STATE-DEPENDENT LEARNING IN SMOKERS:

SEPARATION OF DRUG WITHDRAWAL

FROM CONDITIONING

By

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Abstract

There is considerable debate over the effect of nicotine on human emotion and performance. Some studies suggest that nicotine facilitates performance while elevating overall mood, while others suggest just the opposite. Recent data indicate that learning history plays a significant role in nicotine's effects on performance and emotion. However, previous investigations have not examined the influence of drug withdrawal or subject's drug state during training trials prior to experimental manipulation. Thirty smokers were randomly assigned to one of three groups: 1) No-smoking/Deprived, 2) Smoking/ Nondeprived, and 3) No-smoking/Nondeprived. Subjects underwent 13 nicotine-free training trials on the computerized Walter Reed Performance Assessment Battery (PAB). Subjects completed the Profile of Mood States (POMS), Emotion Assessment Scale (EAS) and a tobacco withdrawal rating scale as indication of moodstate. The No-smoking/Deprived group did not smoke, thus remained drug-deprived. The Smoking/Nondeprived group smoked ad libitum during the final test PAB in order to "cross" their drug state from the training trials. The No-smoking/ Nondeprived group smoked four puffs before the test PAB in order to partially alleviate their state of drug withdrawal, but did not smoke during the test PAB to maintain drug state consistency between training and test trials.

While improvements were noted on subjective mood ratings and withdrawal symptoms following smoking, there was little evidence that overall performance was effected. Overall, the results of the present study suggest that the pharmacological aspects of nicotine may outweigh the role of learning and conditioning in human performance and emotion. State Dependent Learning in Smokers: Separation of

Drug Withdrawal Effects from Conditioning

The negative health consequences of smoking cigarettes are well documented. The three leading causes of death in the United States are heart disease, cancer, and stroke; smoking plays an essential role in all three. However, despite widespread efforts to quit, a large percentage (26%) of our population continues to smoke (USPHS, 1988). Unfortunately, the recent proliferation of smoking cessation programs has met with less than impressive results. As many as eighty percent of smokers who initially stop smoking will relapse within six months to a year (Schwartz, 1987).

Recent studies suggest that cessation relapse is highly correlated with negative mood states such as anxiety, frustration and stress (Shiffman, 1986). Habitual smokers who quit smoking regularly report increased irritability, anxiety, restlessness, difficulty concentrating, and drowsiness (Shiffman, 1979).

The principal psychoactive ingredient in cigarettes is nicotine, and nicotine addiction is the principal factor responsible for continued smoking. The effect of nicotine on human behavior, emotion, and performance is not yet fully understood. There is a great need for basic research on both pharmacological and behavioral consequences of cigarette smoking. Although the present study does not have direct implications for relapse prevention, it could provide fundamental principles of nicotine actions which may lead to eventual treatment considerations.

An important issue is the effect that nicotine has on attention, memory, performance, and emotion. Impairment in functioning has been noted in smokers who are deprived of nicotine (cf. West, 1984, for a review). For example, nicotine deprivation impeded performance in such areas as psychomotor functioning (Heimstra, Bancroft, & DeKock, 1967; Heimstra, Fallesen, Kinsley, & Warner, 1980), simple vigilance tasks (Elgerot, 1976), and complex computerized tests (Snyder, Davis, & Henningfield, 1989; Snyder & Henningfield, 1989).

In other studies, nicotine facilitated performance on various measures. Reaction time (Frankenhauser, Myrsten, Post, & Johansson, 1971), memory (Mangan & Golding, 1978; Peeke & Peeke 1984; Williams, 1980), rapid information processing (Wesnes & Warburton, 1983a), and complex visualmotor performance in a simulated driving task (Heimstra et al., 1967) improved after smoking cigarettes.

Most studies which concluded that nicotine facilitates performance have done so based on data obtained exclusively on habitual smokers. Results of such studies may not actually be produced by the facilitory properties of nicotine, but by the impairment of performance by smokers experiencing acute drug withdrawal effects when placed in "no-smoke" conditions. When nicotine is restricted from habitual smokers, drug withdrawal is likely to occur. This physiological condition has been termed the "tobacco withdrawal syndrome" (Shiffman, 1979) under which performance on most tasks will be impaired.

In addition to the possible confound of nicotine withdrawal, recent evidence suggests that the relationship between smoking, stress, and performance may have both pharmacological and behavioral components. Specifically, if smokers are tested in a situation where smoking always occurs, smoking seems to reduce stress and enhance performance. However, if smokers are tested in a situation where smoking does not normally occur, then smoking appears to increase anxiety and performance decreases (Perkins, Epstein, & Jennings, 1988; Warburton, Wesnes, Shergold, & James, 1986). These results have been interpreted as a state-dependent drug effect on mood and performance. This model indicates that when a task is repeatedly performed under nonsmoking conditions, anxiety will eventually habituate and performance will return to normal levels. However, if the subject is then allowed to smoke, anxiety will increase and performance will be impaired.

Studies using a state dependent learning paradigm can overcome the confound of drug state differences associated with incongruous training and testing situations. However, these studies have not yet addressed the issue of withdrawal within a state dependent learning design. For example, Perkins et al. (1988) supplied their subjects with a constant supply of nicotine throughout training and testing. In order to show that these findings generalize to natural settings (e.g. the workplace) one would have to show that stress/anxiety habituates during states of <u>drug deprivation</u>.

The present study is designed to test the reported state-dependent effects of smoking on mood and performance, and to assess whether or not nicotine deprivation overrides the habituation of anxiety and performance one would expect to see after repeated exposure in "no smoking" conditions. The following review will summarize those studies which have demonstrated nicotine administration to either facilitate or impair various measure of performance. The next section will summarize those studies which have examined the effect of nicotine administration and deprivation on subsequent mood and emotion. Finally, the specific effects of nicotine administration or withdrawal on state dependent learning will be discussed, with a review of the relevant literature.

Smoking and Human Performance

The relationship between cigarette smoking and human performance has been a popular research topic of late. However, it has been difficult to draw firm conclusions from the studies which have been conducted, partly due to the wide variety of measures which have been adopted to assess the diverse areas of functioning. The following sections will discuss the effects of smoking on performance in tests of vigilance/reaction time, simple mental efficiency, and rapid information processing.

Smoking and Vigilance/Reaction Time

In a typical vigilance task, subjects are asked to detect a "target" signal, and react by pressing a switch. These targets are usually presented at infrequent and unpredictable intervals. Performance on vigilance tasks is expected to steadily decrease as the task proceeds, due to difficulty in maintaining concentration over a prolonged period of time. However, this expected decrement may be offset by factors such as learning, rest, or drugs (Mackworth, 1964).

Tarriere and Hartemann (1964) assessed smokers using a visual vigilance task after smoking normally, and again after a twenty-hour period of abstinence. Results revealed that smokers who smoked showed no decrement over the twohour task, while those who were smoking-deprived performed much more poorly. The performance of nonsmokers was intermediate between the two smoking conditions. Likewise, Frankenhauser et al. (1971) found that the reaction times of smokers allowed to smoke were lower than deprived smokers in a visual vigilance task. In a more recent study from the same laboratory, Myrsten, Andersson, Frankenhauser and Elgerot (1975) recruited subjects who preferred to smoke in only high arousing situations, or only in low arousing situations. They found that "low arousal" smokers performed best in a low arousing vigilance task, while the converse was true for smokers who preferred to smoke in highly arousing situations.

A classic study in the area of smoking and vigilance performance was conducted by Heimstra et al. (1967). These investigators assessed the effects of cigarette smoking on sustained performance in a simulated driving task. Nonsmokers, smokers allowed to smoke, and deprived smokers were observed while operating a driving device over a six hour period. Measures of tracking, reaction time, and visual vigilance indicated that the performance of deprived smokers was significantly worse than the other two groups. In addition, Heimstra and his colleagues reported that the decrement in performance which normally occurs over time was more pronounced (though not significant) in the nonsmoking group than in the group of smokers who were allowed to smoke. The authors concluded that this difference was due to the stimulating effects of nicotine. In a follow-up on these results, Heimstra et al. (1980) reported that smokers who were not allowed to smoke performed less well than smokers allowed to smoke on a pursuit tracking task. However, no differences were found in reaction time or visual vigilance on a complex psychomotor device.

Wesnes and Warburton (1978) incorporated signal detection theory into the analysis of vigilance performance. The results were no different, however, as they also found that cigarette smoking improved the performance of smokers on both auditory and visual vigilance tasks. This performance improvement was found to be independent of response bias. Other studies with similar designs have reported comparable results (Mangan, 1982; Mangan & Golding, 1978). Wesnes and Warburton also found that administration of nicotine tablets improved the performance of both smokers and nonsmokers (Wesnes & Warburton, 1983a), suggesting that nicotine is the primary agent contributing to the increased performance found in vigilance type tasks. A note of caution should be taken, however, as studies of pure nicotine administration do not necessarily generalize to cigarette smoking, as other factors (e.g., behavioral) are involved in the act of smoking.

Smoking and Simple Mental Efficiency

Fay (1936) assessed the effect of smoking on both simple and choice reaction times. Nonsmokers were not affected, but habitual smokers who smoked a cigarette experienced decreased reaction times when they had to make a choice between different colored lights. However, on the simple reaction time

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test, smokers showed no improvement after smoking a cigarette, while nonsmokers were adversely affected by smoking before this task. These findings suggest that cigarette smoking by habitual smokers facilitates reaction time only when a mental processing component (e.g. making a choice) is a part of the task. Thus, according to Fay's data, the locus of smokers' elevated performance is cognitive improvement, rather than a quicker motor response.

There is evidence that smoking facilitates mental efficiency in habitual smokers (Friedman, 1972). Smokers allowed to smoke were found to be faster at performing mental arithmetic (mentally adding or subtracting pairs of numbers), than smokers not allowed to smoke, although their accuracy declined. Subsequent studies which have employed this measure of mental efficiency have failed to show differences between smokers smoking and deprived smokers; however, these studies did not assess speed as they evaluated only the accuracy of subject's answers (Elgerot, 1976; Heimstra et al., 1980; Myrsten, Elgerot, & Edgren, 1977).

Further evidence that cigarette smoking facilitates the speed of mental performance was found by Williams (1980), using a letter-cancellation task. Smokers visually scanned more letters after smoking a regular cigarette than after smoking a sham cigarette. Response accuracy was not evaluated. 9

Myrsten et al. (1977) evaluated the effects of smoking abstinence on several measures of cognitive performance. In comparing abstaining smokers to smokers allowed to smoke normally, abstainers were found to perform better on a correction test similar to the letter cancellation task mentioned previously. Abstainers performed somewhat (but not significantly) worse on a modified version of the Stroop test.

Elgerot (1976) compared habitual smokers after five day periods of smoking normally and complete abstinence. These investigators used several measures of cognitive performance which were classified as "simple" or "complex" tests of mental efficiency. Contrary to a majority of the recent data, Elgerot found that smokers actually performed better on the complex measures (e.g., Raven's progressive matrices) when they were abstaining than when they were smoking. No differences were found on the simple mental tasks. These results have been interpreted in terms of differing optimum arousal levels for complex, as opposed to simple cognitive demands.

Rapid Information Processing

Wesnes and Warburton have devised a rapid information processing (RIP) task in which digits are visually presented at the rate of 100 per minute. Subjects are asked to detect three consecutive odd or even digits and press a button as quickly as possible. The task is computerized so that reaction time, correct detections, and false positives are recorded. The authors attest that this task is more sensitive to smoking-induced changes in performance than traditional vigilance tasks. Outcomes of the research using this RIP task have been quite consistent. When smokers smoke cigarettes of higher nicotine content, they perform better in terms of correct detections and response speed than when they smoke a lower nicotine cigarette, non-nicotine cigarette, or no cigarette at all (Wesnes & Warburton, 1983b, 1984a). The only discrepancy to this phenomenon is the cigarettes of very high nicotine content (e.g., >1.7mg) appear to disrupt performance somewhat, yielding an inverse U-shaped relationship between nicotine content and facilitation of performance (Houston, Schneider, & Jarvik, 1980; Wesnes & Warburton, 1983b, 1984a). However, the main finding seems to be relatively consistent within the Wesnes and Warburton laboratory; cigarette smoking appears to offset the decline in efficiency over time by increasing stimulus sensitivity without affecting response bias (Wesnes & Warburton, 1983c). This effect appears to be robust for a single cigarette (Edwards, Wesnes, Warburton, & Gale, 1985), even when subjected to a puffby-puff analysis (Revell, 1988).

The question from these results is precisely how cigarette smoking and nicotine induce these performance enhancements. Wesnes and Warburton (1984b) propose that nicotine has an agonistic effect on the cholinergic system

of the ascending reticular pathway of the cortex, which in turn results in increased arousal, attention, and stimulus selection. Scopolamine, which is an anti-motion sickness drug, is believed to be a cholinergic antagonist and has been shown to disrupt stimulus detection in rats (Brown & Warburton, 1971). Empirical support for the opposing effects of nicotine and scopolamine is mounting, as they appear to have diametric effects on human performance (Wesnes & Warburton, 1984b).

An interesting issue emerged in an attempt to replicate the findings on nicotine and scopolamine. Wesnes and Revell (1984) failed to find a main effect of nicotine on performance in their RIP task. Slight design changes appeared to account for the discrepancy between this study and previous work from this laboratory. The delay between baseline testing and post-drug testing was increased from 10 minutes to 60 minutes because of the slower time course of scopolamine. The authors also observed in a previous study that nicotine only resulted in improved performance on a Stroop task after a second trial was conducted. The authors concluded that nicotine in the doses tested only facilitates performance when it is already depressed by other factors such as fatigue. Therefore, it appears that task-specific fatigue is a necessary condition in order to achieve the observed nicotine-induced facilitation in performance. In summary, despite limited evidence to the contrary (e.g., Elgerot, 1976), it appears that smoking facilitates the performance of smokers in areas such as reaction time, vigilance, simple mental efficiency, and rapid information processing. Nicotine appears to be the primary agent involved in this phenomenon, possibly through its effect on neural pathways which mediate arousal and stimulus selection. Finally, there is little direct evidence that nicotine produces absolute improvements in performance in short-term analysis. Continuous performance and task-specific fatigue appear to be necessary precursors to the facilitory properties of nicotine and cigarette smoking.

Smoking and Learning, Memory, and Attention

In the first major study to assess the effects of smoking on memory, learning, and attention, Hull (1924) found that subjects who sham smoked performed better than subjects who smoked nicotine cigarettes on immediate memory for digits, paired associate learning, and memory for nonsense syllables. However, the conclusions of more recent work have been much more obscure. For example, smokers exhibited a drop in speed and correct answers in verbal rote learning after smoking a single cigarette as opposed to not smoking. However, this picture is reversed after the second cigarette, as the initial impairment diminished with continued smoking. Increased arousal from

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smoking may lead to facilitation of delayed memory, but impaired immediate memory (Andersson, 1975; Andersson & Post, 1974).

Similar results were found in comparing smokers on verbal memory and attention after smoking different doses of nicotine cigarettes (Peeke & Peeke, 1984). Although Andersson's findings were confirmed in that pretrial smoking facilitated delayed memory, a separate experiment by the same authors found that smoking a high nicotine cigarette also enhanced immediate recall. This later finding is contrary to Andersson's results for short-term memory. Houston et al. (1978) corroborated Andersson's finding that smoking impaired short term memory; however, subjects smoking nicotine cigarettes also exhibited deleterious effects on delayed recall. These data contradict Andersson's conclusions for long-term memory. Subsequent studies have replicated Houston et al.'s results for impairment of short-term and long-term memory in both pretrial (Gonzales & Harris, 1980), and post-trial smoking (Mangan, 1983).

Peeke and Peeke (1984) offered an explanation that might account for some of the conflicting results. They suggest that nicotine may exert a nonspecific effect on attention and focusing processes, rather than a direct influence on memory itself. Support for this hypothesis was provided by Andersson and Hockey (1977) who utilized an incidental recall task to assess the role of differential attention to relevant and irrelevant material. The memory task for relevant words revealed no differences between smoking and nonsmoking conditions. However, when tested for incidental and irrelevant material (the position of the words on the screen), the nonsmoking group was far superior to the smoking group. This finding suggests that smoking leads to a more narrow and selective process of attending to one's environment.

Further evidence that smoking increases selective attention was found in assessing the performance of smokers and nonsmokers under conditions of noise-induced interference. Nonsmokers appear to be more adversely affected by interference than smokers on memory and rapid information processing tasks (Hasenfratz, Michel, Nil, & Battig, 1989; Mangan, 1983). Friedman, Hovarth, and Meares (1974) suggested that smoking increases the efficiency of a neuropsychological "stimulus barrier," which screens sensory input. They supported this theory with EEG evidence that revealed increased habituation to stimuli after cigarette smoking.

In summary, studies assessing the role of nicotine on memory, learning, and attention have found mixed, and sometimes conflicting results. It does appear that nicotine may have differential effects on short-term and long-term memory, as measured by immediate and delayed recall. Finally, there is evidence that nicotine may exert its influence on memory and learning through

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facilitation of selective attention, allowing smokers to filter out irrelevant stimuli from the environment.

Smoking, Stress, and Emotion

The paradoxical effects of nicotine on emotion are well documented (cf. Gilbert, 1979, for a review). Nicotine appears to increase autonomic and CNS activity, resulting in general physiological arousal, yet smokers report that nicotine decreases emotionality, providing a state of relaxation. In fact, many smokers report that the affect-reducing property of nicotine is an important motive for smoking (Tomkins, 1966). Although a few studies have failed to find a relationship between smoking and affective states (e.g., Agué, 1973; Cutler & Barrios, 1988; Nowlis, 1965), most have confirmed nicotine's ability to modulate emotion.

Cigarette smoking decreases experimentally induced pain when a subject's arm is placed in ice water (Pomerleau, Turk, & Fertig, 1984), or when stress is produced in the form of mild electric shock (Nesbit, 1973). In addition, smokers also report reductions in subjective anxiety after smoking nicotine cigarettes as opposed to sham smoking (Pomerleau & Pomerleau, 1987). Similar results have been found for nicotine's ability to reduce specific emotions such as aggression (Schecter & Rand, 1974; Cherek, 1981). Inversely, cigarette smoking appears to increase significantly in response to different stressors such as public speaking (Dobbs, Strickler, & Maxwell, 1981; Rose, Ananda, & Jarvik, 1983), shock (Schacter et al., 1977), aversive white noise (Golding & Mangan, 1982), and competitive mental arithmetic (Pomerleau & Pomerleau, 1987).

Westman, Eden, and Shirom, (1985) examined the correlation between specific job stressors and cigarette smoking. They found that hours of work, work addiction, and lack of support, among other variables, were significantly related to smoking intensity. Finally, negative mood states and life stress have been significantly linked to continued smoking and recidivism from smoking cessation programs (Gunn, 1983; Shiffman, 1982). More specifically, workrelated stressors such as conflict, responsibility, and harsh working conditions have been negatively associated with cessation attempts (Westman et al., 1985).

In summary, the literature suggests that nicotine, and thus cigarette smoking, exerts a paradoxical effect on human arousal and emotional response. While psychophysiological measures show that nicotine increases arousal, subjective reports from smokers suggest that smoking makes them feel calmer and more relaxed. In addition, smoking and stress appear to be tightly interrelated. Smoking appears to decrease subjective stress while increased stress leads to increased smoking.

A majority of the literature implicates the psychoactive properties of nicotine as producing relaxation and calmness. However, an alternative explanation has been provided for nicotine's paradoxical effect on physiology and emotionality. Silverstein (1982) suggested that cigarette smoking is not relaxing. Instead, not smoking leads to nicotine withdrawal, which is very upsetting for the habitual smoker. For example, Nesbit's (1973) results revealed that smokers smoking were calmer than nonsmokers, who in turn were calmer than deprived smokers. Silverstein replicated these findings, and conceptualized the results in terms of habitual smokers misinterpreting their withdrawal symptoms as anxiety. When smokers replenish their nicotine supply, the end of withdrawal symptoms is then perceived as relaxing. Evidence suggests that stress reduces the pH of urine, leading to increased renal excretion which then increases the smoker's need for nicotine. When nicotine depletion is prevented in smokers, stress does not appear to lead to increased smoking (Schacter, Silverstein, & Perlick, 1977).

A critical evaluation of the effects of smoking on human performance and emotion reveals very similar influences. Smoking has consistently been shown to improve performance in smokers on vigilance, reaction time, memory, and attentional tasks. Smoking also has a considerable effect in calming, relaxing, and reducing perceived stress in smokers. However, this similar pattern of

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results in the areas of performance and stress also share a similar methodological confound. Nearly all of the studies to date have based their conclusions after comparing smokers allowed to smoke to control groups consisting of smokers in a full or partial state of nicotine withdrawal.

The Tobacco Withdrawal Syndrome

Many physical and emotional symptoms occur upon cessation of smoking, including irritability, depression, hunger, difficulty concentrating, dizziness, and craving. Together, these symptoms have been termed the tobacco withdrawal syndrome (Shiffman, 1979). This syndrome can be reliably produced upon smoking cessation (Hughes, Hatsukami, Pickens, & Svikis, 1984), and can be alleviated by nicotine replacement chewing gum (Hughes et al., 1984; West, 1984).

The social and emotional consequences of nicotine withdrawal appear to be of great significance. Irritation, disturbances in social relations and activities, and lack of social support are frequently reported by smokers attempting to abstain (Elgerot, 1978). However, the emotional repercussions of withdrawal are only part of a larger picture. Snyder and Henningfield (1989; Snyder, Davis, & Henningfield, 1989) have implemented a multi-task computerized assessment battery to evaluate the effects of nicotine withdrawal on cognitive abilities involving memory, concentration and attention. When habitual smokers abstain from smoking for 24 hours, significant increases in reaction time have been observed on all five independent measures of the cognitive performance battery. In addition, data on subject's accuracy exhibits a trend towards committing more errors after cigarette abstinence. The authors also note that performance decrements peak at 24 to 48 hours of abstinence, then begin to return to baseline levels. However, some performance measures remained significantly depressed for a full 10 days after cigarette abstinence. All performance decrements eventually return to baseline levels when smoking is resumed. In contrast to these results, Kleinman, Vaughn and Christ (1973) found that tobacco deprivation leads to improved learning on an easy list of nonsense syllables, but impairs performance on a more difficult list.

It is often difficult to differentiate between studies assessing the effects of nicotine <u>administration</u>, and those which are assessing nicotine <u>withdrawal</u>. Nearly all of the studies cited thus far have employed habitual smokers as subjects in their analysis of smoking/nicotine effects. Because of the ethical difficulty of administering nicotine to nonsmokers, there are little data on how nicotine influences the performance, learning, and mood of people who do not have previous experience with the drug.

In addition, many studies have used partial or full cigarette abstinence of up to 24 hours before implementing their experimental conditions. Many studies have failed to recognize the confound of using habitual smokers under withdrawal conditions, and have inaccurately credited effects of nicotine administration when the results would be more appropriately interpreted from a nicotine withdrawal stance. For example, the Heimstra et al., (1967) study is often cited as supporting cigarette smoking as increasing performance in a simulated driving task. These results, however, can be viewed from a deprivation perspective, as smokers in the nonsmoking condition were without cigarettes for six hours. Heimstra et al.,'s conclusions were that "no significant differences were found between the smoker and nonsmoker groups on any of the performance tasks." However, significant decrements were found for the deprived smoker group. Other similar examples of studies often cited as "nicotine administration" studies include: Tarrier and Hartemann (1964), all habitual smokers, 20 hour abstinence; Frankenhauser et al. (1971) and Wesnes and Warburton (1983b), all habitual smokers, 12 hour abstinence. An additional confound in several investigations has been the use of "training" trials in an attempt to reduce variance due to practice effects on the task measured (e.g. Wesnes & Warburton, 1984a). These investigations rarely detail these practice trials, so it is assumed that they take place in a smoker's "normal" drug state, which is under the influence of nicotine. Prior experience with a task while under a drug state can pose difficulties because, as the following section will

document, previous history or experience with a task can have a significant effect on future performance with that same task.

In summary, habitual smokers undergoing nicotine withdrawal experience severe symptoms affecting areas of mood, concentration, and performance. Since a majority of the studies to date have employed smokers in withdrawal state as subjects, it is difficult to tease out the actual beneficial effects of nicotine from the detrimental effects of drug withdrawal.

One way to assess the complex interaction between pure drug effects and experience or conditioning is through the use of behavioral pharmacology. This emerging field of study represents a unique integration of psychology and pharmacology. Because the organism and its environment are inseparable, it is inevitable that environmental factors will play a significant role in how a drug manifests itself behaviorally. In fact, failure of experimental designs to control for environmental influences has long been cited as a major weaknesses of drugbehavior research (Thompson & Schuster, 1968). It is possible, that through the use of behavioral pharmacological analysis, one could sort out the differential effects of nicotine and conditioning.

State-Dependent Learning and Nicotine

In addition to the withdrawal confound, many studies on nicotine and human performance have not considered the issue of drug-dependent learning. Considerable evidence suggests that memory is better when material is learned and recalled in the same mental state. In this case, mental state could refer to any internal condition in the organism such as mood or a drug-induced state. For example, if retrieval of information takes place in a different drug-state than was present during acquisition, then performance will be impaired. This phenomenon has been referred to as state-dependent learning (SDL).

SDL effects have been shown to be produced by mood incongruence (Teasdale & Russell, 1983), as well as by a variety of drugs including alcohol (Goodwin, Powell, Bremer, Hoine, & Sterne, 1969), marijuana (Darly, Tinklenberg, Roth, & Atkinson, 1974), barbiturate and amphetamine (Bustamente, Jordon, Vila, Gonzalez, & Insua, 1970), methylphenidate (Swanson & Kinsbourne, 1976), and anxiolytics (Jensen, Hutchings, & Poulsen, 1989). The first indication that smoking may produce SDL effects came from Andersson's work on memory for nonsense syllables (Andersson & Post, 1974). As noted earlier, there was an immediate drop in the number of correct responses after the initial cigarette for subjects in the nicotine condition. However, after the second cigarette, there was no subsequent deterioration in performance. These results may be interpreted as SDL in that material which was learned before the first cigarette (in a non-drug state) was more difficult to access after smoking a cigarette. After smoking the second cigarette, SDL again took place, only this time in the same drug state from the first cigarette, thus no differences were observed. Very similar results were found in a follow-up study (Andersson, 1975).

In a related study mentioned earlier, smokers who preferred to smoke in either low or high arousing situations were studied under actual conditions of low or high arousal. Results revealed that "In low-arousal smokers, performance and general well-being were favorably affected by smoking in the low-arousal situation only. Conversely, performance and well-being of higharousal smokers were enhanced by smoking in the high-arousal situation only" (Myrsten et al., 1975), providing strong evidence that state dependent or conditioning processes were in effect.

The first study to directly test state-dependent learning properties of nicotine was conducted by Peters and McGee (1982). The investigators used high (H) nicotine (1.4 mg) and low (L) nicotine (.2 mg) cigarettes. Subjects in the "same-state" smoking condition smoked the same cigarette at acquisition and retrieval (H-H, or L-L), while subjects in the mixed-state condition smoked different cigarettes at acquisition and retrieval (H-L, or L-H). Clear state-dependent learning effects were observed, as subjects recalled more words if they smoked the same nicotine content cigarette during both acquisition and retrieval. Interestingly, there were no differences between the two same-state

groups (L-L, or H-H), suggesting that nicotine itself did not have favorable or adverse effects on memory. Kuzendorf and Wigner (1985) recently found similar SDL effects in comparing smoking and nonsmoking states during memory acquisition and retrieval.

Wesnes and Warburton (1986) used a SDL design to test the effects of both smoking and nicotine tablets on human memory. Results were consistent with previous studies, as smoking and nicotine produce clear SDL effects on memory and learning. However, contrary to the findings of Peters and McGee, these authors cited evidence that nicotine facilitated performance over and above the effects of state dependent learning. Subjects who smoked before learning and retrieval outperformed those who did not smoke in these two conditions. Although it is possible that overnight abstinence (withdrawal) played a role in the magnitude of this effect, the discrepancy from Peters and McGee's study remains to be explained.

Mounting evidence suggests that memory may not be the only faculty effected by SDL. Nesbit (1977) concluded that smokers and nonsmokers exhibited different emotional reactions to the act of smoking a cigarette. His results suggested that smoking leads to less emotionality in smokers, but just the opposite in nonsmokers. Perkins, Epstein and Jennings (1988) provided additional evidence for the role of conditioning in emotional response. Their results implied that regularly experiencing a stressor contiguous with smoking impairs performance and emotional response when the stressor is later encountered without smoking. Interestingly, they also found that smoking contiguously with a stressor which was previously encountered without smoking leads to disrupted performance. This conditioning effect has been interpreted as from a dishabituation model of performance and emotion, and directly contradicts evidence that smoking alone improves performance.

Further evidence for the role of conditioning in the ability of nicotine to affect behavior has been provided by the animal literature (e.g., Epstein, Cagguila, & Stiller, 1988). Tolerance to nicotine's antinociceptive effects appears to be, in part, a learned response. Nicotine tolerance, which was developed in the presence of a specific environment, vanished when nicotine was subsequently administered in a new environment.

In summary, nicotine has recently been added to the mounting list of drugs which have been shown to produce state-dependent learning effects. Evidence from the Wesnes and Warburton lab suggests that, while nicotine does produce clear drug-dependent effects, it also facilitates learning. Other studies have been more skeptical, suggesting that nicotine alone either has no effect (Peters & McGee, 1982), or impairs performance when conditioning factors are controlled (Perkins et al., 1988). There appears to be increasing evidence that learning

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plays a significant role in the effects of nicotine on human behavior and emotion.

Rationale and Purpose of the Present Study

The present study was designed to overcome some of the methodological confounds evident in previous studies. These investigations have not adequately controlled for drug withdrawal when assessing the effects of nicotine on emotion, memory, and performance. In addition, many studies have not controlled for drug state during training trials prior to implementing experimental manipulations, even though evidence has shown that prior conditioning can effect emotional response and task performance. The present study is a preliminary examination designed to separate pharmacological and conditioning factors affecting human functioning. It is hoped that this investigation will help determine how the proposed facilitory effects of nicotine, deleterious effects of nicotine withdrawal, and learning/conditioning factors interact in the analysis of human memory, performance, and emotion.

In order to test these effects, three groups of subjects underwent several nonsmoking "training" trials on a computerized assessment battery. They were assigned to one of three experimental conditions: No-smoking/Deprived, No-smoking/Nondeprived, and Smoking/Nondeprived. Because there is sufficient

literature to suggest that the data may reflect differences in either direction, directional hypotheses were not made.

Method

Subjects

Thirty female cigarette smokers with a mean age of 26 (S.D.= 7.8) years, participated in the study. In order to be included, subjects had to have smoked at least 20 (M= 26.4, S.D.= 8.8) cigarettes per day for more than one year (M= 10.8, S.D.= 8.4), and obtain a grade equivalent of 8.0 on the WRAT-R Arithmetic subtest in order to insure ability to perform simple arithmetic. There are no data to indicate possible gender differences. However, in order to limit variability and reduce the number of subjects required to analyze gender differences, only female smokers were utilized. For their participation, subjects were paid an average of \$25, which included \$16 base pay plus a performancecontingent monetary incentive (M= \$9.25).

Procedure

Subjects were interviewed before participation in order to complete informed consent and obtain a detailed smoking history, measure of expired alveolar air carbon monoxide (COa), and practice filling out the Profile of Mood States (POMS), Emotion Assessment Scale (EAS) and tobacco withdrawal symptom rating scale. Subjects were instructed to abstain from caffeine, alcohol, and smoking from midnight until arriving at the laboratory early the next morning. Sessions were conducted between 8:00 a.m. and 12:00 noon. Upon arrival, subjects provided a COa sample and completed baseline ratings on all mood scales.

Subjects were assessed over a two day period. Each day involved completing seven trials of a computerized performance assessment battery (PAB). Five individual PAB tasks were presented in the same order each time, separated by 30 second breaks. Total time for each battery was approximately 10 minutes. A longer break of five minutes separated each completed battery, during which subjects completed the POMS, EAS and withdrawal rating scale.

Each battery (PAB) represented either a "training" or "test" trial. All batteries on day one, and the first six batteries on day two were designated as "training" trials. Thirteen training trials were selected because previous studies using the PAB indicate that this is the minimum number required to obtain stability in performance (Snyder, Davis & Henningfield, 1989). All subjects completed these training trials without access to cigarettes. The 14th and final battery on day two represented the "test" trial. The break period between the last (13th) training PAB and the "test" PAB marked the induction of the experimental manipulation.

Subjects were randomly assigned to one of three conditions; No-smoking/ Deprived, No-smoking/Nondeprived and Smoking/Nondeprived. The Nosmoking/Deprived group remained drug-deprived, and was tested under the same conditions as they were trained. Therefore, they were not allowed to smoke during the short breaks between each task on the final PAB. They were also not allowed to smoke during the interim between the final training and test trial in order to maintain their state of drug withdrawal. The No-smoking/ Nondeprived group was allowed to smoke four puffs from a cigarette during the interim between the final training and test trials in order to partially alleviate their state of drug withdrawal. Consistent with their training condition, they were not allowed to smoke during the PAB. Finally, the Smoking/Nondeprived group was allowed to smoke four puffs from a cigarette just before the seventh and final PAB. However, they were also allowed to smoke ad libitum during the 30 second breaks between tasks on the test PAB in order to "cross" their drug state from the training trials. All subjects smoked their preferred brand of cigarettes.

Performance Assessment Battery

Five independent tasks were chosen from the Walter Reed Army Institute for Research Performance Assessment Battery (PAB; Thorne, Genser, Sing & Hegge, 1985) to represent diverse areas of cognitive functioning such as visual vigilance, logical reasoning, short-term memory, concentration, and ability to perform simple arithmetic. Order of task presentation did not vary because fatigue and peak drug effect was not likely to be affected due to the short administration time of the battery (10 minutes).

One modification was made to the PAB. In its original form, all tasks required subjects to complete the same number of problems. However, a pilot study indicated that a ceiling effect was taking place, as subjects often received perfect accuracy (and slow reaction times) on several of the tasks. Therefore, the PAB was modified to increase the relevance of response time in the evaluation of a subject's performance. A two minute time limit was set for each task, allowing a subject to complete as many items as they could complete within this time frame. Subjects were told that level of performance was indicated by the total number of correct answers. The end result was that subjects were required to not only answer correctly (accuracy), but respond quickly in order to increase the number of items presented during the allotted time period. The modification was made to all tasks except for Digit Recall, as this task was already a very difficult task which required a high level of vigilance, but relied minimally on response time. Therefore, the task was left in its original form, and every subject was presented with 15 items.

A brief description of each task follows. Additional details have been outlined elsewhere (Thorne, Genser, Sing & Hegge, 1985; Snyder & Henningfield, 1989).

<u>Six-Letter Search</u>. A visual search and recognition task. Subjects are required to determine if the six target letters presented at the top of the computer screen are contained in the random string of 24 letters displayed immediately below. If all six are present in any order, the "S" key is pressed for "Same". If one or more letters are missing, the "D" key is pressed for "Different."

Logical Reasoning. An exercise in transformational grammar. The letter pair 'AB' or 'BA' is presented along with a statement that correctly or incorrectly described the order of the letters within the pair (e.g., 'B follows A' or 'A is not preceded by B'). The subject determines whether the statement is true or false.

Digit Recall. A test of short-term memory capacity. Each problem consists of a row of nine digits appearing simultaneously on the screen for one second, and followed by a three second blank screen. Eight of the original nine digits are then redisplayed, with the object being to identify the missing digit. A given digit may appear no more than twice on each trial. <u>Serial Addition/Subtraction</u>. A machine-paced mental arithmetic task requiring sustained attention. Two digits are presented sequentially on the screen for 250 ms each followed by an arithmetic operator ("+" or "-"). The subject performs the indicated addition or subtraction and enters the least significant digit of the result (e.g., 8, 6 + equals 14, so enter 4). If the result is negative, the correct answer is obtained by adding ten to it (e.g., 3, -9 equals -6, so enter 4). Thus, all correct answers are single digit and of positive value.

<u>Column Addition</u>. A subject-paced mental arithmetic task. Five two-digit numbers are presented simultaneously in column format in the center of the screen. The subject determines their sum as rapidly as possible and enters it from the keyboard. The column of digits disappears with the first key entry, and no aids for the carry operation are allowed.

Subjective Mood Ratings

Subjects completed the Profile of Mood States (POMS; McNair, Loor & Droppleman, 1971), Emotion Assessment Scale (Carlson et al., 1989) and a tobacco withdrawal symptom rating scale (Hughes et al., 1984) upon arrival to the laboratory, and during the break after every third performance assessment battery.

Subjects were asked to respond to the 65 POMS adjectives on a four point scale, ranging from "not at all" to "extremely." Each adjective loaded on one of

the six subscales, including Vigor, Confusion, Fatigue, Hostility, Depression and Anxiety. A higher-order factor, Total Mood Disturbance (TMD), was derived by summing across all six factors (weighing Vigor negatively), as described by the authors. The "right now" version of the POMS was used to measure immediate effects of the experimental manipulation upon mood.

The Emotion Assessment Scale consists of 24 emotional descriptors loading on eight primary factors including Anger, Anxiety, Disgust, Fear, Guilt, Happiness, Sadness and Surprise. Each of the descriptors is rated on a 10-cm visual analogue scale. Visual analogue scales are often preferable to Likert scales when repeated measures are taken during a brief time interval, as they minimize subjects' recall of previous responses (Carlson et al., 1989).

Subjects completed a tobacco withdrawal symptom rating scale, which included cigarette craving, irritability, anxiety, difficulty concentrating, restlessness, headache, drowsiness and gastrointestinal disturbance. Subjects also rated their level of fatigue, impatience, hunger, and listed any somatic complaints they were experiencing. Each symptom was rated on a scale from 0 "not present" to 1 "mild," 2 "moderate," or 3 "severe." The rating scale is based on DSM-III-R criteria for tobacco withdrawal and is similar to a scale used by Hughes et al. (1984) in their study of the tobacco withdrawal syndrome.

Smoking Abstinence/Nicotine Dose Index

Expired alveolar air carbon monoxide (COa) levels were used as an index of pre-and post-cigarette nicotine dose, and to maximize the likelihood of compliance with smoking abstinence. Measurements were taken immediately before and after the four puff administration, and again after the final PAB in which the Smoking/Nondeprived group smoked. COa levels were obtained using a BreathCo (model 29.700) non-invasive, hand-held CO monitor.

Design and Data Analyses

Performance data (Number Correct, Percentage Correct and Response Time) were analyzed using a three-factor $(3 \times 2 \times 4)$ mixed design analysis of variance (ANOVA) with repeated measures on two factors (Day and Trial). The final four trials of each day were subjected to analyses in order to provide three data points prior to the experimental manipulation.

Ratings of moodstate (EAS and POMS) and tobacco withdrawal were also subjected to a three-factor $(3 \times 2 \times 4)$ mixed design ANOVA with repeated measures on Day and Rating. All data points for each day were used in the analyses.

ANOVA's which yielded significant Group X Day X (Trial\Rating) interactions were followed by two-factor ANOVA's for each Day. Significant Group X (Trial\Rating) interactions were then subjected to single-factor ANOVA's for each of the three Groups across Trials or Ratings. A significant Trial\Rating effect for any of the three groups was then followed by Tukey's HSD (honestly significant difference) tests (Tukey, 1953). It was expected that any effects from the experimental manipulation would result in significant Tukey's tests between performance Trials 13 and 14, or mood Ratings 7 and 8. In order to limit Type II errors associated with repeated measures designs, only consecutive pairs of means were subjected to HSD tests. An alpha level of .10 was selected for all analyses due to the investigational nature of this study.

Results

Subject Characteristics

Subjects were interviewed prior to participation to obtain a detailed smoking history and a baseline COa measure. Subject characteristics were analyzed using a single-factor, analysis of variance (ANOVA) to compare the three groups. Results showed that the three groups did not differ with regards to age, F(2,27) = .68, p> .10, years smoked, F(2,27) = 1.48, p> .10, baseline COa level, F(2,27) = .169, p> .10, or mean score on the Tolerance Questionnaire (Fagerstrom, 1978), F(2,27) = 2.33, p> .10. The only significant difference noted was that the No-smoking\Deprived smoked fewer cigarettes per day (21.0) than the No-smoking\Nondeprived (29.7) and Smoking\Nondeprived (28.5) groups, F(2,27) = 3.3, p< .05. The entire subject pool averaged a score of 7.2 (S.D = 1.5) on the Tolerance Questionnaire, a measure of physiological dependence to cigarettes. This score places them in the upper range of medium tolerance. Mean baseline carbon monoxide (COa) level of 22.3 ppm (parts per million) is consistent with norms published for moderate smokers smoking 16 to 24 cigarettes per day (Lando et al., 1991).

Compliance

Subjects were asked to respond honestly to a compliance questionnaire after participation was completed. They were assured that their answers would in no way effect their monetary compensation. All but three subjects reported that they were totally compliant in abstaining from caffeine, alcohol and cigarettes from midnight the previous night. One subject reported drinking alcohol until 1:00 a.m. the previous night, while two subjects reported smoking their last cigarette one hour past the midnight cutoff.

Pre- and post-COa levels were obtained to maximize the likelihood of compliance. Statistical analyses were not conducted on this data because rates of absorption and elimination are known to vary considerably across individuals (Henningfield, Stitzer & Griffiths, 1980). However, observation of the data indicated that nearly all of the subjects exhibited low or decreased levels following overnight abstinence. Because the COa data was not discrepant, compliance was assumed based on self-report.

<u>COa boost</u>

Expired alveolar air carbon monoxide (COa) levels were obtained after every third PAB, and before and after the smoking manipulations on Day 2. The five COa measures from Day 2 were subjected to a 3 (Group) X 5 (COa Measure) mixed design ANOVA with repeated measures on COa Measure. A significant Group X COa Measure interaction, F(8,108) = 17.3, p< .01 was followed by a single-factor ANOVA, which resulted in a significant COa Measure effect for all three groups, F(4,36), all p's < .01). Tukey's HSD tests were conducted between COa Measures 7 (before 4 puffs), 8 (after 4 puffs), and 9 (after ad lib smoking). As expected, there were no differences between consecutive measures for the No-smoking\Deprived group, as their COa levels steady declined. COa levels increased significantly for both Nondeprived smoking groups following the 4 puff manipulation (p's < .01). Following the final PAB, the Smoking\Nondeprived group received another significant (p < .01) COa boost after smoking ad libitum. Mean COa values are presented in Figure 1.

Subjective Mood Ratings

<u>Profile of Mood States (POMS)</u>. The six subscales of the POMS included Vigor, Concentration, Fatigue, Hostility, Depression and Anxiety. These subscales combined to form a higher order factor, Total Mood Disturbance (TMD), which is indicative of overall mood-state. Three-factor ANOVA's (Group X Day X Rating) were performed on each subscale and Total Mood Disturbance (TMD). Results revealed no significant three-factor interactions; TMD, F(6,81) = .73, p> .10; Vigor, F(6,81) = 1.66; Concentration, F(6,81) =.849; Fatigue, F(6,81) = 1.43; Anger, F(6,81) = 1.5; Depression, F(6,81) = 1.3; and Anxiety; F(6,81) = 1.43 (all p's > .10). However, significant two-factor interactions (Group X Rating) were noted for TMD, F(6,81) = 2.1, p< .05; Depression, F(6,81) = 1.9 p < .10; and Anxiety, F(6,81) = 1.9, p< .10. Singlefactor (Rating) analyses were then conducted holding Group constant. For TMD ratings, significant results were found for the Smoking\Nondeprived group F(7,81) = 4.3, p< .01. All three groups exhibited significant differences on Anxiety ratings; No-smoking\Deprived, F(7,81) = 3.56, p< .01; No-smoking\ Nondeprived, F(7,81) = 2.51, p< .05, and Smoking\Nondeprived, F(7,81) = 4.52, p < .01. There were no differences for any group on ratings of Depression.

Tukey HSD tests were conducted on all consecutive pairs of means. The No-smoking\Deprived group exhibited a significant drop in Anxiety between Ratings 4 and 5, p< .01. This difference is not surprising because of the extensive break between the last rating on day one (Rating 4) and the first rating on day two (Rating 5). Neither of the Nondeprived groups exhibited differences in Anxiety between consecutive ratings (p's > .10).

Results of TMD ratings were more positive. The Smoking\Nondeprived group exhibited a decrease in Total Mood Disturbance from Rating 7 to Rating 8, p< .05, indicating overall mood elevation after smoking ad libitum during the final PAB. Day 2 TMD ratings are graphically illustrated in Figure 2, with lower scores signifying more positive mood ratings.

It is interesting to note, of the eight ratings obtained across two days, subjects in the Smoking\Nondeprived group gave their highest ratings of Vigor, and lowest ratings of Depression, Anger, Anxiety and Fatigue immediately after smoking ad libitum during the final PAB. For example, the final Anxiety rating for the Smoking\Nondeprived group (5.6) was a full two points lower than either of the No-smoking groups' ratings at anytime during the experiment. Overall, ratings from the No-smoking\Nondeprived group were in the same direction as the Smoking\Nondeprived, but of lesser magnitude. Ratings from the No-smoking\Deprived group generally remained unchanged. Thus, it appears that none of the individual emotion ratings accounted for a large percentage of the Smoking\Nondeprived group's decrease in Total Mood Disturbance. Rather, small but consistent decreases in Fatigue, Anger and Anxiety, combined with increased Vigor to yield overall mood elevation following cigarette smoking.

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Emotion Assessment Scale (EAS). The eight primary scales of the EAS included Anger, Anxiety, Disgust, Fear, Guilt, Happiness, Sadness and Surprise. Results of three-factor ANOVA's conducted for each scale revealed significant interactions for Happiness, F(6,81) = 1.9 p < .10; Sadness, F(6,81) = 2.4, p < .05; and Guilt, F(6,81) = 2.05, p< .10. Two-factor analyses on these variables resulted in significant interactions (Group X Rating) only on Day 1 for Guilt, F(6,81) = 2.15, p< .10; and Sadness, F(6,81) = 5.44, p< .01. No differences were associated with the experimental manipulation on Day 2 for either of these variables, so no further analyses were conducted. However, a significant Group X Rating interaction on was found on Day 2 ratings for Happiness, F(6.81 =2.6, p< .01). The single-factor (Rating) ANOVA found significant effects for the No-smoking\Nondeprived, F(6,81) = 2.78, p< .05; and Smoking\Nondeprived, F(6,81) = 3.5, p< .01 groups. Tukey HSD tests indicated that the Nosmoking\Nondeprived group was less Happy at Rating 6 than at Rating 5, p< .05. While there is no obvious explanation for this difference, observation of the data indicates that this group's Happiness ratings dropped considerably following the first PAB on Day 1 as well. Most importantly, the Smoking Nondeprived group exhibited a boost in Happiness from Rating 7 (pre-smoking) to Rating 8 (post-smoking), p < .10 (see Figure 3).

Data from the EAS ratings yielded a substantial amount of within-subject variation, which prevented the magnitude of mood changes from reaching statistical significance in several cases. However, the direction of subjects' ratings was quite consistent in showing mood improvement after cigarette smoking, and inconsistent with the notion of mood disruption from the effects of counterconditioning. Changes from rating 7 (pre-manipulation) to rating 8 (post-manipulation) on Happiness and Surprise increased most for the Smoking Nondeprived group, somewhat for the No-smoking\Nondeprived group, while remaining the same for the No-smoking\Deprived group. Anxiety and Anger ratings decreased most for the Smoking\Nondeprived group, somewhat for the No-smoking\Nondeprived group, while remaining the same or increasing for the No-smoking\Deprived group. No differences or pattern emerged on the other four primary emotions of the EAS. This was somewhat surprising for Sadness, but not for emotions like Fear, Guilt and Disgust, which might not be expected to be responsive to pharmacological manipulations.

<u>Withdrawal symptom rating scale</u>. Subjects rated their intensity of eleven different symptoms, which were based on DSM-III-R criteria for tobacco withdrawal. Three-factor ANOVA's conducted for each symptom revealed a significant Group X Day X Rating interaction for Cigarette Craving, F(6,81) =6.6, p< .01. Two-factor analyses revealed significant interactions for Craving (Day 2 only), F(6,81) = 12.5, p < .01; Irritability, F(6,81) = 2.96, p < .05; Anxiety, F(6,81) = 2.38, p < .05; Restlessness, F(6,81) = 2.0, p < .10; Drowsiness, F(6,81) = 2.6, p < .05; and Impatience, F(6,81) = 3.5, p < .01. There were no significant findings for the withdrawal symptoms of Difficulty Concentrating, Headache, Intestinal Disturbance, Fatigue, Hunger or Somatic Complaints (all p's > .10).

Single-factor (Rating) analyses revealed differences for the No-smoking Deprived and Smoking/Nondeprived groups on ratings of Craving, F(6,81) =4.33 and 32.8 respectively; Irritability F(6,81) = 3.43 and 4.01; Anxiety, F(6,81) =4.02 and 3.3; Restlessness, F(6,81) = 3.38 and 3.37; and Impatience, F(6,81) =4.2 and 4.0, (all p's < .01). Only the Smoking/Nondeprived group exhibited different ratings on Drowsiness, F(6,81) = 4.58, p< .01.

Tukey's HSD tests were then conducted on Rating for all consecutive pairs of means. No differences were found in the No-smoking\Deprived ratings, with the exception of Anxiety and Impatience. In both of these cases, Rating 4 was significantly greater than Rating 5 (p's < .05). Again, this finding is not surprising considering the time delay between Rating 4 (final rating of day one), and Rating 5 (first rating of day two). Thus, it appears that the differences observed in the No-smoking\Deprived group were due to variance from the final rating of Day 1 to the initial rating on Day 2, and not from the experimental manipulation itself. There were no differences in ratings of the No-smoking\ Nondeprived group for any of the eleven symptoms.

Contrary to the No-smoking groups, subjects in the Smoking\Nondeprived group exhibited significant reductions in Anxiety, p < .05, Irritability, p < .01, cigarette craving, p < .01, and Impatience, p < .01 immediately after smoking during the final PAB (See Figures 4, 5 & 6). The only difference noted on Drowsiness levels came between Ratings 1 and 2, p < .05, indicating that subjects probably "woke up" after participating in the first PAB. Finally, no changes were observed for Restlessness between Ratings 7 and 8 (p > .10). While the effect size of Restlessness was not sufficient for statistical significance, the group order and direction of change was consistent with that observed on the four variables which met significance levels.

In summary, there were some differences noted in the ratings of the Nosmoking\Deprived group which appeared to be unrelated to the experimental manipulation. As expected, the Smoking\Nondeprived group exhibited immediate reductions in anxiety, irritability, cigarette craving and impatience after smoking ad libitum. Finally, the No-smoking\Nondeprived group exhibited minor reductions in several withdrawal symptoms. However, the magnitude of perceived symptom relief that resulted from smoking just 4 puffs from a cigarette did not reach statistical significance.

Performance Data

Number correct. Number of problems correct on each PAB task was the best indication of overall performance, as it accounted for both accuracy (percentage correct) and reaction time. The final four data points for each day were subjected to statistical analyses for all performance variables. Three-factor (Group X Day X Trial) interactions were noted on Serial Addition F(6,81) =3.0, p< .01, and Column Addition, F(6.81) = 3.5, p< .01. A Group X Trial interaction was found on Six Letter Search, F(6.81) = 2.25, p< .05. Subsequent two-factor ANOVA's revealed Group X Trial effects on Day 2 of Column Addition, F(6,81) = 2.7, p< .05 and Serial Addition, F(6,81) = 2.35, p< .05. Single-factor analyses conducted for each group on Trial indicated that all three groups exhibited significant effects on Six Letter Search. The No-smoking Deprived and Smoking\Nondeprived groups exhibited significant effects on Serial Addition, while only the No-smoking\Deprived group obtained different performance scores on Column Addition.

Tukey's HSD tests indicated no differences between consecutive means on Six Letter Search, with the exception of increased performance from the Nosmoking\Deprived group between the last PAB of day one and the first PAB of day two (p< .05). The only other difference noted was the No-smoking\ Deprived group performed better on PAB 13 for both Serial (p< .10) and Column Addition (p< .05). There were no differences in the number of correct problems for Digit Recall or Logical Reasoning (p's >.10).

In summary, the No-smoking\Deprived group exhibited some performance changes, but they were unrelated to the experimental manipulation. Again, the direction of performance change for the Nondeprived groups was consistent with improved performance following cigarette smoking. On Serial Addition, Column Addition, and Six Letter Search (see Figure 7), the No-smoking\ Deprived group showed no change or lower scores, while both groups that smoked (Nondeprived) exhibited slight improvements in performance.

<u>Percentage correct</u>. Percentage of correct answers on each PAB task indicated accuracy of performance. Analyses indicated a three-factor interaction on Column Addition, F(6,81) = 3.26, p< .01. A subsequent two-factor (Group X Trial) interaction was noted on Day 2 only, F(6,81) = 2.65, p< .05. Additional analyses indicated that the only differences in accuracy were for the No-smoking\Deprived group, as they performed better on PAB 13 than on PAB 12. Significant Day X Group, F(3,81) = 2.27, p< .05 and Day X Trial, F(2,27)= 3.65, p< .05 interactions were found for Logical Reasoning. However, no group differences were noted.

The only other difference of interest was a practice effect for Digit Recall, as all three groups performed better on Day 2 (p< .05). No group differences were observed for Six Letter Search or Logical Reasoning (p's > .10). There was little variation on Six Letter Search due to a ceiling effect, as all three groups hovered close to 100% for all trials.

Interestingly, Logical Reasoning appeared to show signs of disruption in performance following cigarette smoking. The No-smoking\Deprived group remained consistent from trial 13 to 14, while the No-smoking\Nondeprived and Smoking\Nondeprived groups exhibited decreases in performance, relative to the amount smoked (see Figure 8).

In summary, there were no significant changes in performance accuracy as the result of the smoking manipulation. However, the direction of the data for Logical Reasoning appears to indicate performance disruption following cigarette smoking.

<u>Response time</u>. Reaction times consistently improved after cigarette smoking. Three-factor interactions were noted for Digit Recall, F(6,81) = 2.51, p < .05 and Serial Addition, F(6,81) = 2.52, p < .05, while a Group X Trial interaction was found for Six Letter Search, F(6,81) = 2.18, p < .05. Subsequent two-factor ANOVA's resulted in a significant interaction (Group X Trial) on Day 2 of Digit Recall. Single-factor analyses conducted on Trial (PAB) found differences within the No-smoking\Deprived and Smoking\Nondeprived groups on Six Letter Search, and for all three groups on Digit Recall. Tukey's HSD tests indicated that on Digit Recall, the No-smoking Nondeprived group exhibited a small (but statistically nonsignificant) improvement in reaction time, while the Smoking/Nondeprived group exhibited a marked improvement in reaction time, p< .01 (see Figure 9). Similar results were noted on Six Letter Search, as the Smoking/Nondeprived group noticed faster reaction time after smoking as libitum during the final PAB, p< .05.

Although the noted improvements in response time were not statistically significant for all tasks, the direction of effect was very consistent. Both smoking (Nondeprived) groups exhibited faster reaction times after smoking (from PAB 13 to 14) on all five PAB tasks, with the Smoking\Nondeprived group showing the most improvement on four of those five tasks. Times for the No-smoking\Deprived group generally remained the same or were slightly slower.

Discussion

The results of the present study suggest that the pharmacological aspects of nicotine may outweigh the role of learning and conditioning in human performance and emotion. Following 13 no-smoking training trials on a computerized performance assessment battery, two of three groups were allowed to smoke either four puffs or ad libitum. The performance of these two groups would be expected to improve following cigarette smoking if pharmacological factors are primary. Performance decrements would be expected if behavioral or conditioning factors are primary, due to counterconditioning.

Results showed that increased COa levels, elevation in overall mood, and decreases in reported withdrawal symptoms were generally in proportion to the amount smoked, suggesting that the experimental manipulation was effective. Ratings for the tobacco withdrawal symptom checklist were most sensitive to changes associated with smoking deprivation and alleviation. This finding is not surprising as this measure is a more direct reflection of smokers' subjective sense of nicotine withdrawal than more global mood scales.

Although the experimental manipulation appeared to work, the effects on subject performance were difficult to interpret due to extreme variation across the training trials. Previous investigations have utilized training trials in order to decrease variability due to practice effects. These data are rarely, if ever, reported despite evidence that conditions during practice trials can affect future performance. Drug state was controlled because of the evidence implicating state-dependent learning in cigarette smoking (Kuzendorf & Wigner, 1985). Because some investigator's have proposed that nicotine only serves to offset declining performance after prolonged periods of testing (e.g. Mackworth, 1963), fatigue was minimized by providing subjects a five minute break period between PAB's. Finally, subjects were provided monetary incentive, contingent upon level of performance in order to maintain subject motivation across trials. Thus, by focusing on initial experiences with the task (i.e., training trials), the present investigation controlled for many non-pharmacological (behavioral) factors that past investigations have neglected. Unfortunately, by including these initial trials performance analyses, the data obtained is difficult to interpret due to extreme variation across the training trials. The 13 training trials provided only 9 of 15 (3 groups X 5 tasks) data sequences in which the final three (pre-manipulation) scores fell within one standard deviation of the mean (Day 2).

Because of the failure to obtain stable performance before implementing the experimental manipulation, few measures reached statistical significance. However, the direction of the data is consistent with a majority of the literature reflecting small to moderate performance improvements following cigarette smoking (Wesnes & Warburton, 1983c; Heimstra, 1967). Data from the first day consisted of a great deal of variation and virtually no group differences. Day two showed more consistency in performance across trials but few group differences were observed following the smoking manipulation. Specifically, smoking led to statistically insignificant improvements in overall performance for the two smoking groups on Six Letter Search, Serial Addition and Column Addition. Increased performance following smoking has been noted in past investigations using similar performance tasks including mental arithmetic (Friedman, 1972) and letter cancellation (Williams, 1980; Myrsten, 1977). Contrary to many investigations which have concluded that cigarette smoking impairs immediate memory (e.g. Anderson, 1975; Houston, 1978; Mangan, 1983), this study found no effect of smoking on Digit Recall.

While overall performance showed only slight effects from cigarette smoking, reactions times appeared to be more responsive. After smoking, the Smoking\Nondeprived group showed significantly faster reaction times on both Digit Recall and Six Letter Search. The direction of the data was consistent on all five PAB tasks, as both smoking groups exhibited improved response times after smoking. On two of the five tasks, the No-smoking/Nondeprived group exhibited their fastest response time of all 14 trials immediately after they smoked (final trial). The group which smoked the most (Smoking/Nondeprived) exhibited their fastest reaction times on the final trial across all five PAB tasks. While one might argue that these top times were reached due to a culmination of practice effects, this interpretation is unlikely because the nonsmoking group exhibited their fastest reaction times on trial 14 on only one PAB task. These data implicating improved response time following cigarette smoking are consistent with previous findings (e.g. Frankenhauser et al., 1971).

Improvements in reaction time following smoking did not appear to translate into better overall performance. For example, the Smoking/ Nondeprived group exhibited a significant decrease in reaction time on Digit Recall after smoking, but overall performance did not improve because of a concomitant decline in accuracy.

The only measure on which smoking appeared to impair performance was Logical Reasoning. Although statistically nonsignificant, both Nondeprived exhibited disrupted performance immediately after smoking, in proportion to the amount smoked. It is interesting to note that these groups exhibited poorer performance after smoking, even though the latter group was tested under the same drug condition as they were trained. Therefore, it is more likely that the pharmacological properties of nicotine, and not the effects of counterconditioning, are implicated in the performance decrements. Logical Reasoning appears to load more heavily on concentration and complex reasoning than the other PAB tasks, which rely more on vigilance and simple reasoning skills. Elgerot (1976) also found that smokers performed better on complex measures when abstaining than when smoking, suggesting that there may be different levels of optimal arousal for different types of tasks.

Overall, these data replicate previous studies indicating that nicotine alleviates negative mood states (Pomerleau & Pomerleau, 1987) and withdrawal

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symptoms (Hughes et al., 1984) but appears to have equivocal effects on human performance. The data provide virtually no evidence that nicotine disrupts performance or emotion due to the effects of state-dependent learning (Peters & McGee, 1982) or environmental conditioning (Perkins et al., 1988). Caution should be taken in generalizing these results to non-laboratory environments like the workplace. While smoking resulted in significant improvements in overall moodstate, the effects on performance were rarely evident, and appeared modest in magnitude when they were noted. Previous work has indicated that changes in affective state and performance following cigarette smoking may not be correlated (Snyder et al., 1989).

By utilizing a modified state-dependent design, the present investigation was moderately successful in teasing apart the differential effects of nicotine and conditioning upon human emotion, learning and performance. This is the first known study to specifically control for subjects' drug state and learning history prior to implementing experimental manipulations. The present investigation extends the literature on smoking and human performance, indicating that the physiological effects of tobacco withdrawal and pharmacological effects of nicotine influence human performance and emotion even when behavioral and conditioning factors are controlled. Future studies in this area might do well to utilize longer nicotine-free learning histories in order to establish stronger conditioning, and give stress and anxiety a chance to habituate. It appears likely that a more extensive conditioning history is necessary to observe behavioral effects of nicotine on performance. Further work is needed to more precisely differentiate nicotineinduced improvements from reversal of deprivation-related decrements in performance. The recent identification of occasional, non-addicted smokers ("chippers;" Shiffman, 1989) might help researchers overcome the shortcomings of past studies using addicted smokers experiencing acute states of nicotine withdrawal.

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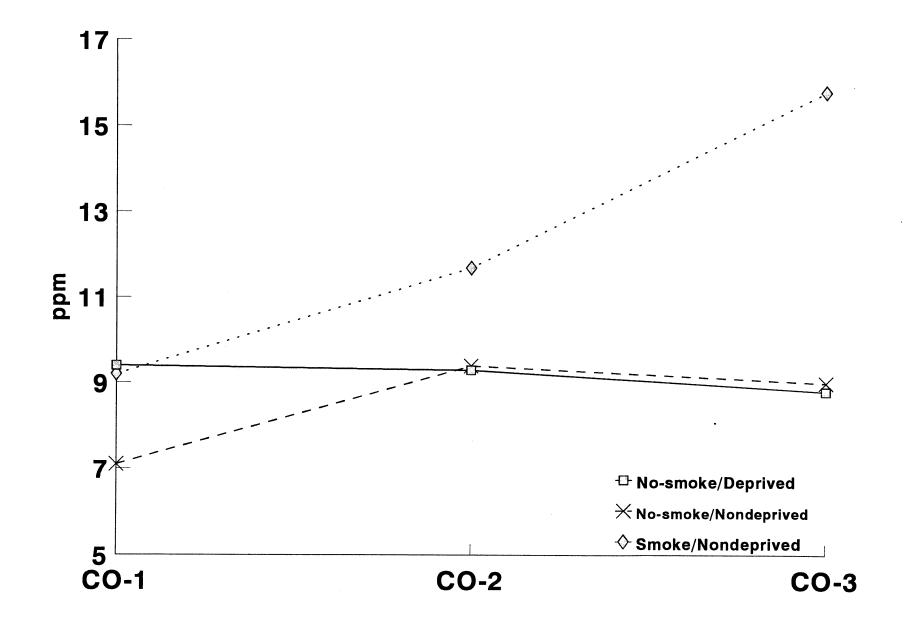
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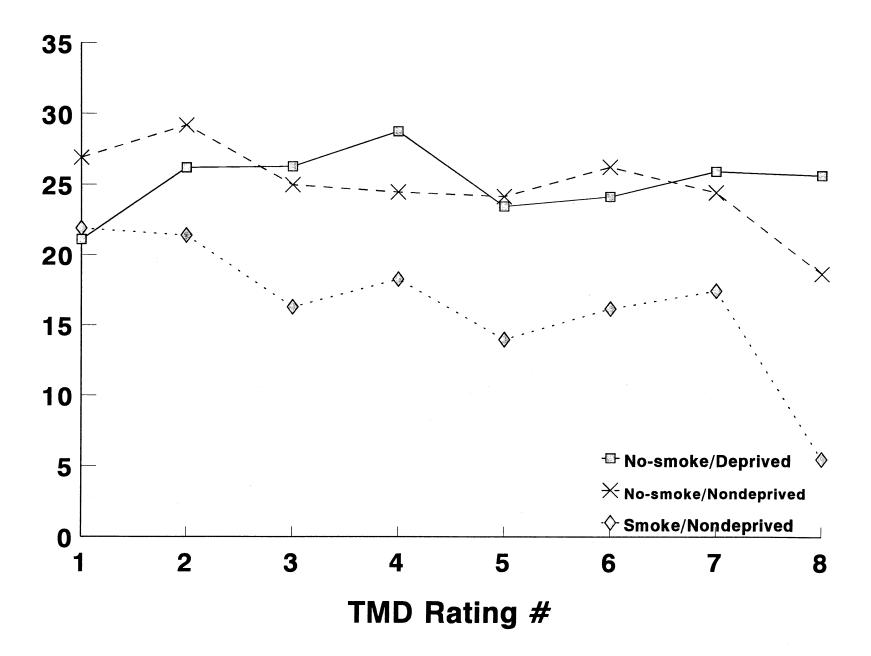
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Figure Captions

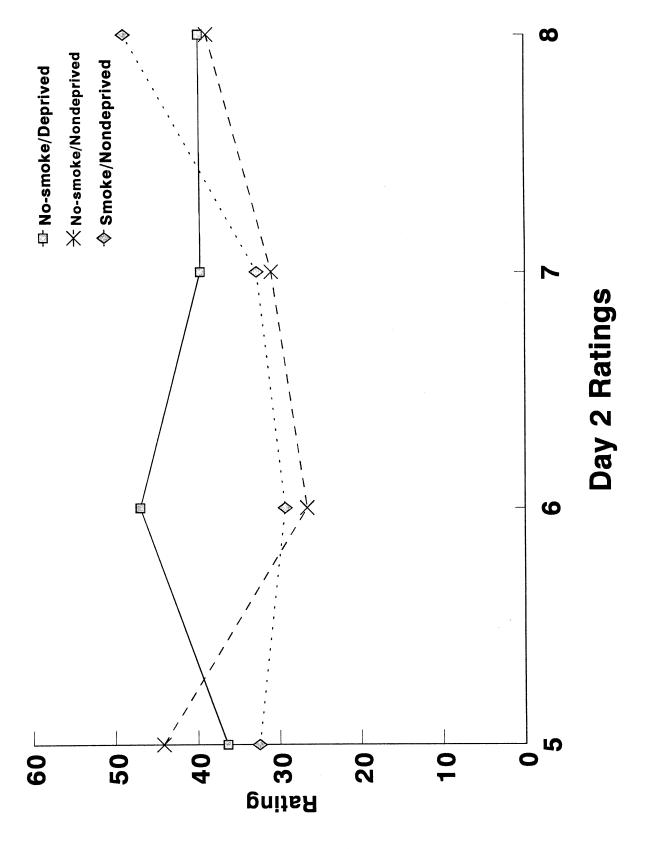
- Figure 1. Expired alveolar air carbon monoxide (COa) level by group.
- Figure 2. Profile of Mood States (POMS) Total Mood Disturbance (TMD) ratings by group.
- Figure 3. Emotion Assessment Scale (EAS) Happiness ratings by group.
- Figure 4. Day two withdrawal symptom ratings of Anxiety by group.
- Figure 5. Day two withdrawal symptom ratings of Irritability by group.
- Figure 6. Day two withdrawal symptom ratings of Impatience by group.
- Figure 7. Number of correct answers on PAB task Six Letter Search by group.
- Figure 8. Percent correct on PAB task Logical Reasoning by group.
- Figure 9. Response time on PAB task Digit Recall by group.



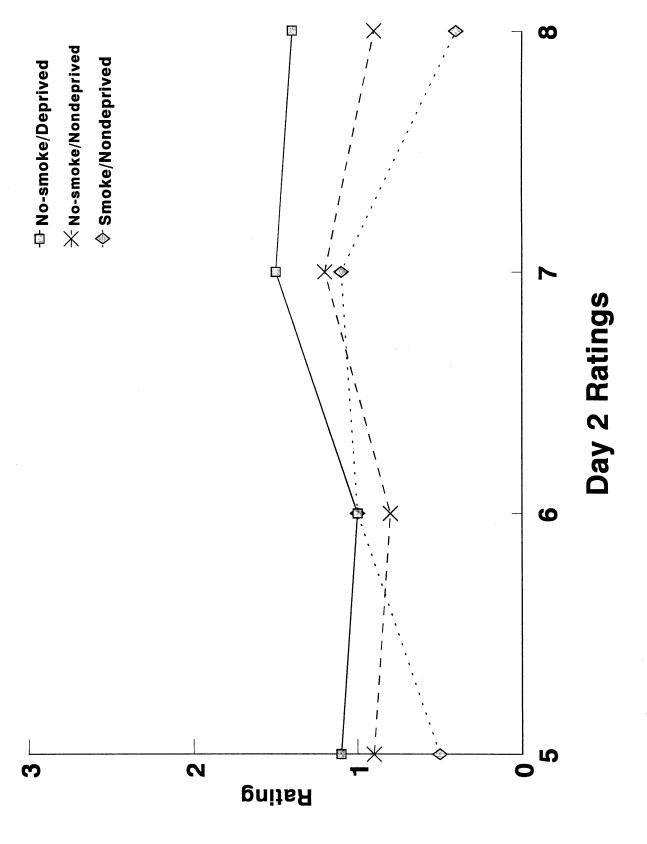
CO-1=pre-manipulation CO-2=post 4 puffs CO-3=post final PAB



TMD7 = pre-manipulation TMD8 = post-manipulation



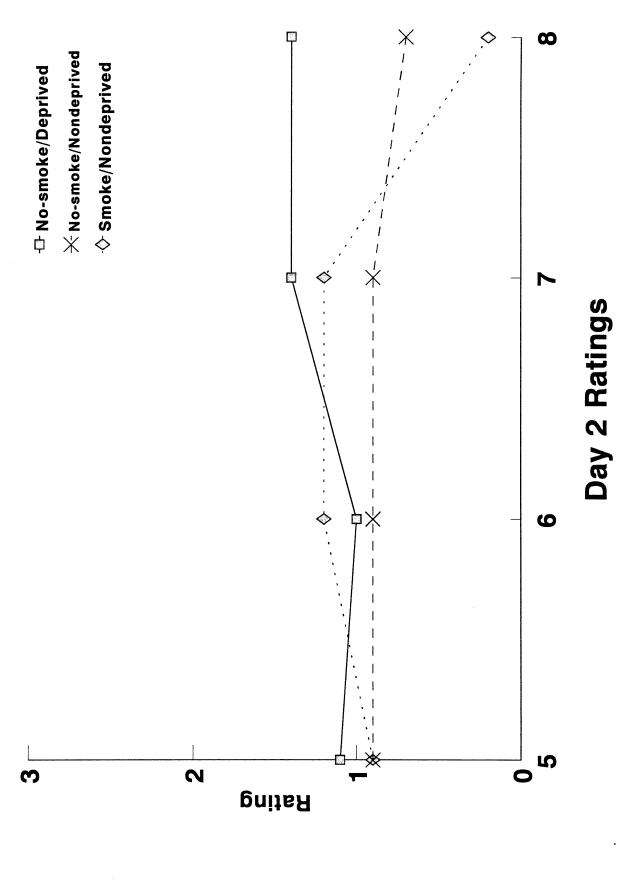
7 = pre-manipulation 8 = post-manipulation



= pre-manipulation

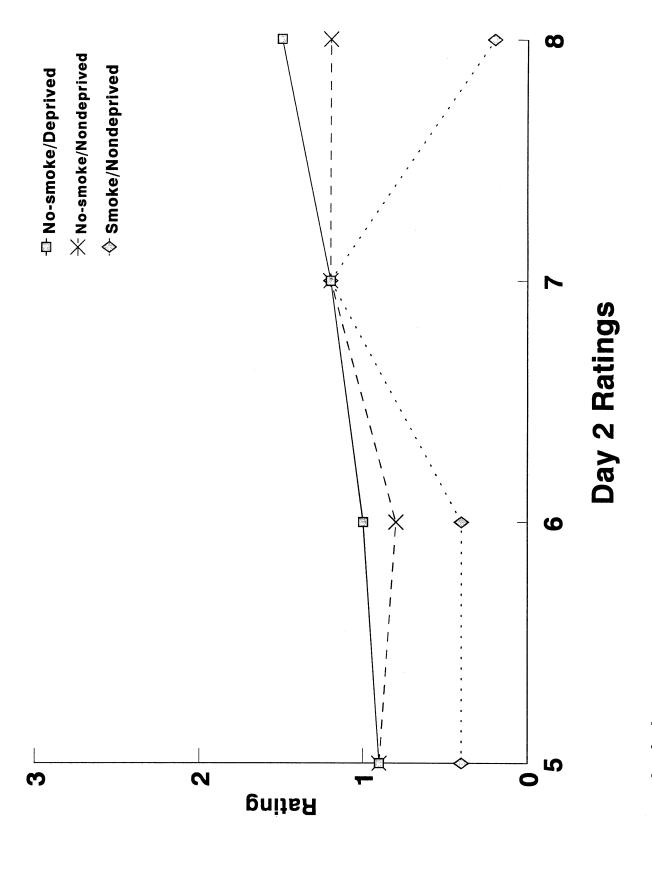
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8 = post-manipulation

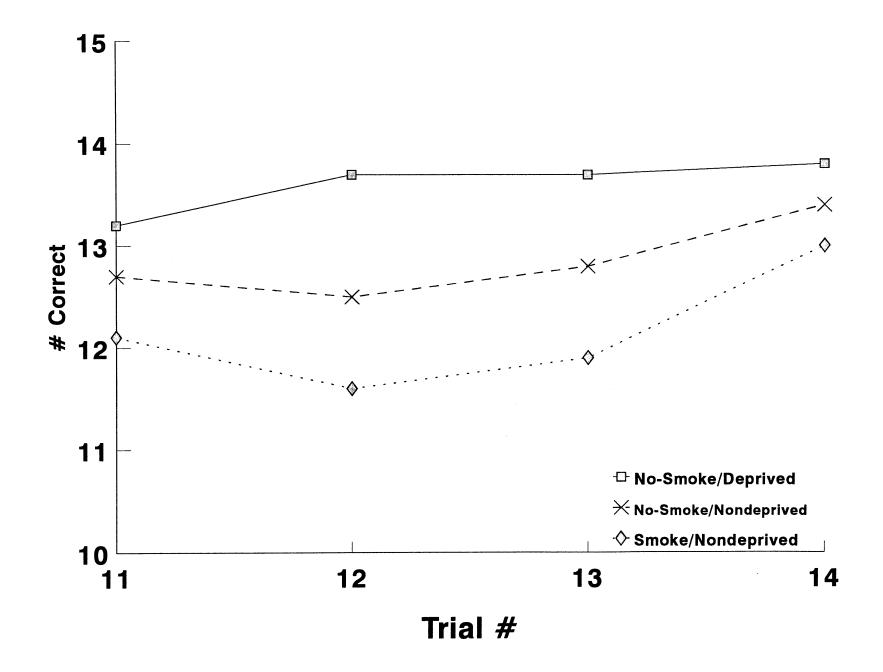


7 = pre-manipulation 8 = post-manipulation

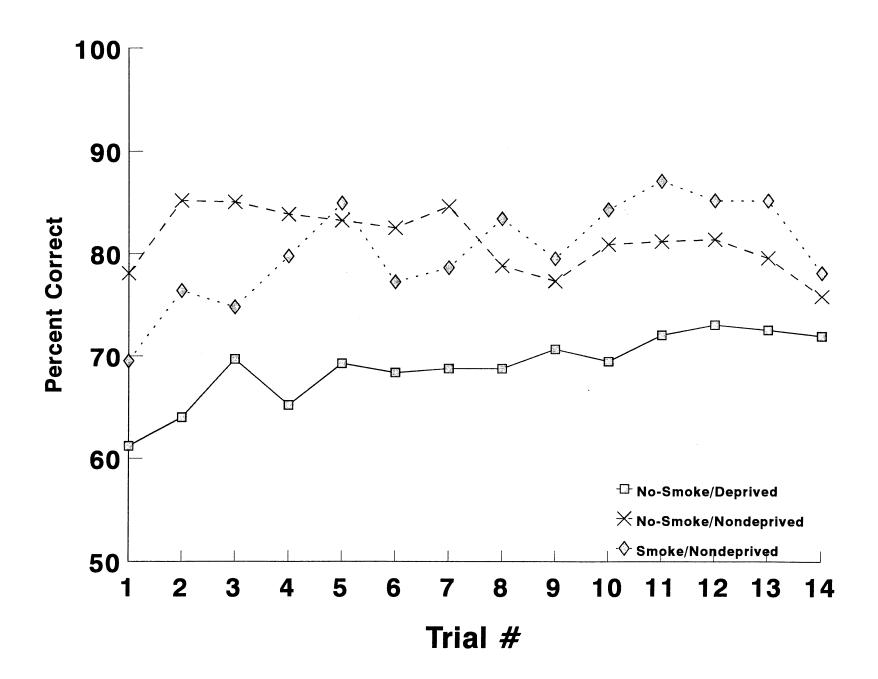
post-manipulation



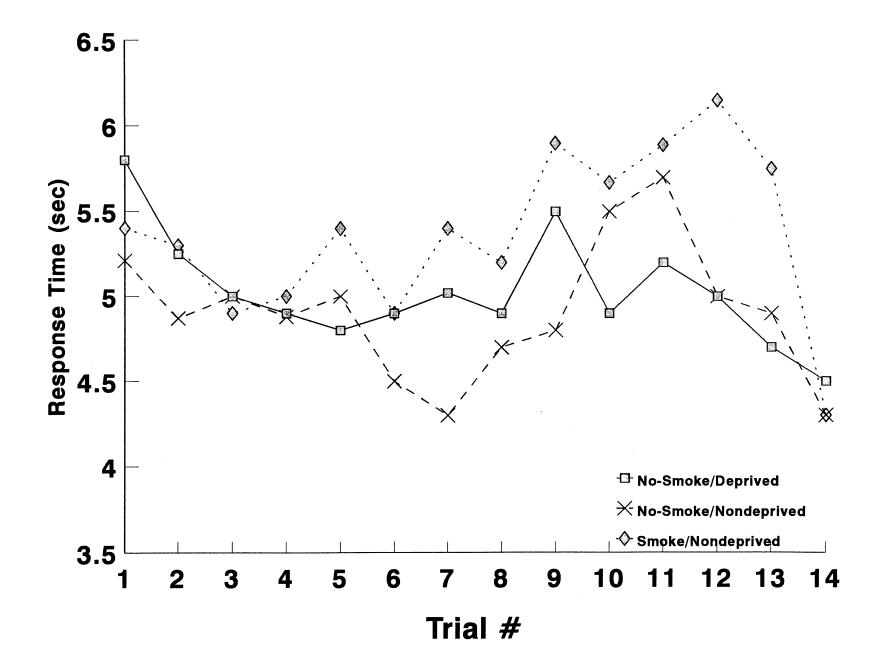
7 = pre-manipulation 8 = post-manipulation



Last 4 trials Day 2



All trials



All trials

VITA

2

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Doctor of Philosophy

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