.20)	.26(.20)	.27(.21)	.72(.18)
nap 2	.73(.19)	.24(.16)	.25(.17)	.22(.19	.80(.14)
nap 3	.81(.15)	.15(.17)	.17(.17)	.17(.13)	.81(.15)
nap 4	.79(.16)	.22(.20)	.26(.21)	.34(.25)	.81(.15)
nap 5	.71(.22)	.25(.22)	.30(.23)	.30(.24)	.78(.15)
Day 1(initial caffeine)(N=19)					
nap 1	.78(.19)	.17(.20)	.17(.18)	.20(.20)	.81(.16)
nap 2	.83(.14)	.17(.21)	.16(.17)	.12(.12)	.82(.19)
nap 3	.80(.18)	.20(.26)	.21(.24)	.20(.20)	.79(.20)
nap 4	.84(.15)	.17(.19)	.19(.22)	.19(.20)	.84(.13)
nap 5	.83(.18)	.16(.20)	.18(.20)	.17(.16)	.85(.15)
Day 14(chronic caffeine)(N=19)					
nap 1	.83(.16)	.18(.22)	.20(.21)	.15(.16)	.77(.27)
nap 2	.87(.11)	.11(.14)	.14(.16)	.13(.15)	.83(.20)
nap 3	.89(.08)	.12(.12)	.14(.17)	.12(.13)	.86(.12)
nap 4	.90(.08)	.08(.06)	.14(.17)	.13(.13)	.86(.19)
nap 5	.86(.14)	.13(.16)	.16(.16)	.15(.15)	.86(.16)

ANOVA-2 w/in subject factors(days and naps).
Significant main effects and interactions only.

Alertness subscale	F	df	p value
Day	7.54	34,2	.006
Nap	3.33	68,4	.04

Effort subscale	F	df	p value
Day	3.65	34,2	.04

Weariness subscale	F	df	p value
Day	4.17	34,2	.04

Sleepiness subscale	F	df	p value
Day	7.22	34,2	.006
Nap	4.37	68,4	.02

Table 5: Correlations between Multiple Sleep Latency Test (MSLT); Stanford Sleepiness Scale (SSS); Global Vigor Summary Measure (GV).

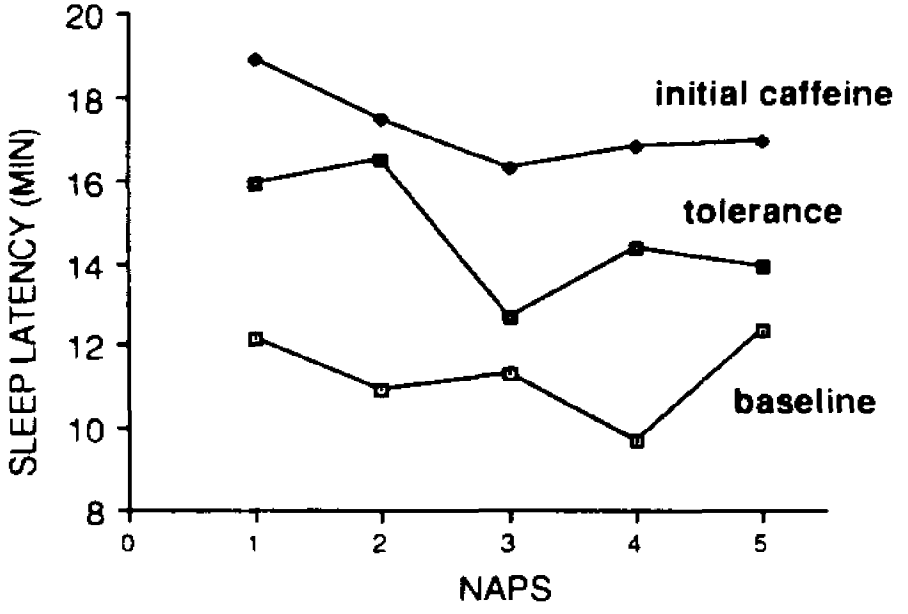
	Correlations		
Times of day	MSLT-SSS	MSLT-GV	SSS-GV
baseline (N=18)			
nap 1	.10	-.15	-.64*
nap 2	-.07	-.04	-.88**
nap 3	-.25	-.01	-.77**
nap 4	-.02	-.24	-.81**
nap 5	-.11	.15	-.78**
mean	.00	-.21	-.81**
Day 1 (N=19)			
nap 1	-.10	-.21	-.61*
nap 2	.02	-.09	-.49
nap 3	-.40	.33	-.74**
nap 4	.01	-.15	-.82**
nap 5	-.19	-.06	-.80**
mean	-.33	-.06	-.74**
Day 14 (N=19)			
nap 1	-.57**	.70**	-.74**
nap 2	-.29	.33	-.50
nap 3	.01	.16	-.75**
nap 4	.06	-.27	-.90**
nap 5	.15	-.07	-.70**
mean	-.01	.11	-.74**

(* < .01, ** < .001)

Table 6: Nighttime sleep parameter findings.
Night 1 = baseline night
Night 2 = night after initial caffeine administration
Night 14 = night after chronic caffeine administration

Variable	Mean (std. dev.)	Comparison	p level
Total dark time:			
Night 1	472.03 (44.32)	N1 vs N2	ns
Night 2	466.40 (46.47)	N2 vs N14	ns
Night 14	479.22 (42.49)		
Sleep efficiency:			
Night 1	95.55 (4.45)	N1 vs N2	.03
Night 2	92.55 (4.05)	N2 vs N14	.006
Night 14	96.23 (3.17)		
Total Stage 1:			
Night 1	23.89 (15.65)	N1 vs N2	ns
Night 2	28.38 (20.10)	N2 vs N14	ns
Night 14	27.01 (23.92)		
Total Stage 2:			
Night 1	236.71 (30.85)	N1 vs N2	ns
Night 2	241.71 (38.81)	N2 vs N14	ns
Night 14	257.78 (42.12)		
Total Slow Wave:			
Night 1	83.53 (36.58)	N1 vs N2	.006
Night 2	63.29 (28.40)	N2 vs N14	ns
Night 14	60.55 (25.89)		
Total REM time:			
Night 1	102.45 (29.41)	N1 vs N2	ns
Night 2	91.82 (18.33)	N2 vs N14	ns
Night 14	112.84 (24.42)		
Wake after sleep onset:			
Night 1	5.53 (9.38)	N1 vs N2	.03
Night 2	8.75 (10.07)	N2 vs N14	ns
Night 14	5.96 (6.44)		
Total Movement time:			
Night 1	4.43 (2.53)	N1 vs N2	ns
Night 2	5.23 (3.72)	N2 vs N14	ns
Night 14	4.67 (3.18)		

Figure 10. Mean Multiple Sleep Latency Test (MSLT) scores on baseline, initial caffeine day, and tolerance test day.



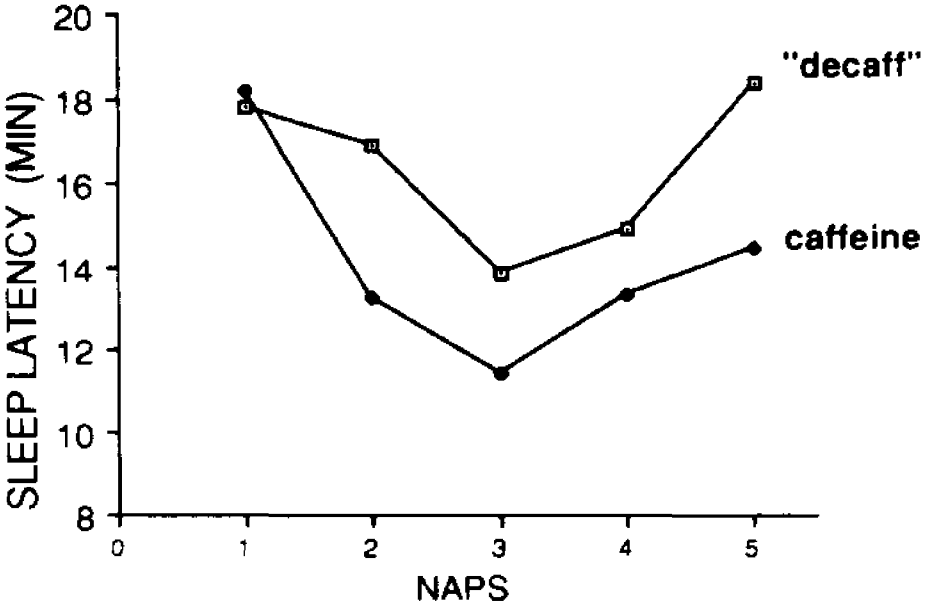
Significant main effect of day; subjects more alerted on initial caffeine day than on baseline ($p<.001$) and chronic caffeine or tolerance test day ($p<.02$).

baseline: no caffeine on day of MSLT.

initial caffeine day: 250 mg. caffeine administered one hour prior to first nap, following 11 prior days of caffeine abstinence.

tolerance test day: 250 mg caffeine administered on hour prior to first nap, following 6 administrations of 250 mg. caffeine distributed over previous two weeks.

Figure 11. Mean Multiple Sleep Latency Test (MSLT) scores for the two conditions on the conditioned tolerance test day.

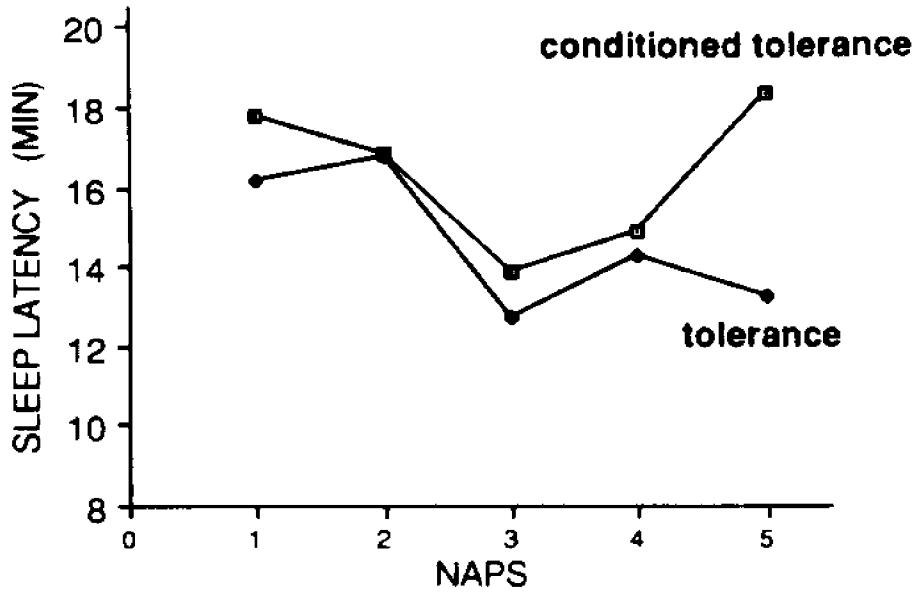


Significant main effect of nap ($p<.01$); subjects less alerted on nap 3 less than on the mean of the other four naps.

caffeine condition: Subjects were correctly told that they had received caffeinated coffee.

"decaff" condition: Subjects were falsely told that they had received decaffeinated coffee but they received caffeinated coffee.

Figure 12. Mean Multiple Sleep Latency Test (MSLT) scores for the "decaff" condition on tolerance test day and conditioned tolerance test day .

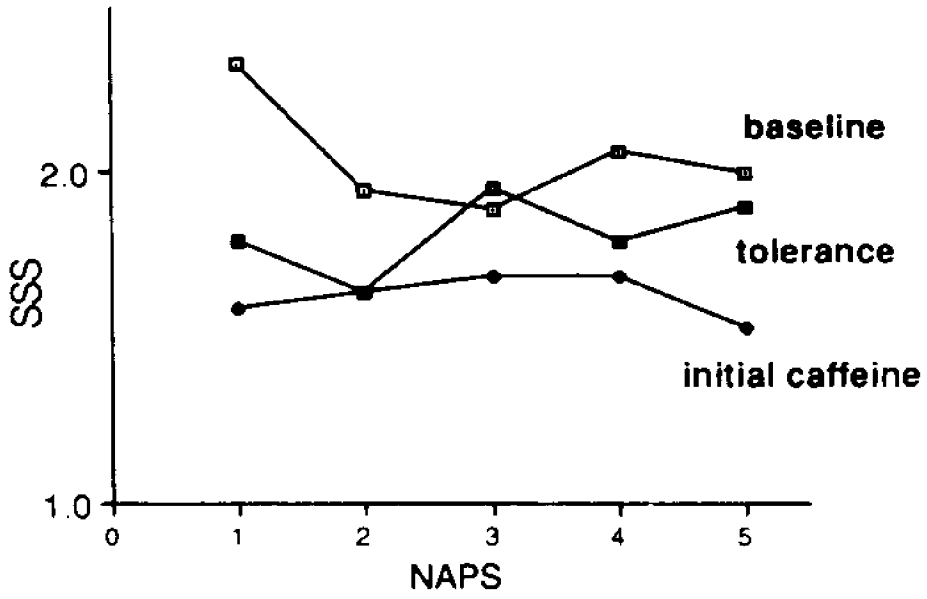


Nonsignificant trend of day ($p<.056$); subjects less alerted on tolerance test day less than on conditioned tolerance test day.

tolerance test day: Subjects were correctly told that they had received caffeinated coffee.

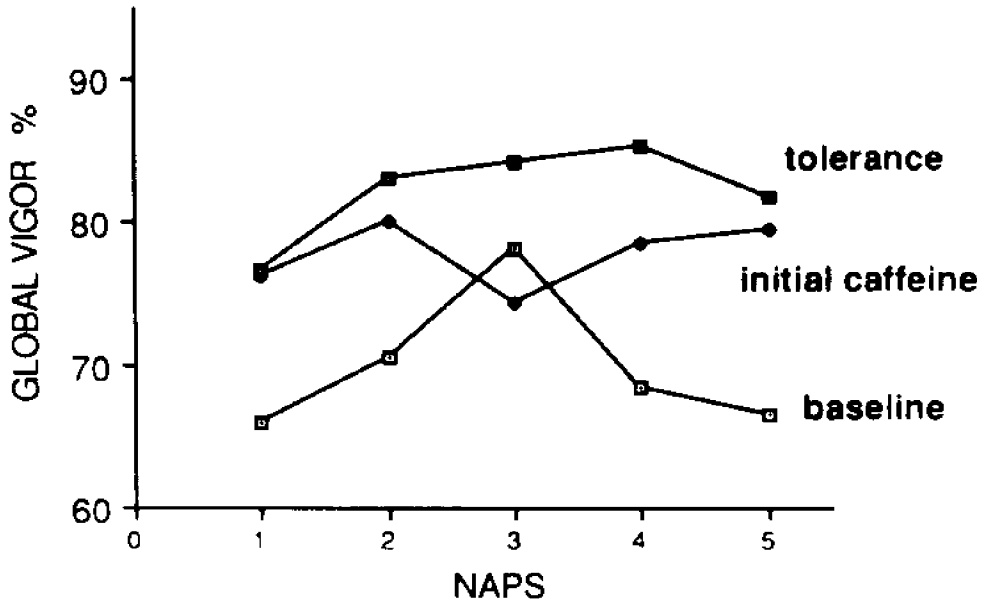
conditioned tolerance test day: Subjects were falsely told that they had received decaffeinated coffee but they received caffeinated coffee.

Figure 13. Mean Stanford Sleepiness Scale (SSS) scores on baseline, initial caffeine day, and tolerance test day.



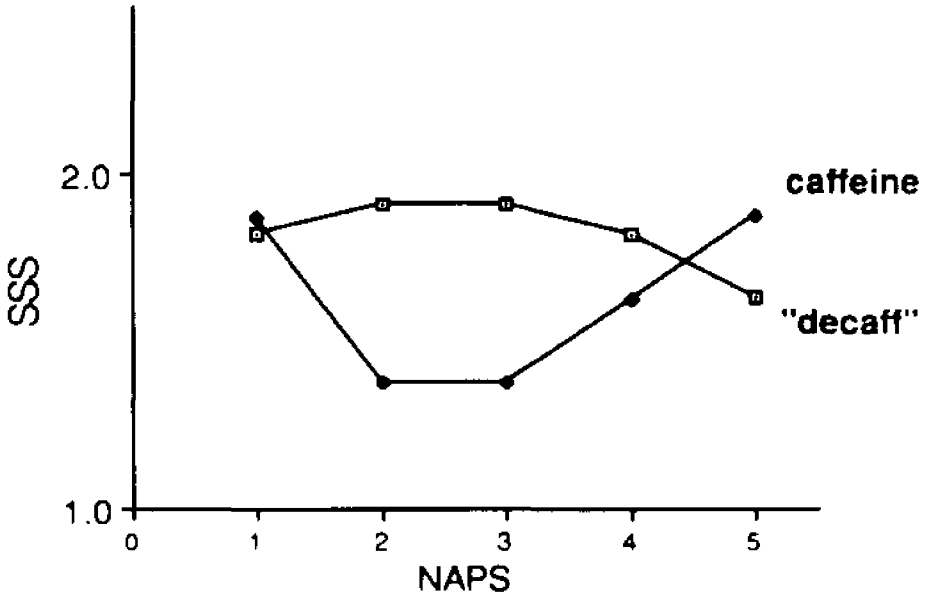
Significant main effect of day ($p<.01$); subjects felt more alert on initial caffeine day than on baseline.

Figure 14. Mean Global Vigor (GV) summary scores on baseline, initial caffeine day, and tolerance test day.



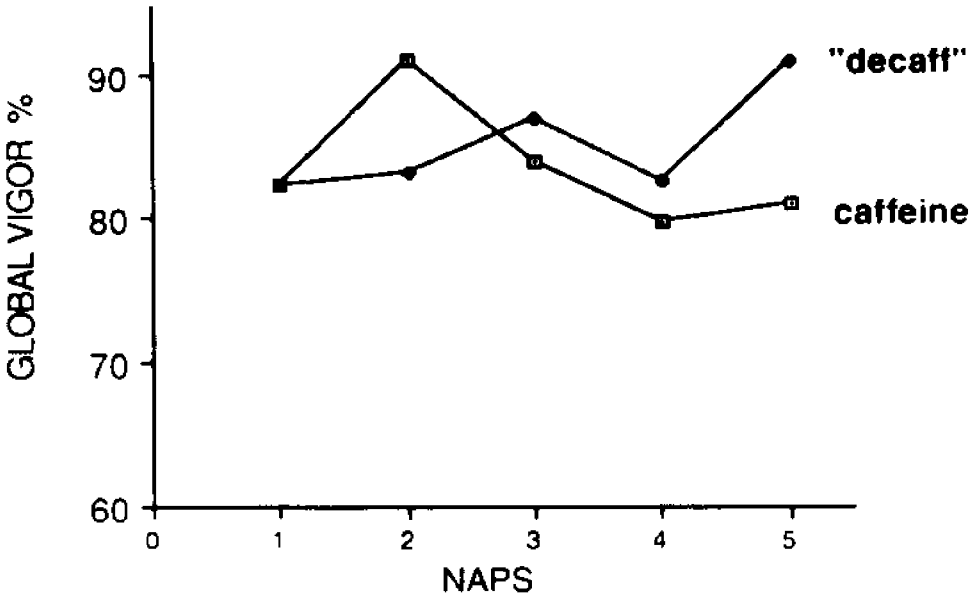
Significant main effect of day ($p<.02$): subjects felt more alert on initial caffeine day than on baseline.

Figure 15. Mean Stanford sleepiness scale (SSS) scores for the two conditions on the conditioned tolerance test day.



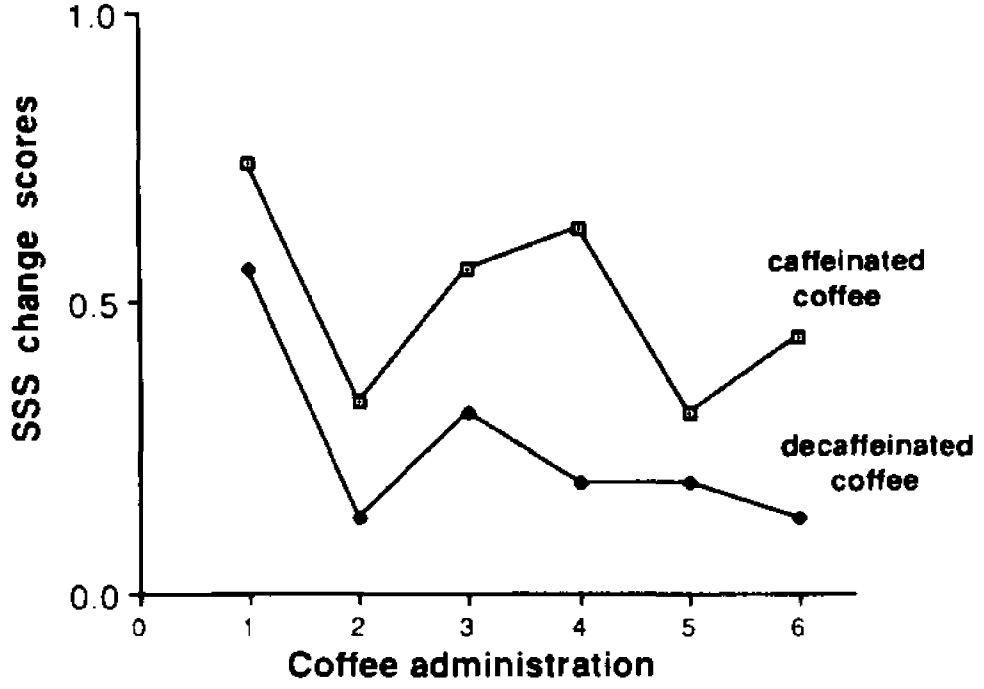
No significant main effects or interactions.

Figure 16. Mean Global Vigor (GV) summary scores for the two conditions on the conditioned tolerance test day.



No significant main effects or interactions.

Figure 17. Difference between Stanford Sleepiness Scale (SSS) scores pre- and post-coffee administration during the conditioning phase.

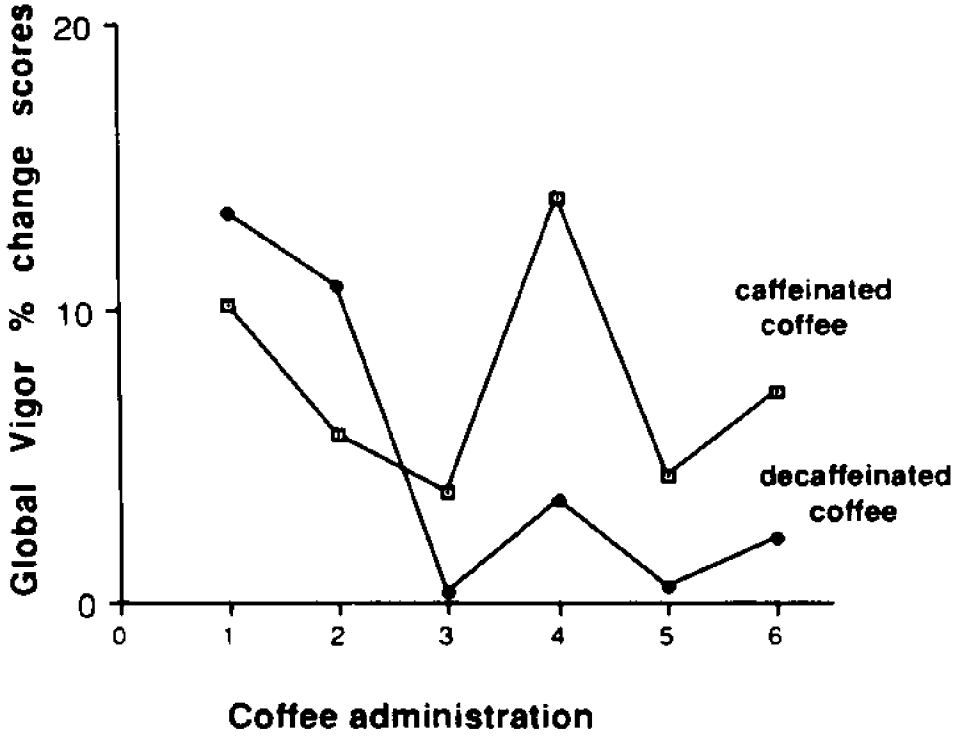


No significant main effects of type of coffee administration (caffeinated or decaffeinated).

conditioning phase: Six administrations each of caffeinated coffee and decaffeinated coffee, resulting in 12 total administrations on 12 days, interpolated between initial caffeine day and tolerance test day.

change scores: pre-coffee minus post-coffee.

Figure 18. Difference between Global Vigor (GV) summary scores pre- and post-coffee administration during the conditioning phase.



No significant main effect of type of coffee administration (caffeinated or decaffeinated).

conditioning phase: Six administrations each of caffeinated coffee and decaffeinated coffee, resulting in 12 total administrations on 12 days, interpolated between initial caffeine day and tolerance test day.

change scores: pre-coffee minus post-coffee.

DISCUSSION

After ten days of caffeine abstinence, 250 mg caffeine significantly increased objective daytime alertness in mild caffeine users up to nine hours after caffeine ingestion. Following a two week interval in which six doses of caffeine (250 mg) were administered, the same dose of caffeine had significantly less of an effect on objective daytime alertness. These findings suggest that tolerance develops to caffeine's alerting effects rather quickly.

These results extend my previous findings of increased alertness after 250 mg caffeine in sleepy young males (Lipschutz et al., 1988), to a normal young male sample. While this previous study also found that the alerting effects of caffeine progressively diminished over four caffeine administrations (250 mg caffeine at 9 am and 1 pm administered over two consecutive days), and the authors suggested that these findings demonstrated that tolerance occurs rapidly, there were design limitations in this previous study.

Since nighttime sleep was monitored by actigraphs, it is difficult to make statements about the quality of nighttime sleep in that study. Thus, it is possible that residual caffeine altered nighttime sleep on the first night causing the subjects to be more tired on the second day of testing. Indeed, in the present study, I found that an initial dose of 250 mg caffeine administered at 9 am significantly disrupted nighttime sleep.

As mentioned earlier, many reviews of the drug tolerance literature have concluded that tolerance can be acquired through both associative and nonassociative routes (Tiffany & Baker, 1985; Goudie & Demellweek, 1986; Siegel, 1988). Since associative drug tolerance has

been shown to be facilitated by lower doses of drugs and longer intervals between drug administration (Siegel, 1988), it is less likely that associative tolerance developed in this two day study. Alternatively, it is possible that the high dose of caffeine and short interdose interval fostered nonassociative tolerance in this previous study.

Support for the development of nonassociative caffeine tolerance can be found in a study by Dr. George Koobs that was recently cited in the New York Times Science section (August 7, 1991). The results demonstrated that rats given 4 mg/kg of caffeine (two to three cups of coffee equivalent) were found to be more active than control rats. Within 3-4 days, however, the animals activity levels after the same dose of caffeine returned to normal and post mortem examination of the caffeine-treated rat brains revealed higher than normal levels of adenosine receptors.

Adenosine is a natural compound in the brain which serves to slow down the release of other chemicals that normally excite the brain. Research has shown that caffeine blocks adenosine receptors and in effect, blocks the natural braking mechanism of the brain. These findings lend support to the notion that nonassociative mechanisms contribute to the development of tolerance to caffeine's alerting effects.

With regards to the main thesis of my dissertation, that caffeine tolerance develops because of associative mechanisms (the compensatory response elicited by pairing the expectation of caffeine with caffeine), the present findings of no difference in objective alertness between the caffeine and "decaff" conditions on the conditioned tolerance day (Day 15) do not support this hypothesis. However, some potentially significant limitations of this experiment suggest that it is premature to

rule out associative tolerance as a viable account of caffeine tolerance in some situations.

One limitation of the present study is the potential ceiling effect of caffeine on the MSLT. On the initial caffeine administration day, 16 of the 19 subjects on the first nap and 9 of the 19 subjects on the second nap had an MSLT score of 20 minutes. This suggests that the range of MSLT scores on this day was significantly constrained by the 20 minute time limit of the test. Also, relative differences between baseline (no caffeine) and treatment (caffeine) MSLT scores were further limited because baseline scores tended to be relatively high and variable (baseline mean MSLT score- 11.3 min $\pm$ 4.3).

A possible solution to the constrained range of MSLT scores found in the present study would be to extend the MSLT limit. In fact, during the initial development of the MSLT, Carskadon and Dement (1975, 1977) used a 90 minute wakefulness-30 minute nap opportunity schedule. However, they abandoned the 30 minute time limit for practical reasons; subjects became bored if they could not fall asleep and there was not enough time for performance testing in between each nap opportunity.

While most laboratories have subsequently standardized the MSLT (five 20 minute nap intervals separated by two hour intervals), lengthening the MSLT to a longer time limit may prove useful, particularly when stimulants are being tested. Also, variability in the present design could be reduced by increasing the sample size, since the size of the standard deviation of the sample is inversely related to the number of subjects.

It should be noted that the nonsignificant increase in objective

alertness in the "decaff" group from Day 14 to Day 15 ($p < .056$) (Figure 3) is consistent with a conditioning interpretation of drug tolerance. Furthermore, although nonsignificant, the increased objective alertness in the "decaff" group when compared to the caffeine group on Day 15 (Figure 11) likewise supports a conditioning analysis of tolerance. These findings also suggest that a larger sample size would optimize the probability of achieving significance.

As stated in the introduction, Dafters and Odber (1989) demonstrated that the assessment of tolerance using a single test dose may produce misleading results. In the present design, tolerance magnitude was inferred from one test dose instead of multiple test doses. Tiffany and Maude-Griffin (1991) have recently suggested that the use of multiple tests doses (dose-response curve methodology, DRC) is advantageous for several reasons.

First, DRC methodology allows one to measure the shift to the right of the dose-response curve and this measurement corresponds to the pharmacological definition of the phenomenon (Fernandes et al., 1977 ; Kalant et al., 1971). Second, the DRC method avoids the possible confounds of ceiling or floor effects found when single test doses are used to measure tolerance magnitude. Third, the effect of changes in dose level on tolerance may be systematically evaluated by using DRC methodology.

Finally, the slope of the dose-response curve may be an index for associative or nonassociative processes. Thus, DRC methodology may provide a useful way to distinguish the relative contribution of associative and nonassociative processes to drug tolerance development. Although obvious disadvantages of DRC methodology are that it is labor

intensive and time consuming, it is possible that the present design may be improved by using multiple doses of caffeine during the tolerance test phase.

Although mild caffeine consumers were selected in this study, it is possible that a different population of caffeine consumers may have yielded different results. Some researchers have found a positive relationship between depression and caffeine use (Furlong, 1975; Gilliland & Andress, 1981; Greden, Fontaine, Lubetsky, & Chamberlein, 1978) and have suggested that caffeine's stimulating effects ameliorate depressive symptoms.

Thus, in depressed subjects, caffeine may be seen as a form of self-medication. Sawyer, Julia, & Turin (1982) suggest that depression may cause changes in biological systems and that caffeine counteracts these changes. However, chronic caffeine in turn may cause the initiation of opposing responses that counter the initial caffeine effect.

In one study mentioned in the introduction, regular caffeine users reported that bedtime caffeine had no deleterious effects on nighttime sleep. Another study, reported that individuals who experience caffeine's effects as beneficial, self-administer more caffeine than subjects who experience caffeine's effects as aversive.

Since there appears to be considerable individual differences with respect to subjective effects of caffeine and the propensity to self-administer caffeine, it is possible that certain individuals (e.g. those that report tolerance to caffeine's alerting effects and those that self-administer caffeine) might be more likely to develop associative tolerance. Kuznicki and Turner (1986) have suggested that the optimal method of assessing the effects of caffeine involves studying two types

of populations concurrently; heavy caffeine users and non-users.

Although efforts were made to control for the different tastes of caffeinated and decaffeinated coffee, it is possible that the "decaff" group on Day 15 suspected that they were drinking caffeinated coffee. If so, the expectation of caffeine in this group may have confounded the results.

Also, recent studies have suggested that other pharmacological constituents of coffee besides caffeine, may have alerting effects (Griffiths & Woodson, 1988a). Furthermore, subjects who drink coffee, have developed associations with the drinking behavior which would most likely confound laboratory assessment of associative caffeine tolerance.

Griffiths and Woodson (1988) have found that the assessment of caffeine's reinforcing effects are most effectively studied by administering it in capsule form. Thus, a possible resolution to the problems surrounding coffee administration in laboratory studies may be to administer caffeine and placebo in capsule form.

In sum, the time limit of the MSLT, the sample size, the caffeine vehicle, the single test dose and the population used in the present study may need to be modified in order to demonstrate that the alerting effects of caffeine are subject to associative tolerance.

A potentially significant limitation of the present study is that practice effects may have confounded the assessment of the caffeine's alerting effects. Although sleep researchers have generally overlooked possible interactions between practice, drugs, and MSLT performance, research with such drugs as morphine, alcohol, amphetamines and benzodiazepines suggest that "intoxicated practice" (repeated testing on

drug) significantly interacts with subsequent performance (Chen, 1968; Corfield-Sumner & Stolerman, 1978; Schuster, Dockens, & Woods, 1966; Vogel-Sprott & Sdao-Jarvie, 1989). As I will develop later on in this section, the potentially significant effects of practice on the assessment of tolerance has implications for the theoretical framework on which drug tolerance research should be based.

Chen (1968) was the first to test the "task practice" hypothesis. In his study, two groups of rats were trained for four days on a circular food maze. In the first group, rats received alcohol (1.2 g/kg) before running the food maze. In the second group, the rats received the same dose of alcohol after running the maze. After several pairings of alcohol with maze running, tolerance was tested by giving alcohol before running the maze to both groups.

The alcohol-before group demonstrated significantly more tolerance (less behavioral disruption) to alcohol than the alcohol-after group. Since both groups received equal dosings of alcohol, Chen interpreted these findings as supporting the notion that subjects given practice on a task while in a drugged state acquire a behavioral strategy to compensate for drug-induced impairment.

An alternative interpretation of his findings, which does not involve learning, proposes that greater functional demands are posed by intoxicated practice and due to these demands, physiological adaptation to the drug is accelerated (Kalant et al., 1971). Still another interpretation of the results of the before-after design studies, which is consistent with a Pavlovian conditioning model of drug tolerance, has been proposed by Hinson and Siegel (1980).

They suggest that during the tolerance acquisition phase, the

alcohol-before group has repeated pairings of the task with the drug's effects and that the task becomes a reliable predictor of the drug's effects. Tolerance in the alcohol-before group is seen as a summation of the drug's effects and the compensatory response elicited by the task. On the other hand, the alcohol-after group's first exposure to the task-drug pair occurs during the tolerance test phase. Thus, it is the novel experience of task and drug in the alcohol-after group that explains the lack of tolerance in this group.

Due to the ambiguity in the interpretation of between subject before-after designs, within subject research designs have been employed. A typical paradigm used to study the effects of practice on the development of tolerance involves holding the predictive cues constant while manipulating the consequence of the performance used as the dependent variable.

In one such study, Schuster et al. (1966) trained rats to bar press for food under two different types of schedules; differential low rate of response (DRL) and fixed interval (FI). On a DRL schedule, delivery of the reinforcer is dependent on the rat performing a certain number of bar presses. With FI schedules, delivery of the reinforcer (food) is not associated with the bar pressing behavior but instead is dependent on the passing of a fixed interval of time. After baseline training, rats were administered d-amphetamine before each bar pressing session for 30 days. The results demonstrated that tolerance to the behavioral effects of d-amphetamine occurred only when animals performed under the DRL schedule.

Since the drug state and the functional demands were held constant under these two different reinforcement schedules, the authors

interpreted these findings as support for the notion that tolerance will only occur when the drug disrupts the behavioral requirements necessary to obtain reinforcement. Such learning is often referred to as instrumental conditioning because the reinforcement contingencies are instrumental in manipulating the behavior. When the behavioral effects of a drug enhance or do not affect the probability of reinforcement, tolerance will not occur. Thus, under situations where behavior and drug states interact so as to decrease reinforcement, instrumental learning may play a role in the development of tolerance.

Researchers have found that instrumental learning may contribute to tolerance with other drugs such as morphine and benzodiazepines (File, 1985; Griffiths & Goudie, 1986; Demellweek & Goudie, 1983). In a review on psychostimulants, Demellweek and Goudie (1983) assert that the instrumental learning hypothesis accounts for the available data on tolerance to stimulants more effectively than conventional pharmacological theories or other learning theories. They conclude that if a drug causes changes in the behavior studied that result in a decrease in reinforcement, tolerance will occur and that tolerance develops to the behavior not to the drug itself.

It is conceivable that in certain situations, caffeine may interact with performance in such a way as to disrupt behaviors that will optimize reinforcement. In the present study, the MSLT which measures tendency to fall asleep, was the dependent variable used to assess the development of tolerance to caffeine's alerting effects. After the initial caffeine administration, sleep latency significantly increased and anecdotally, many subjects remarked that it was difficult to stay in bed for so long and that they felt "anxious", "highly aroused" and sometimes

"claustrophobic" during the test. These observations suggest that when objective alertness was significantly increased by caffeine, the MSLT became an unpleasant experience and termination of the MSLT represented the removal of an unpleasant stimulus.

It is possible that in a highly alert subject, falling asleep quickly on the MSLT may be negatively reinforced by the removal of the unpleasant stimuli that are associated with trying to fall asleep or with inactivity (e.g. small bedroom, darkness, quiet, anxiety).

In this view, one could hypothesize that practice with the MSLT on caffeine might lead to a facilitation of the behavior of falling asleep. In the present investigation, the subjects had ample exposure to the MSLT on caffeine (10 sleep latency tests) before the test of conditioned tolerance on Day 15. Thus, it is possible that instrumental conditioning confounded the assessment of associative tolerance.

The only study that remotely addressed the issue of practice and MSLT scores was done at the Henry Ford Hospital by Zwyghuizen-Doorenbos et al. (1988). They found that MSLT latency did not significantly change when administered 4-14 months later. However, there were no drugs used in this study and if learning occurred on the first day of testing, it is unlikely that it would be retained over this long a time interval. Unfortunately, there are no other studies to date that directly address the issue of the effects of drug and practice on MSLT scores.

Perhaps a more provocative question that arises from such inquiry into practice effects is, to what extent can the behaviors sleep and falling asleep be learned or conditioned responses? As early as 1927, Pavlov found that after repeated pairings of the injection procedures with

morphine (hypnotic), rats fell asleep during the preliminary injection procedures. Clemente, Sterman, & Wyrwicka (1962) paired a sequence of tones (CS) with stimulation in the preoptic forebrain area (produces sleep) in cats and found that after repeated pairings, the CS alone elicited sleep. Levitt (1964) found that after 11 trials of morphine injections, sterile water injections alone caused sleep in dogs. However, Levitt and Webb (1964) were unable to condition the sleep response in rats using injection ritual cues as the CS and pentobarbital as the UCS.

Since these early studies on sleep as a conditioned response, there has been little research in this area. However, recently Spielman et al. (1987b) investigated the effects of repeated hypnotic administration on objective daytime alertness in humans. In this study, .125 mg triazolam was paired with a tone on the MSLT (one day/week; 8 consecutive weeks). The preliminary data demonstrated that the pairing of the tone with the hypnotic promoted sleepiness. Thus, there is some evidence to suggest that stimuli associated with sleep may become capable of eliciting the sleep response.

Clinicians have also become interested in the conditionability of sleep or sleeplessness (Bootzin & Nicassio, 1978; Spielman et al., 1986; 1987a; 1987b). As reviewed by Spielman et al. (1987a), it has been suggested that rituals associated with bedtime (e.g. nighttime T.V. programs, reading, clock watching) may become discriminative cues that either promote or inhibit sleep onset. The authors further hypothesize that in some cases of insomnia, bedtime ritual cues may be an important perpetuating factor of sleeplessness. Thus, some clinicians have incorporated behavioral principles in the treatment of insomnia.

Although an in-depth description of the treatments used in insomnia

is beyond the scope of this dissertation, three such treatments are: stimulus control instructions, sleep restriction therapy and sleep hygiene recommendations.

Despite some clinical and research efforts on the relationship between sleep and conditioning, it appears that our current understanding on this subject is quite poor. Indeed, the following statement written by Wilse Webb in 1957, could have easily been written in 1991: "Psychologists have done very little about experimentally analyzing the antecedents of sleep. When they have shown interest in sleep, such interest typically has been directed toward the consequences of sleep deprivation on nonsleep activities or in describing the response itself."

It appears then, that theories which attempt to explain the development of tolerance to caffeine's alerting effects must not only account for stimuli repeatedly accompanying caffeine administration but should also be cognizant of the present and past associations formed with the sleep response itself. Although the issue is complicated at best, a recent theory proposed by Vogel-Sprott and Sdao-Jarvie (1989) accounts for the influence of both Pavlovian and instrumental procedures on the development of tolerance.

According to their theory, there are two types of associations that are formed; stimulus expectancy and response expectancy. Stimulus expectancy refers to the association that is formed between the stimulus and the drug. While the stimulus evokes a multiplicity of responses, the one of interest for drug tolerance is the compensatory response. A response expectancy is formed when the procedure used to assess drug tolerance provides some systematic consequence for the compensatory response. The association that is formed in a response expectancy is

between the learned response and the incentive value (positive, negative, or neutral) of learning that response.

These two types of associations have two different outcomes that need not be correlated. For example, the reliable pairing of caffeine with the expectation of caffeine may elicit a compensatory response that is de-alerting, however, the drug-compensatory response may have a negative incentive value if the subject is required to drive a car. Thus, caffeine tolerance may not be observed in a situation where the outcome of the compensatory response is negatively valued.

To predict how each source of learning may contribute to the tolerance displayed, Vogel-Sprott and Sado-Jarvie present a model that is illustrated in Table 7. Briefly, tolerance will be greatest when reliable pairings of stimulus and drug occur and when the drug-compensatory response optimizes performance. It is further hypothesized that there will be less tolerance when Pavlovian and instrumental procedures result in conflicting outcomes. Finally, drug sensitization will occur when no reliable cues precede drug and when instrumental training associates compensatory performance with an aversive consequence.

Table 7: Tolerance as a function of stimulus expectancy for drug and expected consequence of a drug-compensatory response.

	Response expectancy		
Stimulus expectancy	Absent(0)	Positive(+)	Negative(-)
Present (+)	0+	++	-+
Absent (-)	00	+0	-0

Applying this model to the present investigation, the reliable pairing of the expectation of caffeine with caffeine and the repeated administration of the MSLT on caffeine may have optimized caffeine tolerance and the results on Day 14 confirm such a prediction. On Day 15, the "decaff" group had the novel situation of expecting decaffeinated coffee but the coffee administration occurred in the same environment as it had been administered previously. Thus, stimulus expectancy may have been lessened but was probably not entirely absent.

Also, the reward of falling asleep quickly on the MSLT did not change and thus, it is possible that instrumental learning contributed to the tolerance seen in this group. Although nonsignificant, the results suggested that the "decaff" condition was less tolerant than the caffeine group on Day 15 which is consistent with the predictions made by this model. The ability of this model to account for the results of the present investigation suggests that it may provide a useful theoretical framework on which to base future research on the development of caffeine tolerance.

In the present investigation, subjective alertness like objective alertness, increased after the initial administration of caffeine. However, subjective alertness did not show the same decrease in alertness as the MSLT after repeated administrations. Instead, there was a nonsignificant trend towards an increase in subjective alertness after repeated exposure to caffeine. Thus, these results suggest that subjective impressions of alertness do not always reflect objective measures of alertness.

Furthermore, even though the two subjective measures were highly correlated suggesting that the SSS and GV are measuring the same

underlying construct, there was no relationship between the MSLT and the SSS or MSLT and GV measure.

Numerous studies have also found no relationship between objective and subjective measures of sleepiness. In a sample of 80 young adult good sleepers, Johnson, Freeman, Spinweber, & Gomez (1991) found no overall significant relationship between objective and subjective measures of sleepiness. Other researchers have studied clinical sleep disorder populations and found similar negative results. Roth, Hartse, Zorick, & Conway (1980) and Seidel, Ball, Cohen, Patterson, Yost & Dement (1984) found that apneic patients had significantly shorter sleep latencies on the MSLT than controls but rated themselves as more alert than controls.

Roth et al. (1980) also found that after nasal CPAP treatment for sleep apnea, subjective assessment of alertness was significantly higher posttreatment versus pretreatment but MSLT scores did not significantly change. Valley and Broughton (1981) found that subjective assessment of sleepiness did not reliably predict objective measures in narcoleptics. The lack of correlation between the MSLT and subjective estimates of alertness has led some researchers to question the construct of sleepiness.

According to Carskadon and Dement (1982), sleepiness is differentiated by the method of measurement. While the MSLT measures physiological tendency for sleep to occur, subjective alertness measures manifest sleep tendency and is dependent on many alerting factors (light, noise, room temperature, activity level, motivation, hunger, thirst, anxiety level, etc). Such alerting factors may change

from moment-to-moment, however, it is only when such factors are stripped away that physiological and manifest sleep tendency approach each other.

Broughton (1982) addresses the issue of sleepiness from a different perspective and attempts to explain sleepiness as a heterogeneous state composed of at least three biologically different dimensions; REM sleep, NREM sleep, and wake. In his view, sleepiness may be a function of REM sleepiness, NREM sleepiness or an impaired waking mechanism. Thus, differences in subjective and objective measures of alertness may reflect the multidimensionality of sleepiness.

In sum, the present results along with many other studies suggest that different measures commonly used to assess alertness/sleepiness may not be measuring the same underlying mechanism. Furthermore, it is evident that the relationship between these different measures is dependent upon many factors (e.g. time of day, motivation, state of subject). Thus, it would appear that further study is required to understand whether sleepiness is a unitary or multidimensional construct.

Although quite unexpected, the present findings demonstrated that 250 mg caffeine administered at 9:00 am had deleterious effects (increased sleep latency and wake after onset and decreased sleep efficiency and slow wave sleep) on nighttime sleep 14 hours later. This is the first study to date to demonstrate that morning caffeine disrupts nighttime sleep.

These findings are particularly interesting given that there is some controversy over whether bedtime caffeine disrupts subsequent nighttime sleep. In particular, many studies have shown that caffeine (100-300 mg) administered at or near bedtime produces such sleep disturbances as

reduced sleep time, increased sleep latency and number of awakenings (Brezinova, 1974; Karacan et al., 1977; Okuma, Matsuoka, Matsue, & Toyomura, 1982), however, some studies have failed to demonstrate disruption of sleep, particularly at lower caffeine doses (50-200 mg) (Clubley et al., 1979; Nicholson & Stone, 1980).

It is possible that some of the problems mentioned earlier which influence the assessment of caffeine's alerting effects during the daytime (population studied; variability in dose and caffeine vehicle; sleep measure) might also confound the research of caffeine's effects at night.

Final Conclusions

In summary, the present dissertation demonstrated that 250 mg caffeine objectively and subjectively alerted young normal-sleeping males with a previous history of mild caffeine use. After six caffeine and six decaffeinated coffee administrations, tolerance to caffeine's objective alerting effects was demonstrated. While the present data does not support a Pavlovian analysis of drug tolerance, problems with the time limit of the MSLT, the small sample size, the caffeine vehicle and the population tested as well as the theoretical model used to design the experiment might have impacted adversely on the results. Also, there was a lack of correlation between subjective and objective measures of alertness which suggest that these two measures may not be assessing the same underlying construct. This is the first study to demonstrate that morning caffeine produces nighttime sleep disturbances. Further research is needed to investigate the issues of associative caffeine tolerance, measurements of sleepiness, and sleep disruptive effects of acute and chronic morning caffeine.

Appendix 1

EFFECTS OF CAFFEINE ON DAYTIME SLEEPINESS AND ALERTNESS

TELEPHONE STUDY DESCRIPTION

Purpose: To study the effect of caffeine on daytime sleepiness and alertness and the development of tolerance to caffeine.

Subject criteria: 18- 35 years old, healthy males a normal nighttime polysomnograph recording, and an MSLT less than 15 minutes and greater than 5 minutes. Nonsmoker, nonalcoholic, < 250 mg caffeine/ day, reported regular sleep habits.

Time requirements: There is an overnight polysomnograph recording on a friday night and next day MSLT screenIf passed- the study will be continued over the next15 day period. Thus the full study starts on a friday night till two sundays later. You will spend 5 nights in the laboratory, the first and third friday and saturday nights. You will also spend the first and third saturday and the third sunday in the lab. All other days in between, you will spend 45 minutes in the early morning in the lab except for the middle sunday.

Procedure: On all nights and days that polysomnograph recording and evoked potentials, are done, electrodes will be applied on the scalp, chest and face and on the first night also on the legs and a thermister under the nose to check for airflow. The wiresfrom the electrodes are tied in the back of the head and peoplefind them relatively non-intrusive. On all mornings during the study, you will receive a coffee beverage in the morning and will be allowed 15 minutes to consume the beverage.

On all nights that you come to the lab, you will arrive an hour and a half before bedtime and the next day will awake at you raverage waketime. One to two hours after waketime, you will drink a coffee beverage with 250 mg of caffeine in decaffeinated coffee, this is roughly equivalent to 2.5 cups of coffee or you will drink a cup of decaff. coffee. Approximately 2 hours before and 1, 3,5, 7, 9 hours after the coffee, we will run the Auditory Evoked Potentials and the MSLT (explain briefly).

On days that you are not in the laboratory, you will arrive 15 minutes before your scheduled coffee administration and leave around a half hour later. You will also fill out the sleep log for the previous nights sleep and some mood scales.

Other information:
-We are located on the City College Campus at the NAC building on the 8th floor room 213. The facility has bathrooms, showers, T.V., VCR, a desk,

Appendix 1 (continued)

and a kitchen. Bring something to do, there will be free time between naps.

-No smoking, drug use or drinking alcohol or coffee (except what we administer) is allowed during the study.

- Sheets are laundered on the beds and towels provided. Bring your own soap, shampoo, shaving equipment and pajamas.

-After completion of the study and screen, you will receive ____. If you do not pass the screen, you will be compensated at a rate of _____for the night and next day and _____ for the first night only. If you complete one week, you will receive ____ and if you complete two weeks, you will receive _____. The payment will be in 1 lump sum and you should receiveit within 3 weeks.

Appendix 2

Telephone Screening Questionnaire

1 Name _____ SS#_____Age___

2 Address _____

3. Home Phone # ( )_____ Work # ( )_____

4. do you smoke cigarettes regularly? Yes No

5. Do you drink caffeinated beverages? Yes No
If Yes, what?_____ How many cups/bottles/day_____
Do you need it in the morning ? Yes No

6 Do you drink alcohol? Yes No

7. What is the average alcohol consumption/week?_____

8. Have you ever been a heavy drinker?_____

9. Do you take any medication or drugs?_____
If yes, what and how often?_____

10. Are you allergic to any medications? _____
If yes, what?_____

11. Do you have any difficulty sleeping at night? Yes No

12. What time do you usually go to bed? _____
How much does this vary?_____

13. What time do you typically get up in the morning? _____
How much does this vary? _____

14. How many hours do you typically sleep per night?_____

15. Are you generally sleepy during the day? _____

16. How often do you take naps during the day? _____

17. How long does it usually take for you to fall asleep? _____
Comments:

Appendix 3

SLEEP LOG

	DAY						
	DATE						
[illegible] in bed before going to sleep (e.g. sleep, watching TV, reading)? [illegible] the time you got into bed last night							
2. The time you turned the lights out or began trying to fall asleep							
3. How long it took you to fall asleep							
4. The time you finally got out of bed this morning							
5. Your estimate of the total amount of [illegible] were asleep last night							
6. The number of times you woke up							
[illegible] woke up and didn't [illegible]							
[illegible] were physically [illegible] during the night							
[illegible] last night							
[illegible] was waking up and [illegible] this morning [illegible] 5 [illegible] 7 Very difficult							
[illegible] Yesterday [illegible] that were outdoors							
[illegible] number of brief [illegible] yesterday							
[illegible] of sleep while [illegible] yesterday							
[illegible] number of cups of coffee plus [illegible] of caffeinated beverages							
[illegible] number of ounces of liquor plus [illegible] of wine plus glasses of beer yesterday							
[illegible] you exercise yesterday? If YES, [illegible] The time of day was the: Morn / Midday / Eve							
17. Rate your ALERTNESS yesterday 1 2 3 4 5 6 7 least alert — most alert							
18. Rate your FATIGUE yesterday 1 2 3 4 5 6 7 least fatigued — most fatigued							

Appendix 4

Consent- Caffeine and daytime sleepiness

Agreement to participate in a research study on the effect of caffeine on daytime functions

I have been asked to participate in a research study which will involve the administration of caffeine. The purpose is to determine caffeine affects my alertness and ability to function over time. After an initial telephone screening, I will fill out nightly sleep logs for one week and abstain from caffeine for seven days prior to the beginning of the study. The first night and next day of the study is considered the screening and involves an overnight sleep recording and the following day, a Multiple Sleep Latency Test (MSLT) and Auditory Evoked Potential Test (AEP). I have been told that the study will be conducted over a 17-18 day period, from a friday night till two sundays or mondays later.

I understand that the night of the recording, electrodes will be applied on the scalp and face and on the legs and chest for the screening night. A wire will placed under the nose and mouth to check for airflow. I will sleep and awake at times that are consistent with my average sleep and waketimes on the sleep logs. I agree to retrain from drinking caffeinated beverage for the whole study

On the next day, time zero will be 1 hour after waketime and naps and subjective measurements of sleepiness will be run +1 hour, +3 hours, +5 hours, +7 hours, and +9 hours after time zero. At these naptimes, I will lie down in a sleep chamber and be asked to "go to sleep". On these same days, AEP's will be run one half hour before my coffee beverage and before naps 1,3 and 5. If I pass the screen, I will continue the study. On all nights, I will sleep and wake at my average sleeptime and waketime as determined by my sleep logs. I will spend 5 or 6 nights in the laboratory, the first and third friday and saturday nights and the first and possibly third sunday night. Electrodes will be applied on the scalp and face. On the next morning and on all other mornings, At time zero, I will receive a coffee beverage and will be allowed 5 minutes to consume the beverage. On the first and third saturday and sunday and possibly third monday, I will be tested for sleepiness using the same daytime schedule as in the screen. On all other days that I am not spending in the laboratory doing the MSLT and AEP's, I will come to the lab 15 minutes before time zero and then spend 45 -60 minutes there before leaving the lab.

I, the volunteer, have been made aware of the following:

1) I have read this document and all of these things have been explained to me by Lauren Lipschutz, who has offered to answer any question I may have during the research study. I am aware that I should contact Dr. Spielman at 650-5397 and/or the research office at 650-5396 if I have any questions regarding the research, research subjects' rights or my participation in the study and its outcome.

2) I realize that no medical benefit will necessarily accrue to me from participation in this study. I understand that I will be told of any significant new findings which develop during this study which may relate to my willingness to continue to participate in this study. I understand that study information identifying me will remain confidential and will not be disclosed outside of the center except with my written permission or as required by law.

3) I understand that I will be paid $150.00 for the study if I complete the 17-18 day and night study. If I do not pass the screen, I will be compensated at a rate of $25 for the night and next day, or $15 for the first night when daytime testing is not required. If I complete one week, I will receive $40.00 and if I complete two weeks, I will receive $60.00.

Appendix 4 (continued)

4) I understand that caffeine consumption (other than that supplied), alcohol consumption and tobacco intake and naps should be avoided at all times during the study. The use of over-the -counter drugs and prescription drugs must be approved by the Director of the Sleep Center.

5) I have been told that the powdered caffeine is pharmaceutical grade and that the dosage is 250 mg, roughly the equivalent of ingesting two and a half cups of brewed coffee. The caffeine powder will be dissolved in one teaspoon decaffeinated coffee and lactose in hot water. On other days I will receive lactose and decaffeinated coffee in hot water only. Caffeine in the dosage to be administered may produce restlessness and stomach irritation. In rare cases, it may cause insomnia, headache, nausea and vomiting. If any untoward reaction takes place the technician will contact the medical director of the Sleep Disorders Center to determine what action to take.

6) I understand that in the event of physical injury resulting from the research procedures used in this study, only immediate essential treatment, as determined by the technician on duty or Dr. Spielman will be available for the injury without charge to me personally; there will be no monetary compensation.

7) In giving my consent, I acknowledge that my participation in this research study is voluntary and that I may withdraw from it at any time without prejudice to me. I also understand that I may elect not to participate in this research study at all. In addition, my participation may be terminated without regard to my consent by the investigator for violation of the protocol or for administative reasons.

Subject Signature _____ Date _____

Age _____ Weight_____

Witness Signature _____ Date _____

Caffeine Study
POLYGRAPH MONTAGE
MULTIPLE SLEEP LATENCY TEST (MSLT)

Subject's Initials ____ Subject Number ____

Polygraph ____ Room Number ____
(this sheet for LOW and HIGH rooms)

Date _____

Session _____
Note any changes to montage on this sheet. Channels marked by "." may be sacrificed if necessary. Δ may be sacrificed if absolutely necessary.

chan	derivatn	LOW	HIGH	sensitivity	pin #'s
1	C4/A1,A2 central EEG alt: C3	0.3	60	7.5 uV/mm	13/A1,A2
2	O2/A1,A2 occipital EEG	0.3	60	7.5 uV/mm	15/A1,A2
3	LOC/A1,A2	0.3	60	7.5 uV/mm	16/A1,A2
4	ROC/A1,A2	0.3	60	7.5 uV/mm	17/A1,A2
5	LOC/ROC	3.0	60	7.5 uV/mm	16/17
6	chin EMG	10	90	1 uV/mm	18/19
7	EKG	0.1	90	50uV/mm (adjust)	
8	C4/O2 bipolar EEG	0.3	60	7.5 uV/mm	13/15

Appendix 6

[illegible] QUESTIONNAIRE

Date [illegible]

1\. [illegible] you take any NAPS today? [illegible] yes [ ] no

If yes, what time? 1______, 2______, 3______, 4______, 5______

How long? 1______, 2______, 3______, 4______, 5______

2\. Have you taken any PRESCRIBED MEDICATIONS today? [ ] yes [ ] no

If so, what? 1______, 2______, 3______, 4______, 5______

When? 1______, 2______, 3______, 4______, 5______

Have you taken any NON-PRESCRIBED MEDICATIONS today? [ ] yes [ ] no
(cold remedies, aspirin, diet pills, etc.?)

If so, what? 1______, 2______, 3______, 4______, 5______

3\. Have you had any ALCOHOL today? [ ] yes [ ] no

If yes, what______ how much?______ when ______

4\. [illegible] had ANY LIQUIDS OTHER THAN WATER [illegible]? [ ] yes [ ] no
[illegible]

[illegible] ______ how much ______ when______

5\. [illegible] you FEEL ILL today or do you feel ill now? [ ] yes [ ] no

If yes, how______ and when ______

6\. Did anything OUT OF THE ORDINARY happen today? [ ] yes [ ] no

If yes, what?______

7\. Did you FEEL SLEEPY today? [ ] yes [ ] no

If yes, when? 1______, 2______, 3______, 4______, 5______

8\. When did you eat YOUR LAST MEAL? ______

Compared to usual was it: [ ] less, [ ] same, [ ] more.

9\. How TIRED do you feel right now?

[ ] not at all, [ ] a little, [ ] quite a bit, [ ] extremely

10\. How SLEEPY to you feel right now?

[ ] not at all, [ ] a little, [ ] quite a bit, [ ] extremely

11\. How ALERT do you feel right now?

[ ] not at all, [ ] a little, [ ] quite a bit, [ ] extremely

COMMENTS______

Appendix 7

CAFFEINE MOOD SCALES

I drank _____ this morning.
(choose caffeinated coffee or decaffeinated coffee)

How alert do you feel?

very little ——————————————————— very much

How much of an effort is it to do anything?

very little ——————————————————— very much

How weary do you feel?

very little ——————————————————— very much

How sleepy do you feel?

very little ——————————————————— very much

Overall, how do you feel?

very bad ——————————————————— very good

Stanford Scale (SSS)

Instructions: Please choose the number of the statement which best describes how you fee right now.

1. Alert. Wide awake. Energetic.
2. Functioning at a high level, but not at peak. Able to concentrate.
3. Awake, but not fully alert.
4. A little foggy, let down.
5. Foggy. Beginning to lose interest in remaining awake. Slowed down.
6. Sleepy. Prefer to be lying down. Woozy.
7. Cannot stay awake. Sleep onset soon.

Appendix 8

The Sleep Disorders Center
The City College of New York

CAFFEINE STUDY:

Subject's name: _____
Date: _____ Day _____

The time is _____.

I ate breakfast at _____.

I ate _____for breakfast.

I drank _____.
(write caffeinated coffee or decaffeinated coffee)

Signature:_____

REFERENCES

Adams. W. J., Yeh, S. Y., Wood, L., & Mitchell, C. L. (1969). Drug-test interaction as a factor in the development of tolerance to the analgesic effect of morphine. *Journal of Pharmacology & Experimental Therapeutics*, 168, 251-257.

Axelrod, J., & Reichenthal, J. (1953). The fate of caffeine in man and a method for its estimation in biological material. *Journal of Pharmacology & Experimental Therapeutics*, 107, 519-523.

Baker, T. B., & Tiffany, S. T. (1985). Morphine tolerance as habituation. *Psychological Review*, 92 (1), 78-108.

Bennett, D., & Krank, M. D. (1985). Conditioning and amphetamine-induced enhancement of tolerance to the sedative effect of morphine. *Canadian Psychology*, 26 (2a), 28.

Bolles, R. C. (1972). Reinforcement, expectancy and learning. *Psychological Review*, 79, 394-409.

Bootzin, R. R., & Nicassio, P. M. (1978). Behavioral treatments for insomnia. In Progress in Behavior Modification. Vol 6. New York:Academic Press.

Brezinova, V. (1974). Effect of caffeine on sleep: EEG study in late middle age people. *British Journal of Clinical Pharmacology*, 1, 203-208.

Cappell, H., & LeBlanc, A. E. (1981). Tolerance and physical dependence. In Y. Israel, F. B. Glaser, H. Kalant, R. E. Popham, W. Schmidt, R. G. Smart (eds.). Research advances in alcohol and drug dependence (Vol. 6, pp. 159-196), New York: Plenum.

Carskadon, M. A., & Dement, W. C. (1975). Sleep studies on a 90-minute day. *Electroencephalography Clinical Neurophysiology*, 39, 145-55.

Carskadon, M. A., & Dement, W. C. (1977). Sleep tendency: An objective measure of sleep loss. *Sleep Research*, 6, 200.

Carskadon, M. A., & Dement, W. C. (1982). The MSLT: What does it measure? *Sleep*, 5, S67-S72.

Carskadon, M. A., Dement, W. C., Mitler, M. M., Roth, T., Westbrook, P., & Keenan, S. (1986). Guidelines for the multiple sleep latency test (MSLT): A standard measure of sleepiness. *Sleep*, 9, 519-524.

Chen, C. S. (1968). A study of the alcohol-tolerance effect and an introduction of a new behavioral technique. *Psychopharmacologia*, 12, 434-440.

Clemente, C. D., Sterman, M. B., & Wyrwicka, W. (1962). Forebrain inhibitory mechanisms: conditioning of basal forebrain induced EEG synchronization and sleep. *Experimental Neurology*, 7, 440-417.

Clodore, M., Foret, J., & Benoit, O. (1986). Diurnal variation in subjective and objective measures of sleepiness: The effects of sleep reduction and circadian type. *Chronobiology International*, 3, 255-263.

Clubley, W., Bye, C. E., Henson, T. A., Peck, A. W., & Riddington, C. J. (1979). Effects of caffeine and cyuclizine alone and in combination on human performance, subjective effects and EEG activity. *British Journal of Clinical Pharmacology*, 7, 157-163.

Colton, T., Gosselin, R. E., & Smith, R. P. (1968). The tolerance of coffee drinkers to caffeine. *Clinical Pharmacological Therapeutics*, 9, 31-39.

Corfield-Sumner, P. K., Stolerman, I. P. (1978). Behavioral tolerance. In D.E. Blackman & D.J. Sanger (eds.), Contemporary Research in behavioral pharmacology. New York: Plenum Press.

Dafters, R., & Bach, L. (1985). Absence of environment-specificity in morphine tolerance acquired in non-distinctive environments: Habituation or stimulus overshadowing? *Psychopharmacology*, 87, 101-106.

Dafters, R., & Odber, J. (1989). Effects of dose, interdose interval, and drug-signal parameters on morphine analgesic toelrance: Implications for current theories of tolerance. *Behavioral Neuroscience*, 103, 1082-1090.

Davis, M. (1970). Effects of interstimulus interval length and variability on startle-response habituation in the rat. *Journal of Comparative and Physiological Psychology*, 72, 177-192.

Demellweek, C., & Goudie, A. J. (1983). Behavioural tolerance to amphetamine and other psychostimulants: The case for considering behavioural mechanisms. *Psychopharmacology*, 80, 287-307.

Dews, P. B. (1982). Caffeine. *Annual Review Nutrition*, 2, 323-341.

Domjan, M. & Burkhard, B. (1982). The principles of learning and behavior. Monterey, Cal: Brooks/Cole.

Dyck, D. G., Greenberg, A. H., & Osachuk, T. A. G. (1986). Tolerance to drug-induced (poly I:C) Natural Killer (NK) cell activation: Congruence with a Pavlovian conditioning model. *Journal of Experimental Psychology: Animal Behavioral Processes*, 12, 25-31.

Ehrenpresis, S., Light, J., & Schonbuch, G. H. (1972). Use of the electrically-stimulated guinea-pig ileum to study potent analgesic. In J.M. Miller, & H. Lal (eds.), Drug Addiction: Experimental Pharmacology, 61, 31-38.

Eikelboom, R., & Stewart, J. (1982). Conditioning of drug-induced physiological responses. *Psychological Review*, 89, 507-528.

Fanselow, M. D. & German, C. (1982). Explicitly unpaired delivery of morphine and the test situation: Extinction and retardation of tolerance to the suppressing effects of morphine on locomotor activity. *Behavioral Neural Biology*, 35, 231-241.

Fernandes, M., Kluwe, S., & Coper, H. (1977). The development of tolerance to morphine in the rat. *Psychopharmacology*, 54, 197-201.

File, S. (1985). Tolerance to the behavioral actions of benzodiazepines. *Neuroscience Biobehavioral Review*, 9, 113-121.

Finch, G. (1938). Salivary conditioning in atropinized dogs. *American Journal of Physiology*, 124, 136-141.

Folstein, M. F., & Luria, R. (1973). Reliability, validity and clinical application of the visual analogue mood scale. *Psychological Medicine*, 3, 479-86.

Furedy, J. J. & Schiffman, K. (1973). Concurrent measurement of autonomic and cognitive processes in a test of the traditional discriminative control procedure for Pavlovian electrodermal conditioning. *Journal of Experimental Psychology*, 100, 210-217.

Furlong, F. W. (1975). Possible psychiatric signficance of excessive coffee consumption. *Journal of Canadian Psychiatric Association*, 20, 577-583.

Gilliland, K., & Andress, D. (1981). Ad lib caffeine consumption, symptoms of caffeinism and academic performance. *American Journal of Psychiatry*, 138, 512-514.

Goldstein, A., Warren, R., & Kaizer, S. (1965). Psychotropic effects of caffeine in man. I. Individual differences in sensitivity to caffeine-induced wakefulness. *Journal of Pharmacology and Experimental Therapeutics*, 150, 156-159.

Goldstein, A. R., Kaizer, S., & Whitby, O. (1969). Psychotropic effects of caffeine in man. IV. Quantitative and qualitative differences associated with habituation to coffee. *Clinical Pharmacology Therapeutics*, 10, 489-497.

Grabowski, J., & O'Brien, C. B. (1981). Conditioning factors in opiate use. In N. Mello (ed.) Advances in substance abuse, 2:69-121, Greenwich Ct:JAI Press.

Greden, J. F., Fontaine, P., Lubetsky, M., & Chamberlin, K. (1978). Anxiety and depression associated with caffeinism among psychiatric inmates. *American Journal of Psychiatry*, 13, 963-966.

Greeley, J., Le, D. A., Poulos, C. X. & Cappell, H. (1984). Alcohol is an effective cue in the conditional control of tolerance to alcohol. *Psychopharmacology*, 83, 159-162.

Griffiths, R. R., Bigelow, G. E. & Liebson, I. A. (1986). Human coffee drinking: Reinforcing and physical dependence producing effects of caffeine. *Journal of Pharmacology and Experimental Therapeutics*, 239 (2), 416-425.

Griffiths, J. W., & Goudie, A. J. (1986). Analysis of the role of drug-predictive environmental stimuli in tolerance to the hypothermic effects of the benzodiazepine. *Psychopharmacology*, 90, 513-21.

Griffiths, J. W., & Goudie, A. J. (1987). Associative cues in the development of tolerance to the benzodiazepine midazolam. *Neuropharmacology*, 26, 201-9.

Griffiths, R. R., & Woodson, P. P. (1988a). Reinforcing properties of caffeine: Studies in humans and laboratory animals. *Pharmacology, Biochemistry, & Behavior*, 29, 419-27.

Griffiths, R. R., & Woodson, P. P. (1988b). Reinforcing effects of caffeine in humans. *Journal of Pharmacology & Experimental Therapeutics*, 246 (1), 21-9.

Hartmann, E. (1968). On the pharmacology of dreaming sleep. *Journal of Nervous Mental Disorder*, 146, 165-173.

Hinson, R. E., & Rhijnsburger, M. (1984). Learning and cross drug effects: Thermic effects of pentobarbital and amphetamine. *Life Sciences*, 34, 2633-2640.

Hinson, R. E., & Siegel, S. (1982). Nonpharmacological bases of drug tolearnce and dependence. *Journal of Psychosomatic Research*, 26, 495-503.

Hoddes, E., Dement, W. C., & Zarcone, V. (1972). The development and use of the Stanford sleepiness scale (SSS). *Psychophysiology*, 9, 150.

Huyn-Feldt, J. (1982). *Journal of Educational Statistics*, 69, 82.

Kalant, H. (1973). Biological models of alcohol tolerance and physical dependence. In S.S. Gross (ed.), Alcohol intoxication and withdrawal (pp. 3-13). New York: Plenum.

Kalant, H., LeBlanc., A. E., & Gibbins, R. (1971). Tolerance to and dependence on some nonopiate psychotropic drugs. *Pharmacological Review*, 23, 135-191.

Karacan, I., Thornby, J. I., Anch, M., Booth, G. H., Williams, R. L., &

Salis, P. J. (1977). Dose-related sleep disturbances induced by coffee and caffeine. *Clinical Pharmacological Therapeutics*, 20, 682-689.

King, D. A., Bouton, M. E., & Musty, R. E. (1987). Associative control of tolerance to the sedative effects of a short-acting benzodiazepine. *Behavioral Neuroscience*, 101 (1), 104-14.

Krank, M. D. (1987). Conditioned hyperalgesia depends on the pain sensitivity measure. *Behavioral Neuroscience*, 101 (6), 854-857.

Krank, M. D., Hinson, R. E., & Siegel, S. (1981). Conditional hyperalgesia is elicited by environmental signals of morphine. *Behavior & Neural Biology*, 32, 148-151.

Krank, M. D., Hinson, R. E., & Siegel, S. (1984). The effect of partial reinforcement on tolerance to morphine-induced analgesia and weight loss in the rat. *Behavioral Neuroscience*, 98, 79-85.

Kremer, E. F. (1971). Truly random and traditional control procedures in CER conditioning in the rat. *Journal of Comparative and Physiological Psychology*, 76, 441-448.

Kremer, E. F., & Kamin, L. J. (1971). The truly random procedure: Associative or nonassociative effects in rats. *Journal of Comparative and Physiological Psychology*, 74, 203-210.

Kuznicki, J. T., & Turner, L. S. (1986). The effects of caffeine on caffeine users and non-users. *Physiology & Behavior*, 37, 397-408.

Levitt, R. A. (1964). Sleep as a conditioned response. *Psychonomics Science*, 1, 273-274.

Levitt, R. A., & Webb, W. B. (1964). The effect of pentobarbital sodium on sleep latency and length. *Nature*, 20, 135-137.

Lipschutz, L., Roehrs, T., Spielman, A., Zwyghuizen, H., Lamphere, J., & Roth, T. (1988). Caffeine's alerting effects in sleepy normal. *Sleep Research*, 17, 49.

Mackintosh, N. J. (1987). Neurobiology, psychology and habituation. *Behavioral Research & Therapy*, 25, 81-97.

Mazur, J. E. (1986). Learning and Behavior. Englewood Cliffs, N.J.:Prentice Halls, Inc.

Monk, T. H. (1987). A visual analogue scale technique to measure global vigor and affect. *Psychiatry Research*, 27, 89-99.

Monk, T. H., Fookson, J. E., Moline, M. L., & Pollak, C. P. (1985). Diurnal variation in mood and performance in a time-isolated

environment. *Chronobiology International*, 2, 1-34.

Mucha, R. F., Kalant, H., & Linesman, M. A. (1978). Quantitative relationships among measures of morphine tolerance and physical dependence in the rat. *Pharmacology, Biochemistry & Behavior*, 10, 397-405.

Nicholson, A. N., & Stone, B.M. (1980). Heterocyclic amphetamine deratives and caffeine on sleep in man. *British Journal of Clinical Pharmacology*, 9, 195-203.

Okuma, T., Matsuoka, H., Matsue, Y., & Toyomura, K. (1982). Model insomnia by methylphenidata and caffeine and use in the evaluation of Temazepam. *Psychopharmacology*, 76, 201-208.

Papini, M. R., & Bitterman, M. E. (1990). The role of contingency in classical conditioning. *Psychological Review*, 97 (3), 396-403.

Pavlov, I. P. (1927). Conditioned reflexes. London: Oxford University Press.

Post, R. M., Contel, N. R., & Gold, P. W. (1980). Impaired behavioral sensitization to cocaine in vasopressin deficient rats. *Society Neuroscience Abstracts*, 6, 111.

Rescorla, R. A. (1967). Pavlovian conditioning and its proper control procedures. *Psychological Review*, 74, 71-80.

Rescorla, R. A. (1988). Pavlovian conditioning: It's not what you think it is. *American Psychologist*, 43 (3), 151-160.

Rechtshaffen, A., & Kales, A. (1968). A manual of standardized terminology techniques and scoring system for sleep stages of human subjects. National Institutes of Health Publications 204, Government Printing Office, Washington DC.

Ritchie, J. M. (1975). Central nervous system stimulants (continued), the xanthines. In L. S. Goodman and A. Gilman (eds.), The Pharmacological Basis of Therapeutics, New York: Macmillan.

Roth, T., Hartse, K. M., Zorick, F., & Conway, W. (1980). Multiple, naps and the evaluation of daytime sleepiness in patients with upper airway sleep apnea. *Sleep*, 3, 425-439.

Sawyer, D. A., Julia, H. L., & Turin, A. C. (1982). Caffeine and human behavior: Arousal, anxiety, and performance effects. *Journal of Behavioral Medicine*, 5 (4), 415-439.

Schull, J. (1979). A conditioned opponent theory of pavlovian conditioning and habituation. In G. H. Bower (ed.), The psychology of learning and

motivation: Advances in research and theory, Vol 13. New York: Academic Press.

Schulz, R., Seidl, E., Wuster, M., & Herz, A. (1982). Opioid dependence and cross-dependence in the isolated guinea-pig ileum. *European Journal of Pharmacology*, 84, 33-40.

Schuster, C. R., Dockens, W. S., & Woods, J. H. (1966). Behavioral variables affecting the development of amphetamine tolerance. *Psychopharmacologia*, 9, 170-182.

Seidel, W. F., Ball, S., Cohen, S., Patterson, N., Yost, D., & Dement, W. C. (1984). Daytime alertness in relation to mood, performance, and nocturnal sleep in chronic insomniacs and noncomplaining sleepers. *Sleep*, 7, 23-238.

Siegel, S. (1975). Evidence from rats that morphine tolerance is a learned response. *Journal of Comparative & Physiological Psychology*, 89 (5), 498-506.

Siegel, S. (1976). Morphine analgesic tolerance: Its situation specificity supports a pavlovian conditioning model. *Science*, 193, 323-325.

Siegel, S. (1977). Morphine tolerance acquisition as an associative process. *Journal of Experimental Psychology: Animal Behavioral Processes*, 3 (1), 1-13.

Siegel, S. (1978b). Tolerance to the hyperthermic effect of morphine in the rat is a learned response. *Journal of Comparative and Physiological Psychology*, 92, 1137-1149.

Siegel, S. (1988). Pharmacological conditioning and drug effects. In M.W. Emmett-Oglesby & A.J. Goudie (eds.), Tolerance and sensitization to psychoactive drugs. New Jersey: Humana Press.

Siegel, S., Hinson, R. E., & Krank, M. D. (1978a). The role of predrug signals in morphine analgesic tolerance: Support for a pavlovian conditioning model of tolerance. *Journal of Experimental Psychology: Animal Behavioral Processes*, 4 (2), 188-196.

Siegel, S., & Sdao-Jarvie, K. (1986). Reversal of ethanol tolerance by a novel stimulus. *Psychopharmacology*, 88, 258-261.

Siegel, S., Sherman, J. E., & Mitchell, D. (1980). Extinction of morphine analgesic tolerance. *Learning and Motivation*, 11, 289-301.

Solomon, R. L., & Corbitt, J. D. (1974). An opponent-process theory of motivation: I. Temporal dynamics of affect. *Psychological Review*, 81, 119-45.

Spielman, A. J. (1986). Assessment of insomnia. Clinical *Psychological Review*, 6, 11-25.

Spielman, A. J., Caruso, L., & Glovinsky, P. (1987a). A behavioral perspective on insomnia treatment. *Psychiatric Clinics of North America*, 10 (4), 541-553.

Spielman, A. J., Saskin, P., & Thorpy, M. J. (1987b). Treatment of chronic insomnia by restriction of time spent in bed. *Sleep*, 10, 45-56.

Stephenson, P. E. (1977). Caffeine. *Journal of the American Dietetic Association*, 71, 240-247.

Stern, K. N., Chait, L. D., & Johanson, C. E. (1989). Reinforcing and subjective effects of caffeine in normal human volunteers. *Psychopharmacology*, 98, 81-88.

Subkov, A. A., & Zilov, G. N. (1937). The role of conditioned reflex adaptation in the origin of hyperergic reactions. *Bulletin de Biologie et de Medecine Experimentale*, 4 294-296.

Taukulis, H. K. (1982). Attenuation of pentobarbital-elicited hypothermia in rats with a history of pentobarbital-LiCl pairings. *Pharmacology, Biochemistry & Behavior*, 17, 695-697.

Tiffany, S. T., & Baker, T. B. (1981). Morphine tolernce in rats: Congruence with a Pavlovian paradigm. *Journal of Comparative & Physiological Psychology*, 95 (5), 747-762.

Tiffany, S. T., & Maude-Griffin, P. M. (1988). Tolerance to morphine in the rat: Associative and nonassociative effects. *Behavioral Neuroscience*, 102, 534-543.

Tiffany, S. T., Maude-Griffin, P. M., & Drobes, D. J. (1991). *Behavioral Neuroscience*, 105 (1), 49-61.

Tiffany, S. T., Petrie, E. C., Baker, T. B., & Dahl, J. (1983). Conditioned morphine tolerance in the rat: Absence of a compensatory response and cross-tolerance with stress. *Behavioral Neuroscience*, 97, 335-353.

Valley, V., & Broughton, R. (1981). Daytime performance deficits and physiological vigilance in untreated patients with narcolepsy-cataplexy compared to controls. *Review EEG Neurophysiology* (Paris), 11, 133-9.

Vitiello, M. V., & Woods, S. C. (1977). Evidence for withdrawal from caffeine by rats. *Pharmacology, Biochemistry & Behavior*, 6, 553-555.

Vogel-Sprott, M., & Sdao-Jarvie, K. (1989). Learning alcohol tolerance: the contribution of response expectancies. *Psychopharmacology*, 98, 289-296.

Wagner, A. R. (1979) Habituation and Memory. In A. Dickinson & R.A. Boakes (eds.), Mechanisms of learning and motivation (pp. 53-82). Hillsdale, NJ: Erlbaum.

Walter, T. A., & Riccio, D. C. (1983). Overshadowing effects in the stimulus control of morphine analgesic tolerance. *Behavioral Neuroscience*, 97, 658-662.

Wilkinson, L. (1990). Systat: The system for statistics. Evanston, IL:Systat, Inc.

Zwyghuizen-Doorenbos, A., Roehrs, T., Schaefer, M., & Roth, T. (1988). Test-retest reliability of the MSLT. *Sleep*, 11, 562-565.

Zwyghuizen-Doorenbos, A., Roehrs, T. A., Lipschutz, L., Timms, V., & Roth, T. (1990). Effects of caffeine on alertness. *Psychopharmacology*, 100, 36-39.