Performance-Based Testing for Drugs of Abuse: Dose and Time Profiles of Marijuana, Amphetamine, Alcohol, and Diazepam

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Abstract

The time courses of the effects of acute doses of amphetamine (5 and 10 mg/70 kg), alcohol (0.3 and 0.6 g/kg), diazepam (5 and 10 mg/70 kg), and marijuana (2.0% and 3.5% Δ9-THC) on performance engendered by each of four computerized behavioral tasks were evaluated in six human subjects. These performance-based tasks have potential commercial utility for drug-use detection in the workplace. Alcohol and marijuana effects were reliably detected for up to three hours following dose administration with most procedures. Amphetamine and diazepam effects were also detected, but the dose effects and time courses were variable. The profile of behavioral effects varied across drugs, suggesting that performance-based testing procedures might be useful in discriminating which drug was administered and the time course of the drug’s effects. Results indicate that repeated measurement with performance-based drug detection procedures can provide immediate indications of performance impairment in a cost-effective and noninvasive manner and, as such, would be a useful supplement to biological sample testing for drug-use detection.

Introduction

Testing for evidence of drug use by the workforce has escalated in the past decade. Reasons for workforce testing include preemployment screening, promotion decisions, and efforts to reduce workforce drug use, increase safety and productivity, limit illegal activity, foster public trust, and comply with federal regulations (1,2). The ability to accomplish these objectives would be enhanced if procedures for accurate detection of both drug use and performance decrements were available in the workplace.

Biological sample testing (particularly urine) has emerged as the most common method of drug testing in the workplace. Standards for ensuring accurate drug-use detection with sample testing have been established (3–6), making this an effective procedure for drug-use evaluation. However, biological sample testing procedures have limitations which hamper their effectiveness, including problems of legality (7,8), their inability to accurately detect or predict behavioral impairment (8,9), their inconvenience, and the amount of time required for sample analysis. Performance-based detection procedures, designed to measure behavioral impairment, are not subject to the same limitations as biological sample testing and have been identified as a possible supplement to biological sample testing (10). Performance-based tests can provide immediate feedback about drug-induced impairment and, as such, can serve as an objective indicator for biological sample testing. However, a significant limitation of performance-based detection procedures is their lack of reliability and validity (11). The main purpose of this study was to investigate the sensitivity of behavior engendered by performance-based detection procedures to drug effects.

Practical issues must be considered in the selection of performance-based drug-detection procedures for commercial application. Such procedures should (a) require minimal training and practice, (b) require minimal time and cost to administer, (c) generate stable performance over unlimited observations, and (d) engender behavior that is sensitive to a variety of drugs. Four procedures that satisfy the initial three criteria were selected for drug testing. Two of the procedures were being developed or were in use in commercial settings for the detection of behavioral impairment, and two were selected from a multitude of laboratory performance tasks that had been reported to be sensitive to a range of drugs.

Given the administration of a sufficiently large drug dose, many dimensions of performance will be altered. However, a practical performance-based drug-detection procedure must also be sensitive to the drug doses typically used by the general population. As such, clinical doses of d-amphetamine (AMPH) and diazepam (DZP), as well as commonly used doses of marijuana (MJ) and ethanol (ETOH), were tested. These drugs are representative of the classes of drugs that are most often detected in urine samples collected from the workforce (12).

Methods

Subjects

Six adult male volunteers reporting occasional alcohol and marijuana use received medical and psychiatric examinations, provided written consent, and participated in 13 4.5-h sessions...
over a three-week interval. Table I presents subject characteristics and drug-use patterns. Subjects agreed to abstain from drug use, other than alcohol, caffeine, and nicotine, during the study and received financial compensation, consisting of a per diem ($10), daily task earnings (approximately $9), and bonuses for compliance ($20/session for promptness; $20/session for drug-free urine and breath samples, excluding drug given during the study) and study completion ($200). The study was approved by The Johns Hopkins University School of Medicine Joint Committee on Clinical Investigation.

**Apparatus**

Performance tasks were completed in private chambers equipped with both Apple IIe® and IBM PC® computers. Pupilometry was completed in a common area using a Pupilscreen® (Applied Science Laboratories, Waltham, MA).

**Procedure**

Subjects arrived for daily sessions at 9:00, delivered breath and urine samples, and completed the first of five daily assessment sessions presented once per hour. A variety of noncaffeinated beverages were available throughout the day, but no solid food was permitted. Urine samples were analyzed with fluorescence polarization immunoassays. Each assessment session required approximately 21 min to complete and included the Multiple-Performance Assessment Battery (MPB, approximately 10 min), the Alluisi task (5 min), the Number Recall task, (NR, approximately 3 min), and a minimum of three pupil scans (approximately 3 min). The first hourly session provided a daily pre-drug baseline, and subjects rested between sessions.

**MPB**

The MPB (NTI, Inc., Dayton, OH) consisted of the simultaneous presentation of spatial-orientation (left half of CRT) and number-recognition (right half of CRT) trials on a computer monitor. Only one task was operative during each trial. A symbol at the bottom of the monitor indicated which task was active, and subjects were required to complete the active task, ignoring the inactive task, on each trial. The battery consisted of 150 trials, and each task was active on approximately 50% of the trials.

**Spatial orientation.** During each trial, one of six standard-sized letters or numbers (G, J, R, 2, 5, or 7), rotated 0, 90, 180, or 270 degrees, was displayed normally or as a reverse, or mirror image. On active trials, subjects were required to respond as quickly as possible on each trial by pressing one of two keys based on whether the figure was normal or a mirror image, regardless of its orientation. Each key was correct on 50% of the active trials.

**Number recognition.** During each trial, two random numbers between zero and nine were displayed, one above the other. Subjects were instructed to respond on each trial by pressing one of two keys as quickly as possible based on whether the top number was the same as or different than the bottom number during the previously active trial. Each key was correct on 50% of the active trials.

Reaction time and accuracy were analyzed as a function of trial type (left or right) and previous trial type (whether a transition from one task to another was required). Subjects were paid 1 cent per correct trial.

**Alluisi**

The Alluisi battery consisted of the simultaneous presentation of four tasks on the computer monitor for 5 min (13). In contrast to the MPB, all four tasks were continuously operative, and performance produced immediate changes on a point counter displayed at the bottom center of the monitor.

**Math task.** Three three-digit numbers were displayed horizontally in the middle of the monitor. Subjects were required to add the first two numbers, subtract the third, and type in the result on the keyboard. Eight sets of numbers were presented during the 5-min battery. Three points were added to a counter displayed at the bottom of the screen for each correct answer (maximum of 24 points from this task during the battery). No changes occurred following incorrect responses.

**Dial task.** Four six-column dials were displayed in the upper left corner of the monitor, each with an asterisk moving along the base of the columns. Normally, the asterisks moved without bias under the columns in each dial. However, intermittently, a position bias occurred such that an asterisk remained predominantly under the left or right half of the columns in a dial. Any of the four dials could display a position bias at any time. One point was added to the point counter if a response was made on the key corresponding to the dial in which a position bias was occurring, and a point was subtracted for each false alarm (i.e., key press in the absence of an appropriate stimulus condition).

**X task.** An “X” alternated in a regular fashion between two vertically-stacked boxes displayed in the lower left corner of the monitor. At random intervals, the “X” stopped alternating. A point was added to the counter for each response on the appropriate key when the “X” stopped moving, and a point was subtracted for a false alarm.

**G task.** A “G” typically remained motionless in the upper box of two vertically stacked boxes displayed in the lower right corner of the monitor. At random intervals, the “G” was replaced with an “R” in the lower box. A point was added to the counter for responses on the appropriate key when the “R” was displayed, and a point was subtracted for a false alarm.

The total number of points and number of correct math trials completed during the math task were analyzed, as were the frequency of correct responses, missed opportunities, and false alarms during the dial task. The latter three measurements were also pooled across tasks and analyzed. Subjects received 1 cent per point.

**Table I. Subject Characteristics**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Cigarettes (number per day)</th>
<th>Ethanol (occasions per month)</th>
<th>Marijuana (occasions per month)</th>
<th>Cocaine (occasions per month)</th>
</tr>
</thead>
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<td>180</td>
<td>73</td>
<td>8</td>
<td>16</td>
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<td>168</td>
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<td>10</td>
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<td>21</td>
<td>14</td>
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</tr>
</tbody>
</table>

**NR**

The NR task (14) consisted of ten trials, each signaled by a computer-generated tone. During each trial, an eight-digit number was displayed on the screen for 3 s. No duplicate numbers were presented on any trial. Immediately after the display, subjects were required to type the eight digits in the same
order as displayed. Time to complete trials, as well as the number of correct digits, inversions (displayed digits typed in an incorrect order), and intrusions (typed digits that were never displayed), were analyzed. Subjects were paid 1 cent per correct trial.

Pupilometry
Dynamic change in right pupil diameter following a 0.3-s light flash (565-nm peak wavelength, 3-ft-candle intensity) was measured 20 times per second (880-nm peak infrared wavelength, with intensity adjusted based on eye color to maximize measurement accuracy) over a 3-s interval. Subjects centered their gaze on a standardized object in the scanner (ambient light was eliminated) and initiated a trial by releasing a button. Trials were completed until three continuous curves (without blinks or eye movements) were obtained. Initial, minimal, and final pupil diameter, constriction and dilation velocities (slope of best-fit lines representing diameters measured during constriction, 0.3 to 0.5 s after light flash, and dilation, 1.1 to 1.5 s after light flash), and response amplitude were analyzed.

Drug administration
Drug was administered during a 10-min interval immediately preceding the second trial of each session (following a minimum of 50 min of food deprivation). Subjects consumed a beverage, consisting of 16 oz of a 75% cranberry–apple drink, 25% tonic-water solution containing placebo, AMPH (5 and 10 mg/70 kg, Dexedrine®), DZP (5 and 10 mg/70 kg, Diazepam Oral Solution®), or ETOH (0.3 and 0.6 g/kg, 95% ethanol), during a 5-min interval, and smoked a 1-g MJ cigarette (0, 2.0, or 3.5% Ag-THC, w/w, provided by the National Institute on Drug Abuse) during the interval, and smoked a 1-g MJ cigarette (0, 2.0, or 3.5% Δ9-THC, w/w, provided by the National Institute on Drug Abuse) during the remaining 5 min. Placebo beverages contained 2 mL of 95% ETOH floated on top. Five puffs (one per minute) were taken on the marijuana cigarette. The topography of each puff was controlled using a series of lights that signaled a 5-s inhalation, 10-s breathhold, and 45-s rest sequence, according to a procedure established in previous studies (15). The procedure typically resulted in the pyrolysis of the entire cigarette.

Doses were administered according to four randomized 3-day blocks. Subjects received each dose on one day, and no more than one active dose was administered per day. Placebo was administered on day 1, and drug blocks were presented on days 2 through 13. Subjects received placebo and both active doses of a given drug in a counterbalanced order within a 3-day block, and order of exposure to drug blocks was varied across subjects.

The doses were selected to sample the range typically used for therapeutic purposes or available for nonmedical purposes; no effort was made to equate these drugs for potency on any index. Subjects were informed prior to the start of the study that they would receive marijuana, alcohol, stimulants, and sedatives during the study, but were given no indication of the order in which the drugs would be administered.

Training
Prior to the start of the study, subjects received training and repeatedly practiced the tasks until no systematic changes were observed over ten consecutive trials on each task.

Data analysis
The purpose of this study was to determine whether performance on a given task was sensitive to the effects of a drug during a 3-h interval following dose administration. The null hypothesis that the results of a given trial on active drug days were not different from those of the corresponding trials following placebo administration were tested using planned comparisons. The results of a given trial on active drug days were compared with pooled results from the corresponding trials on placebo days (excluding day 1). Separate analyses were completed for each drug, trial, and dose (F[1,120]). Results were considered significant at p<0.05, and significant results were displayed graphically. Between-drug comparisons were not conducted because doses were not equated for potency prior to the study.

Results
Marijuana
MPB. The left column of Figure 1 presents THC effects on performance of the MPB task. Reaction time for the orientation and recognition trials is displayed in panels A and B, and accuracy for these two trials is displayed in panels C and D. A small but significant (F=4.78, p<0.05) decrease in reaction time for the spatial orientation task (panel A) was observed during baseline on the lower dose (2.0% THC) day. The lower dose decreased accuracy on the spatial orientation task (panel C) immediately following drug administration, and the effect dissipated by one hour after drug administration. The higher dose (3.5% THC) increased reaction time and decreased accuracy on the number-recognition task for up to one hour (panels B and D), and on the orientation task one hour after administration (panels A and C). Accuracy remained decreased on the orientation task (panel C) for up to three hours following drug administration.

Alluisi. The middle column of Figure 1 presents THC’s effects on performance of the Alluisi task. As displayed in panel E, the number of points earned during the 5-min task was decreased in a dose-related manner immediately following drug administration, and the magnitude of drug effect decreased across trials. Significant changes in point earnings were observed for up to two hours following the lower dose, and for up to one hour following the higher dose. Similar patterns of performance decrements were observed for correct math trials (panel G). As with points and math trials, the magnitude of the drug effect on missed dial signals (panel F) decreased across trials, with significant changes observed for up to one hour following the lower dose, and for up to two hours following the higher dose. A similar pattern was observed for total missed signals (data not presented).

NR. The right column of Figure 1 presents THC effects on performance of the NR task. As with the Alluisi task, dose-related changes in several dimensions of performance, including correct digit recall (panel H), time to complete trials (panel I), intrusions (panel J), and inversions (panel K), were observed immediately following drug administration, with the magnitude of the drug effect decreasing across trials. Following high dose administration, significant changes in the number of correct digits (panel H) and intrusions (panel J) were observed up to three hours following drug administration.

Pupilometry. Figure 2 presents THC effects on pupil response to a brief light flash. Dose-related decreases in the amplitude of the constriction response (panel A), as well as pupil constriction (panel B) and dilation (panel C) velocities, were observed immediately following drug administration, with peak effects observed one hour later. The magnitude of the drug effect decreased across trials, but significant changes were still observed three
Figure 1. Marijuana. Mean performance effects on the Multiple Performance Battery (MPB) and the Alluisi and Number Recall tasks as a function of time following THC administration in smoked marijuana cigarettes. Spatial-orientation trial reaction time (panel A) and accuracy (panel C) and Number Recognition trial reaction time (panel B) and accuracy (panel D) during the Multiple Performance Battery are displayed in the left column. Total points earned during the 5-min test interval (panel E), missed dial-task signals (panel F), and correct math trials (panel G) during the Alluisi task are displayed in the middle column. Number of correct digits recalled (panel H), mean time to complete trials (panel I), intrusions (panel J), and inversions (panel K) during the Number Recall task are displayed in the right column. Filled symbols represent data points that are significantly different from placebo ($p<0.05$), and error bars represent $\pm 1 SE$. 
hours later. A different pattern of results was obtained with pupil diameter (right column). The magnitude of marijuana's effects were small (minimum diameter, panel E) or absent (initial and final diameters, panels D and F) immediately following drug administration but increased across trials. Significant increases in initial and final pupil diameters were not obtained until two or three hours later.

Alcohol

MPB. The left column of Figure 3 presents alcohol's effects on MPB task performance. Small increases in reaction time on both the spatial orientation (panel A) and number recognition (panel B) trials were observed three hours after lower dose (0.30 g/kg) administration. Dose-related decreases were observed in accuracy on the spatial-orientation task (panel C) one hour following drug administration.

Alluisi. On the dial task, three hours following higher dose (0.60 g/kg) administration, false alarms increased significantly to 4.68 ± 1.29 (mean ± SEM) from 2.71 ± 0.47 on placebo days (F=7.41, p<0.01). Two hours after administration, total false alarms decreased to 2.66 ± 1.86 from 4.83 ± 0.75 on placebo days (F=5.53, p<0.05). No other significant alcohol effects were observed on performance of this task.

NR. No significant changes in performance of the NR task were observed following alcohol administration.

Pupillometry. The right column of Figure 3 presents alcohol's effects on pupil response to a brief light flash. A complex pattern of results was obtained. Immediately following higher dose administration, initial (panel D), minimum (panel E), and final (panel F) pupil diameters were increased. However, no changes in constriction or dilation velocity were observed, indicating a shift in diameter baseline, rather than a change in the reflexive response to light. In contrast, one to two hours following lower and higher dose administration, initial, minimum, and final pupil diameters were significantly decreased. Dilation velocity was also decreased one hour following higher dose administration (panel G), indicating a change in both resting pupil diameter and reflex response.

Amphetamine

MPB. No significant changes in performance of the MPB task were observed following amphetamine administration.

Alluisi. Three hours following higher dose (10 mg/70 kg) administration, total points were increased to 36.83 ± 3.03 from 31.75 ± 1.41 on placebo days (F=5.21, p<0.05). No other significant changes in performance of the Alluisi task were observed following amphetamine administration.

NR. No significant changes in performance of the NR task were observed following amphetamine administration.

Pupillometry. Figure 4 summarizes amphetamine's effects on pupil response to a brief light flash. Immediately following both lower (5 mg/70 kg) and higher dose administration, initial (panel A) and final (panel C) pupil diameters were increased compared to placebo. The minimum (panel B) pupil diameter was also increased immediately following higher dose administration. However, no changes in constriction or dilation velocity were observed during these trials, indicating a shift in diameter baseline, rather than a change in the reflexive response to light. Two hours after lower dose administration, the constriction amplitude was also decreased to 1.87 ± 0.12 mm from a mean of 1.96 ± 0.05 mm on placebo days (F=7.41, p<0.01).

Diazepam

MPB. The left column of Figure 5 presents diazepam's effects on MPB task performance. An increase in reaction time on recognition trials, which were preceded by spatial-orientation trials (i.e., transition trials, panel A), was observed one hour after lower dose (5 mg/70 kg) administration. An increase in reaction time on spatial-orientation trials was also observed prior to drug administration, preceding lower dose adminis-
Dilation (F=4.29, p<0.05). No other significant changes in MPB-task performance were observed following diazepam administration.

Alluisi. The middle column of Figure 5 presents diazepam's effects on Alluisi-task performance. A significant increase in total points earned per 5-min task (panel B) was observed two hours after lower dose administration, resulting primarily from a significant decrease in the total number of false alarms (panel C). Three hours after lower dose administration, the number of correct dial responses was increased to 9.00 ± 2.00 from 7.54 ± 0.77 on placebo days (F=5.15, p<0.05). No other significant changes in Alluisi-task performance were observed following diazepam administration.

NR. Immediately following lower dose administration, the number of intrusions during the NR task increased to 1.83 ± 1.80 from a mean of 0.33 ± 0.12 on placebo days (F=10.85, p<0.005). No other significant changes in NR-task performance were observed following diazepam administration.

Pupilometry. The right column of Figure 5 presents diazepam's effects on pupil response to a brief light flash. A significant decrease in the initial (panel D) and final (panel E) pupil diameters was observed two hours after higher dose (10 mg/70 kg) administration. Two hours after lower dose administration, the amplitude of pupil response to the light flash was also decreased to 1.85 ± 0.14 mm from a mean of 1.96 ± 0.05 mm on placebo days (F=5.95, p<0.05). No changes in constriction or dilation velocity were observed during these trials, and no other diazepam effects were observed.

Discussion

The present results indicate clearly that performance-based procedures can identify drug-induced behavioral impairment. The effects of amphetamine, marijuana, diazepam, and alcohol on behavior engendered by four performance-based drug detection procedures were investigated. Each of the four procedures was computerized, required minimal training and practice, took less than ten minutes to complete, provided immediate feedback on performance, and generated stable performance over 65 separate tests. The immediacy of the test results obtained in a relatively noninvasive manner offers important advantages that will complement the more commonly used biological sample testing procedures.

Marijuana altered behavior on all four performance-based drug detection procedures, often in a dose-related manner. The potency of the marijuana used in this study (2.0% and 3.5% Δ9-THC) is within the potency levels obtained from marijuana samples confiscated from the general population (16). In general, peak effects were observed immediately or one hour following smoke administration, and diminished across time. Significant effects were observed for up to three hours following dose administration on some measurements, which is consistent with previous reports of the time course of marijuana's effects (17). Given these results, it is likely that testing with any of these performance-based drug detection procedures could be used in workplace settings to identify behavioral impairment resulting from marijuana use.

Alcohol altered behavior generated by the MPB and pupilometry procedures. The doses...
used in the study (0.3 and 0.6 g/kg) were approximately equivalent to 1.5 and 3 commercial cocktails for a 70 kg male; these doses produce effects on human behavior that are relevant for the workplace (18). Peak effects were typically observed one hour following dose administration, and significant effects were observed up to three hours after dosing with the pupillometry procedure. Either task could be used in a commercial setting to detect impairment associated with alcohol use, but since pupillometry measures were sensitive to the effects of alcohol over a longer interval, this procedure might be preferred.

The sensitivity of behavior engendered by these procedures to the effects of diazepam and amphetamine were more variable. Doses used were consistent with those recommended for clinical use (19), and other studies suggest that these doses produce behavioral effects that may be relevant for the workplace (20–22). Laboratory studies, however, indicate that the reinforcing effects of diazepam may be limited to larger doses (23). The lower dose of diazepam produced significant changes in performance of the NR task one hour following administration, and of the Al-lusi task two hours following administration. The higher dose altered pupil diameter two hours following administration. Amphetamine also altered pupil diameter in a dose-related manner immediately after administration, but this time course is not consistent with previous reports of the behavioral effects of amphetamine (24,25). It is not clear that any of these four performance-based procedures would be successful for accurate detection of clinically relevant doses of amphetamine or diazepam. In contrast, accurate detection of the use of therapeutic doses of amphetamine and diazepam was achieved by analyzing urine samples collected from subjects the morning after dose administration in this study. However, the inability of biological sample detection procedures to accurately discriminate between therapeutic and larger-than therapeutic dose consumption may be problematic (9,26). If additional research indicates that performance-based detection procedures can be used to discriminate between these dose levels, further support for the complementary status of biological and performance-based testing procedures would be provided.

The drug doses tested in this study were representative of those used for therapeutic purposes (amphetamine, diazepam) or available through licit or illicit sources (alcohol, marijuana). No attempt was made to equate the drugs based on behavioral potency, and no cross-drug comparisons of pharmacological profiles were attempted. In addition, no attempt was made to select performance-based testing procedures that would predict workplace-relevant changes in behavior. One should not assume, based on the results of this study, that abuse liability in the workplace is different across these drugs.

Multiple dependent measurements were obtained from each performance-based drug detection procedure. These measurements were not equally sensitive to drug effects and showed different time courses. The profiles of drug effects across measurements were different among drugs. For example, during pupillometry, alcohol decreased resting pupil diameter and increased dilation velocity, while diazepam decreased pupil diameter without changing velocity. Marijuana, on the other hand, increased resting pupil diameter and decreased dilation velocity. Profiles of drug effects on multiple measurements could also be used to evaluate time since drug use. For example, immediately following marijuana administration, pupil dilation velocities were decreased, but resting diameters were not changed. In contrast, three hours after smoking marijuana, dilation velocity was near baseline, but a significant increase in pupil diameter was apparent. Additional research would be required to ensure that these profile differences were consistent across a wider range of doses.

Jaffe (11) has argued that the reduction of illicit drug use by the workforce is a sufficient justification for the use of testing procedures. In the current study, drug consumption was accurately

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**Figure 4.** Amphetamine. Mean performance effects during Pupilometry as a function of time following amphetamine administration. Initial (panel A), minimum (panel B), and final (panel C) pupil diameters are presented. Filled symbols represent data points that are significantly different from placebo (p<0.05), and error bars represent ± 1 SE.
Figure 5. Diazepam. Mean performance effects during the Multiple Performance Battery (MPB), the Alluisi task, and Pupilometry as a function of time following diazepam administration. Number Recognition reaction time on transition trials (panel A) during the Multiple Performance Battery are displayed in the left column. Total points earned during the 5-min test interval (panel B) and total false alarms (panel C) during the Alluisi task are displayed in the middle column. Initial (panel D) and final (panel E) pupil diameters are presented in the right column. Filled symbols represent data points that are significantly different from placebo ($p<0.05$), and error bars represent $\pm 1$ SE.

Acknowledgments

This research was supported by grants DA-03476 from the National Institute on Drug Abuse and AA-07302 from the National Institute on Alcohol Abuse and Alcoholism. The assistance of Jerry Locklee, Lisa King, Emily Serpick, and Michelle Woodland are gratefully acknowledged. The Pupilscreen was loaned by Applied Science Laboratories, and software to run the MPB was provided by NTI, Inc.
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Manuscript received March 24, 1992; revision received February 16, 1993.