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The Effects of Repeated Amphetamine Exposure on Multiple Measures of Human Behavior

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KELLY, T H , R W FOLTIN AND M W FISCHMAN *The effects of repeated amphetamine exposure on multiple measures of human behavior* PHARMACOL BIOCHEM BEHAV **38**(2) 417–426, 1991 —Two groups of three healthy adult male volunteers (n = 6) participated in 15-day residential studies Each study day was divided into a private work period (1000 to 1630), during which subjects had access to four work tasks, and a social period (1700 to 2330), during which subjects had access to a number of recreational activities available under social or private conditions Occasionally during the study, access to high-probability activities was made contingent upon participating in low-probability activities Tobacco cigarettes and food were available throughout each day (0900 to 2330) Each subject received active and placebo d-amphetamine doses (0 or 10 mg/70 kg) twice daily during two, three-consecutive-day intervals Active and placebo dose intervals were presented in an alternating fashion, with order of exposure counterbalanced between groups Amphetamine consistently decreased food intake, improved accuracy of performance on some work tasks, and increased verbal interaction and cigarette smoking No tolerance to these effects was observed Increases in VAS ratings of dose "potency" and "liking," as well as "stimulated" and "anxious," and decreases in "sedated" were observed during initial amphetamine exposure, but tolerance to these effects developed rapidly The simultaneous measurement of multiple dimensions of human behavior establishes a profile of amphetamine's effects which is useful for comparison with the behavioral profiles of other drugs, such as marijuana

d-Amphetamine Residential laboratory Human Cigarette smoking Social behavior Performance Food intake Motivation Subjective effects

AMPHETAMINE produces a variety of behavioral effects in humans, including anorectic effects [e g., (2,28)], performance enhancement (32), and changes in social behavior [e.g., (7–9, 18, 20, 22, 31)] and tobacco cigarette smoking (4,21). In addition, amphetamine produces a consistent pattern of interoceptive stimulus effects, as indicated by verbal reports of drug effects [e g , (23)], and the drug functions as a reinforcer in normal volunteers [e.g , (23)] While it is clear that amphetamine affects a variety of measures of human performance, it is unclear whether there are differences in sensitivity to the effects of amphetamine across these various dimensions There have been reports that amphetamine reduces food intake at doses that have minimal effect on other dimensions of human behavior [e.g., (11)]; however, few studies have collected measures of the effects of amphetamine on more than a small sample of behaviors, and comparisons of amphetamine's effects on multiple behavioral dimensions across studies are complicated by procedural differences across studies and by individual-subject differences in response to amphetamine within studies [e.g., (9,23)].

In the present study, a dose of d-amphetamine known to reduce food intake (10 mg, b.i d.) was administered to six subjects in a residential laboratory. The effects of amphetamine on a variety of measures, in addition to food intake, were collected to determine amphetamine's behavioral profile at a dose with known anorectic potency. This profile was then compared with that produced under similar conditions by a different pharmacological agent, smoked marijuana, in order to assess the specificity of this profile.

METHOD

Subjects

Six volunteers, between 21 and 38 years of age, each passed medical and psychiatric examinations and signed consent forms prior to participating in a 15-day residential study. Table 1 presents the subject characteristics Four were tobacco cigarette smok-

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TABLE 1

SUBJECT AGE AND VERBAL REPORTS OF FREQUENCY OF DRUG USE

Subject	Age	Cigarettes	Ethanol	Marijuana	Cocaine	Heroin
S1	38	20/D	2/W	4/W	1/W	1/W
S2	21	5/D		2/W		
S3	28	30/D		5/W		
S4	27		2/W	2/W		
S5	21	15/D	2/M	2/M	2/M	
S6	32		3/W			

D Day, W Week, M Month

ers who continued to smoke throughout the study, and all reported occasional drug use.

Laboratory

The study was completed in a residential laboratory designed for the continuous observation and analysis of human behavior over extended time periods (3). The residential facility consisted of six rooms interconnected by a single hallway. Three identical rooms, each equipped with a kitchen, bathroom, desk, and bed, functioned as private apartments, and each subject was assigned to a specific room. Subjects were not allowed to enter the other private rooms. Access to the remaining three social rooms, including a recreation room, containing kitchen facilities, lounge furniture, a videogame system, board games and a television used for displaying videotaped movies; an exercise room, equipped with exercise and laundry facilities; and a bathroom, were available to all three subjects at programmed times

Output from video and audio equipment located throughout the residential facility terminated in an adjacent control room. Subjects were continuously monitored except while in private dressing and bathroom areas. A computerized observation program (1) provided the structure for continuous recording of each subject's behavior in categorical form All communications between subjects and experimenters occurred over a networked computer system Computer terminals were located in each private room and in the recreation room, as well as in the control room. Communications between subjects and experimenters were limited to the reporting of food consumption and protocol compliance. No other communication was permitted, and, to limit the potential effects of external events on behavior, telephones, television, newspapers, and mail were not available. No clocks or watches were available, but subjects received time prompts via the computerized communication system when activity changes occurred.

Food

Each morning, all subjects received a box of food items, including a variety of snack and sandwich items, such as bread, meat, cheese, tuna, beverages, candy, fruit, cakes, cookies and chips A list of frozen food items was displayed near each private terminal, and subjects could also request meals, such as spaghetti, chicken, and pizza. Food items were available from 0900 to 2330, and intake was restricted only by the requirement that items be reported via the communication system immediately prior to consumption. Details of food consumption monitoring have been described previously (17)

Tobacco Cigarette Smoking

Each room in the facility, with the exception of the bathrooms, was equipped with pressure sensors connected to color-coded plastic cigarette holders with PVC tubing. Subjects were each assigned a specific color and required to smoke all tobacco cigarettes through appropriately colored cigarette holders. The pressure sensors provided electrical signals for the duration of each puff. Output from the sensors was timed and recorded by a computer and generated tones in the adjacent control room to allow the experimenters to monitor compliance with the smoking system. Subjects could smoke tobacco cigarettes anywhere in the facility, except in bathroom areas. Subjects had no access to matches, and all cigarette lighters were under camera surveillance for additional insurance of compliance with the smoking procedures. Subjects had access to their preferred brands of tobacco cigarettes and were allowed to smoke ad lib from 0900 to 2330 As a safety precaution, smoking was prohibited during sleeping hours, and lighters were removed during this interval Additional details concerning the smoking procedures are available elsewhere (26).

Recording the beginning and end of successive puffs provided a variety of measures of tobacco cigarette smoking topography, including puff bouts per day, puffs per bout, puff duration and interpuff interval. Interpuff intervals greater than five minutes defined the boundaries of individual puff bouts. Puff bouts usually, but not always, coincided with individual cigarettes Puffs separated by interpuff intervals shorter than 0.2 seconds were combined into single puffs measured from the start of the initial puff to the end of the subsequent puff.

Drug Administration

d-Amphetamine elixir (Dexedrine®, 1 mg/ml of d-amphetamine in a 10% ethanol solution, Smith, Kline & French, Philadelphia, PA) was added to 177 ml of concord grape juice (Welch Foods, Inc., Concord, MA) to produce doses of 10 mg/70 kg body weight. Placebo beverages consisted of 10 ml of 6% ethanol concord grape wine (Manischewitz, Naples, NY) added to the grape juice. At 0930 and 1630, subjects attached finger plethysmographs (Model No. 77066, Lafayette Instrument Co., Lafayette, IN) to their index fingers and were instructed to sit quietly at their desks for ten minutes Assuming heart rate was stable and less than 90 beats per minute, subjects were then instructed to consume the entire beverage as quickly as possible No doses were withheld due to heart-rate considerations. Subjects received two doses per day, at 0930 and 1630, and both doses were either active or placebo All three subjects in a group received the same doses each day Placebo was substituted for the 1630 active dose on day 9 for S5, due to his reports of GI discomfort.

The two groups differed in that they received active doses in a counterbalanced order. No doses were administered to either group on day 1. Group 1 received active doses on days 5–7 and 11–13, and placebo on the remaining days. Group 2 received active doses on days 2–4 and 8–10 and placebo on remaining days.

Visual Analog Rating Scale

At 2330, each subject completed a rating scale consisting of six visual-analog scale (VAS) items ("Liking," "Potency," "High," "Stimulated," "Sedated," and "Anxious") for each dose administered during the day. Subjects were instructed to complete the form based on their overall impression following each dose for each of the six adjectives by placing a mark along a continuum indicated by a 100 mm line anchored with endpoints of "Not at all" on the left and "Extremely" on the right ("Like" and "Dislike" on the "Liking" scale). Items were scored for each dose separately by measuring the distance between the subject's mark and the left endpoint. This rating scale is sensitive to

the effects of stimulants [e.g., (5,12)].

Private Period Activities

Subjects were restricted to their private rooms each day from 1000 to 1630. Four work activities were available: a computerized digit-symbol-substitution task (DSST), a computerized vigilance task, a manual bingo-chip sorting task and a manual nonsense word-sorting task.

The DSST task consisted of nine random three-row by three-column patterns of asterisks and dashes (one asterisk per row) displayed across the top of the screen. The patterns were labeled 1–9 from left to right across the screen, and the label was centered directly below each pattern. A randomly generated number, between one and nine, was displayed in the center of the monitor, indicating which of the nine patterns displayed at the top of the screen should be copied by the subject on a particular trial. During each trial, subjects were required to press only the keys in a three-row by three-column keypad that corresponded to the positions of asterisks in the appropriately labeled pattern. Three responses were required per trial (one response in each row), and a new randomly generated number was displayed in the middle of the screen immediately after each trial. Following the completion of 25 trials, a new random pattern of dashes and asterisks was displayed at the top of the screen. Subjects determined the rate of DSST trial completion, and overall trial and error rates during successive 25 trial sequences were monitored

The vigilance task required subjects to observe a counter located in the middle of the computer screen The counter increased by one or two units once every 1.25 seconds. Subjects were required to press a key whenever the counter increased by two, rather than one, unit. This occurred on a random basis on 10% of the trials. Correct key presses resulted in the presentation of a "HIT" message on the screen. If the key was not pressed within 1.25 seconds after the counter increased by 2 units, a beep was presented and the message, "MISS," was flashed on the screen. A key press occurring when the counter increased by only a single unit resulted in a beep and the message, "FALSE ALARM," presented on the screen. Proportion of hits and number of false alarms were monitored.

Two noncomputerized tasks, a bingo-chip sorting task and a word-sorting task, were also available during the private period. Subjects were provided a container of approximately 7360 plastic bingo chips of varying colors and designs and were instructed to place the chips into separate compartments according to color and design. The rate of chips sorted, without regard for sorting accuracy, was measured. Subjects were also provided with an unlimited supply of 8.5" × 11" sheets of paper containing 33 of 300 randomly generated 7 letter nonsense words, placed in three columns. Each sheet contained a different randomly generated list of words. Subjects were instructed to cut out each individual word and sort it alphabetically. The rate of word sorting was also measured without regard for sorting accuracy.

Social Period Activities

From 1700 to 2330, subjects had access to six recreational activities. They could remain in their private rooms, engaging in one of five private activities (reading, writing, artwork, model building or playing private games). The sixth activity consisted of engaging in any activity in the social area, such as videogames, or exercise.

Social Behavior

Social behavior was monitored during the social-access period. The amount of time under social conditions was determined by measuring the amount of time a subject spent in the social area in the presence of at least one additional subject. Social behavior was further analyzed by determining the proportion of each subject's social time that was spent in verbal interaction with one or more subjects. Verbal interactions were scored beginning with the emission of a verbal response by a subject and continued until 60 seconds elapsed without any additional verbal response (13)

TABLE 2

EXPERIMENTAL DESIGN

Group 1	Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
	Drug	N	P	P	P	A	A	A	P	P	P	A	A	A	P	P
	Condition		BASE 1			BASE 2			CONT 1			CONT 2				
Group 2	Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
	Drug	N	A	A	A	P	P	P	A	A	A	P	P	P	P	P
	Condition		BASE 1			BASE 2			CONT 1			CONT 2				

Drug N = no drug, P = placebo, A = active (10 mg/70 kg, d-amphetamine)

Condition BASE 1 = no restrictions on activities, phase 1, BASE 2 = no restrictions on activities, phase 2, CONT 1 = contingency restriction, as determined during BASE 1, CONT 2 = contingency restriction, as determined during BASE 2

Behavioral Contingencies

At any time during the private-work period, subjects had the option of taking one thirty-minute break. At all other times, subjects were instructed to engage in one of the four work activities. Recreational activities were available throughout the social-access period, but no instructions were required to maintain continuous participation in these activities.

During baseline conditions, the amount of time each subject spent on each activity during the private and social periods was recorded, and behavior probability hierarchies, based on the relative amounts of time subjects allocated to the available activities, were determined. Separate hierarchies were determined during the private and social period. During contingency phases, access to the most probable activity (i e., the activity engaged in most often under baseline conditions) was made contingent on engaging in the least probable activity (the least common activity under baseline conditions). Subjects were required to increase the amount of time spent on the low-probability activity under baseline conditions by a factor of four in order to maintain baseline levels of the amount of time spent on the high-probability activity. For example, if under baseline conditions, 10% of the available time was devoted to the least-probable activity and 60% was devoted to the most-probable activity, then under contingency conditions, a subject would be required to spend 40% of the time on the least probable activity in order to maintain 60% of the time for the most-probable activity.

Table 2 presents the baseline and contingency conditions present during the private and social periods. Baseline and contingency conditions were operative between days 2–7 and 8–13, respectively. These conditions were parallel but independent across the private and social periods

During baseline conditions, subjects were allowed to engage in activities without restriction. Baseline activity patterns were measured separately during days 2–4 and 5–7, corresponding to active and placebo dose conditions. Two contingency conditions, derived from these baseline patterns, were presented on days 8–10 and 11–13. Contingency conditions consisted of making ac-

cess to high-probability activities dependent on engaging in low-probability activities [(e.g., (27)]. High- and low-probability activities were empirically determined during each baseline phase Placebo baseline and contingency conditions occurred during days 2–4 and 8–10, respectively, while baseline and contingency conditions for the active dose occurred during days 5–7 and 11–13, respectively, for Group 1. Conditions were counterbalanced for Group 2. Placebo baseline conditions were operative during days 14 and 15

During contingency conditions, high-probability, or contingent, activities were available unless a red restriction light, located in the social room and in each subject's private room, was illuminated. If a subject engaged in a contingent activity when the restriction light was on, he immediately received a "Restriction is on Credit time is used up." message on his computer. Time earned for the contingent activity accumulated as long as the subject performed the low-probability, or instrumental, activity, and as long as time had been earned, subjects were free to engage in any activity. Subjects were never restricted from engaging in the instrumental or in intermediate-hierarchical activities. The amount of time earned for the contingent activity accumulated over the three days of each contingency condition Each day, at the beginning of both the social and private work periods, subjects received written instructions describing the contingencies in effect for the upcoming period, but no information related to the amount of earned time or number of days remaining in a contingency condition was provided. After the first three-day contingency condition, subjects received the message "This is a new restriction. Credit has been reset to zero" with the period instruction. These contingencies have been described in detail elsewhere (14,15).

Standard Day

The daily schedule was constant throughout the study. Subjects were awakened at 0900 and weighed. Output from the scale was not available to subjects Each subject then received a food container. The first dose was administered at 0930 The private period occurred between 1000 and 1630 At 1630, the second dose was administered. The social period occurred from 1700 until 2330. At 2330, subjects were required to return their unconsumed food and complete the drug-rating scale. Cigarette lighters were also removed. Subjects were restricted to their private rooms between 2330 and 2400, and lights were turned out at 2400

Data Analysis

Measures of tobacco cigarette smoking topography (puff bouts per day, puffs per bout, puff duration and interpuff interval) and social behavior (social time and verbal interaction) were analyzed by using repeated measures analysis of variance (ANOVA) with phase (first vs second exposure), dose (active vs. placebo) and day (1–3) serving as factors A fourth factor, time of dose (a.m. vs. p.m), was included in the analysis of VAS ratings. In addition to phase, dose and day, period of the day (private vs social) and activity (instrumental vs contingent) were included as factors in the analysis of amphetamine effects on allocation of time to activities during baseline and contingency conditions in the private and social periods.

Not all subjects participated on each task every day To determine whether performance on the tasks changed across days, an ANOVA was conducted with phase, dose, and day serving as factors In the absence of any day effects, the daily means of measures of performance on the four tasks were averaged within each drug-phase condition, and the resulting means were analyzed with repeated-measures ANOVA using dose and phase as factors.

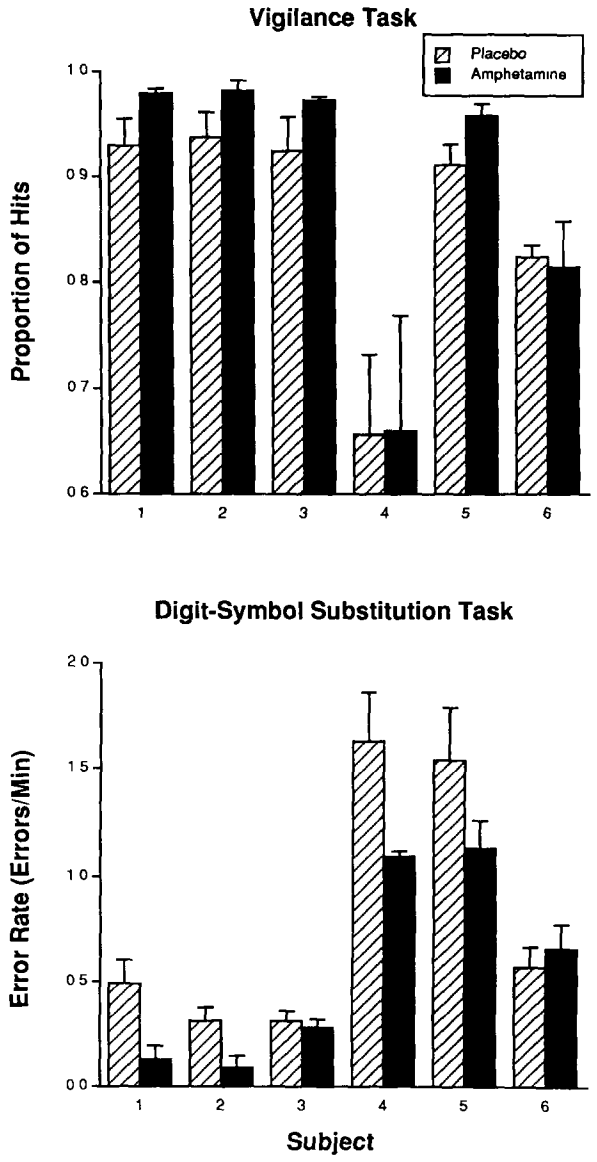

FIG 1 The proportion of the total signals that were correctly identified (hits) during placebo and amphetamine sessions for subjects participating on the vigilance task (top panel), and the rate of incorrect trials during placebo and amphetamine sessions for each subject participating on the digit-symbol substitution task (bottom panel) Error bars represent 1 SEM

RESULTS

Task Performance

Amphetamine administration was associated with improved performance of both computerized tasks. The top panel of Fig. 1 presents the proportion of signals responded to by subjects (i.e., "hits") during the vigilance task. Small but significant improvements in vigilance accuracy were observed following amphet-

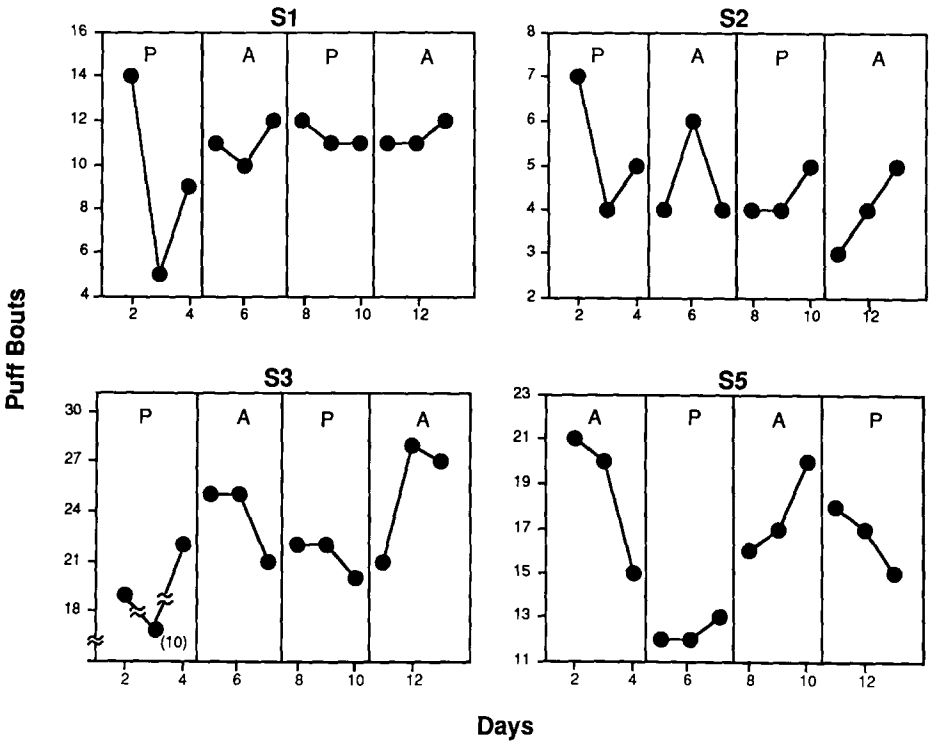

FIG 2 The number of puff bouts over successive sessions in four tobacco cigarette smokers Data from days 2 through 13 are presented Vertical lines represent transition between placebo (P) and amphetamine (A) dose conditions

amine administration, $F(1,5)=8.08$, $p<0.05$ Amphetamine increased accuracy in four of six subjects (S1, S2, S3, S5) Performance also improved across the study, as indicated by a significant phase effect, $F(1,53)=5.00$, $p<0.05$, but there were no interactions between drug and either day or phase. No changes in false alarm rates were observed following amphetamine administration.

The bottom panel of Fig 1 presents the rate of incorrect trials on the DSST task. As with the Vigilance task, amphetamine enhanced performance, as evidenced by a small but significant decrease in error rates, $F(1,5)=6.57$, $p=0.05$. Again, the effect was observed in four of six subjects (S1, S2, S4, S5). Performance remained stable across the study, and no drug interactions were observed Overall trial rate and correct trial rate were not altered by amphetamine. No significant changes in rates of word or disk sorting were observed as a function of phase, drug or day.

Food Intake

Amphetamine significantly decreased food intake along multiple dimensions, including intake from both snacks and meals. These results have been previously reported (17)

Tobacco Cigarette Smoking Topography

Figure 2 presents daily number of puff bouts for each of the four tobacco cigarette smokers Amphetamine increased daily smoking rates in two subjects (S3, S5) and had no effect on smoking rates in the other two subjects Puffs per bout, puff duration and interpuff intervals remained unchanged across drug conditions. No statistically significant amphetamine effects were observed on any topography measure in these four smokers.

Behavioral Contingencies

During the private work period, the contingent activity during both placebo and amphetamine dose conditions was word sorting for S1, S2, S3 and S5, and vigilance for S4. For S6, the contingent activity during the placebo condition was disk sorting and during the amphetamine condition was word sorting. During this period, the instrumental activity during both placebo and amphetamine conditions was disk sorting for S1, S2 and S3, and DSST for S5 For S4, the instrumental activity during the placebo condition was disk sorting and during the amphetamine condition was word sorting For S6, the instrumental activity during the placebo condition was vigilance and during the amphetamine condition was DSST. During the social period, the contingent activity during both placebo and amphetamine conditions was use of the social area for all subjects. The instrumental activity during both placebo and amphetamine conditions was private games for S1 and S2, reading for S3 and S4, and artwork for S5 For S6, the instrumental activity during the placebo condition was private games and during the amphetamine condition was writing

Figure 3 presents the cumulative time allocated to instrumental and contingent activities during three-day baseline and contingent phases for placebo and amphetamine conditions during the private and social periods. Over the entire study, subjects allocated greater amounts of time to contingent activities (bottom two panels) than to instrumental activities [top two panels, $F(1,5)=$

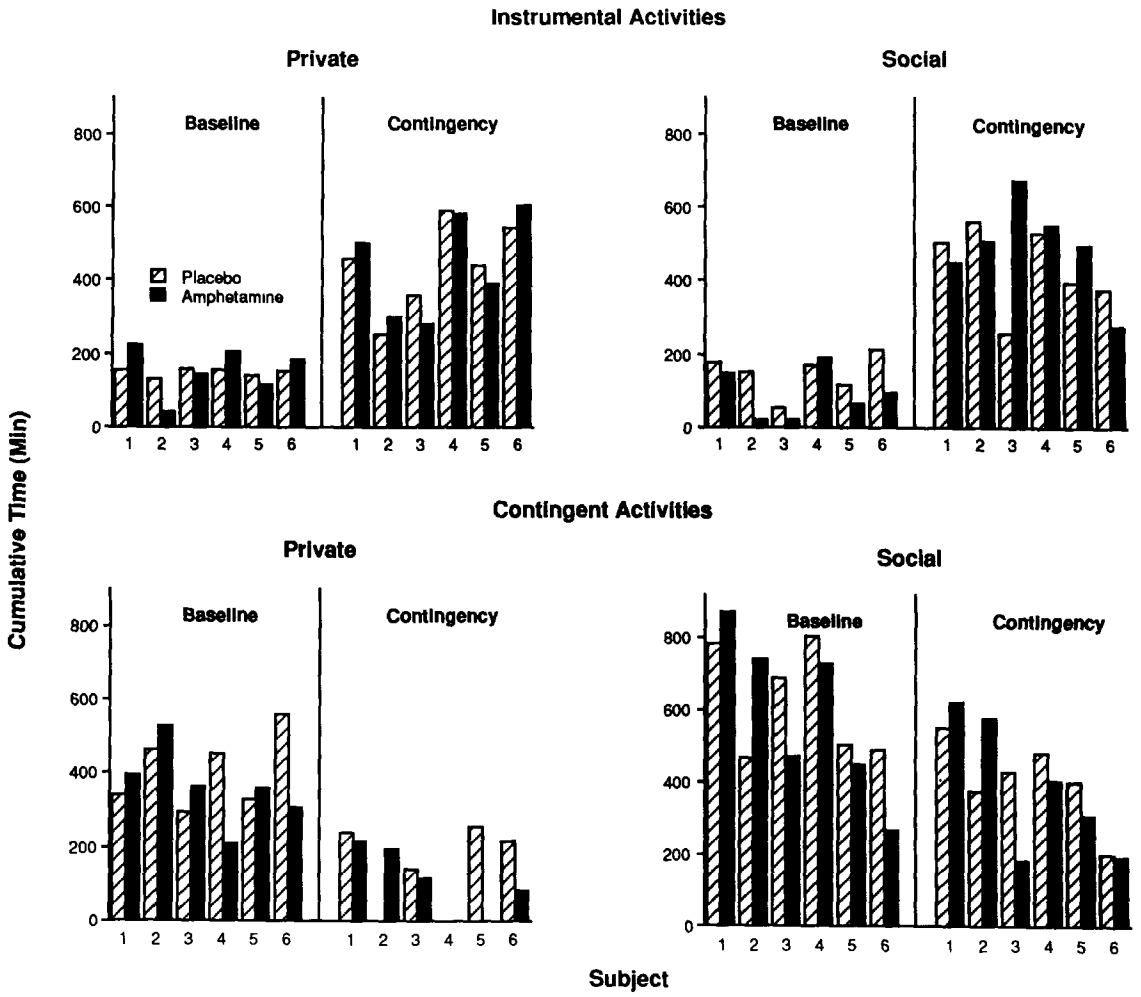

FIG. 3 Total time spent on instrumental (low-probability) and contingent (high-probability) activities during either the private work period (1000 to 1630) or the social period (1700 to 2330) during baseline (days 2–7) and contingency (days 8–13) phases during either placebo or amphetamine administration Each subject received placebo and amphetamine for three consecutive days during both the baseline and contingency phases Each bar represents time on the activity cumulated over a three-day drug interval The upper left panel displays instrumental activities during the private period. The lower left panel displays contingent activities during the private period The upper right panel displays instrumental activities during the social period, and the lower right panel displays contingent activities during the social period Activities are identified in the text

6.33, $p=0.05$]. Subjects allocated significantly more time to instrumental and contingent activities, combined, during the social period (right two panels) than during the private period [left two panels, $F(1,5)=7.93$, $p<0.05$]. In addition, subjects allocated significantly more time to both the instrumental and contingent activities, combined, during the contingency phase (right half of each panel) than during the baseline phase [left half of each panel, $F(1,5)=23.06$, $p<0.005$]. Allocation of time to instrumental activities was similar during private and social periods (top two panels), but significantly greater amounts of time were allocated to the contingent activities during the social period (lower right panel) than during the private period (lower left panel), as indicated by a period by task interaction, $F(1,5)=16.03$, $p<0.05$. As expected, based on the contingency, a significant interaction between phase and task was observed, $F(1,5)=267.76$, $p<0.001$, as instrumental activities increased (top two panels) and contingent activities decreased (bottom two panels) between baseline and contingency phases. No significant drug effects were observed.

Social Behavior

Use of the social area was the contingent activity for all subjects. Therefore, during the contingency phase of the study, subjects were occasionally restricted from the social area. The top panel of Fig. 4 presents the amount of time subjects spent under social conditions during baseline and contingency phases. Subjects spent more time under social conditions during the baseline phase of the study (i.e., days 2–7) than during the contingency phase [i.e., days 8–13, $F(1,5)=27.36$, $p<0.005$]. A significant day effect, $F(2,10)=12\ 97$, $p<.005$, was also observed, resulting from subjects spending less time in social settings during day 1 than during days 2 or 3 in baseline and contingency conditions. Amphetamine produced no significant effects on total social time

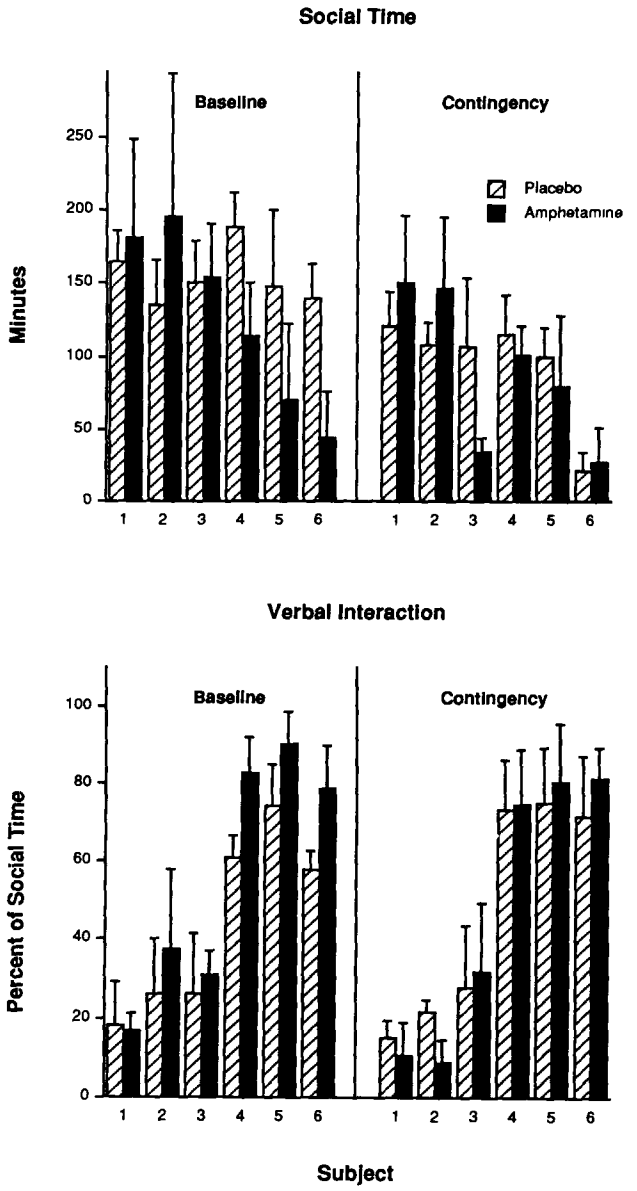

FIG 4. The upper panel displays the mean daily time spent in the social area in the presence of one or two other subjects during placebo and amphetamine sessions over baseline (days 2–7) and contingency (days 8–13) phases The bottom panel displays the mean daily percentage of social time that subjects spent talking during placebo and amphetamine sessions over baseline (days 2–7) and contingency (days 8–13) phases Error bars represent 1 SEM

during either baseline or contingency phases.

The amount of verbal interaction while under social conditions was also measured. The bottom panel of Fig. 4 presents the percent of time that each subject engaged in verbal interaction while under social conditions. Amphetamine produced a marginally significant increase in verbal interaction, $F(1,5) = 4\ 78$, $p = 0.08$, and a significant interaction between drug and phase was also observed, $F(1,5) = 9.41$, $p < 0\ 05$. Amphetamine increased verbal interaction during the baseline phase, but no changes in verbal interaction were observed during the contingency phase. A significant interaction was also observed between drug and day, $F(2,10) = 48.98$, $p < 0.001$. Amphetamine increased verbal interactions primarily on day 1, relative to placebo values, but no changes were evident on days 2–3. This pattern was observed during both baseline and contingency conditions.

VAS Ratings

Amphetamine's effects on VAS ratings were characterized by increases in "Anxious," "Potency," "Liking" and "Stimulated" (decreases for "Sedated") on the first day of drug administration, especially during the first drug phase. This pattern was evidenced by significant drug by session, $F(2,10) = 4.87$, $p < 0.05$, and phase by drug by session, $F(2,10) = 5.67$, $p < 0.05$, interactions on the "Anxious" scale, marginally significant drug by session interactions with "Stimulated," $F(2,10) = 3.58$, $p = 0.067$, and "Liking," $F(2,10) = 3.65$, $p = 0\ 064$, a marginally significant drug by phase interaction with "Sedated," $F(1,5) = 5.77$, $p = 0.062$, and a marginally significant four-way interaction between time-of-day, phase, dose and day with "Potency," $F(2,10) = 3.29$, $p = 0.08$. Amphetamine's effects on the "Potency" scale (increases) were limited to ratings of the a.m. dose on the first day of the first exposure to amphetamine. No significant changes of ratings on the "High" scale were observed

Table 3 presents the change from placebo VAS ratings of "Liking," "Potency" and "Anxious" following daily exposure to amphetamine. The interactions described above were related primarily to amphetamine's effects in S3, S4, S5 and S6 These subjects exhibited substantial changes in VAS ratings on the first day of the first exposure to drug, but changes were smaller or absent on the second and third days. Occasional increases in VAS ratings were also observed on day one during the second exposure to amphetamine on the "Anxious" and "Liking" scales Little change in VAS ratings occurred in S1 and S2. Placebo ratings for individual subjects were variable.

Individual subjects also had different rating patterns across these scales. For example, while increased "Liking" was evident on day 1 during the first exposure to amphetamine in S3, S4 and S5, only S3 and S4 showed similar increases on the "Anxious" and "Potency" scales. S6 exhibited increases in "Potency" and "Anxious," but not on the "Liking" scale. A composite rating was calculated by adding scores on the "Liking," "Anxious," "Stimulated" and "Potency" scales and subtracting scores on the "Sedated" scale. Analysis of "Composite" scores indicated significant session effects, $F(2,10) = 8\ 12$, $p < 0.01$, along with significant time-of-day by session, $F(2,10) = 8.12$, $p < 0.01$, and drug by session, $F(2,10) = 6.38$, $p < 0.05$, interactions.

DISCUSSION

The results indicate that amphetamine's effects can best be characterized with reference to specific behavioral measures. As has been previously reported (17), food intake by these subjects was decreased by 10 mg/70 kg, b.i.d., which is consistent with previous reports [e.g., (2,28)]. This substantial decrease in food intake contrasts with other reliable effects including small but consistent improvements on some measures of task performance, increased verbal interaction between subjects in the absence of social restriction, and increased tobacco cigarette smoking in two of four smokers. Changes in VAS ratings of "Anxious," "Stimulated," "Potency," "Liking" and "Sedated" were also observed, although for the most part, these changes were limited to the first day of drug exposure during the first and occasionally during the second drug phase. No changes in social time or in the allocation of time to available work and recreational activities were observed

TABLE 3

AMPHETAMINE-INDUCED CHANGES IN PLACEBO VAS RATINGS OF "LIKING," "POTENCY," "ANXIOUS" AND A COMPOSITE SCORE

	0930 Dose						1630 Dose					
	Phase 1			Phase 2			Phase 1			Phase 2		
Subject	D1*	D2	D3	D1	D2	D3	D1	D2	D3	D1	D2	D3
						"Liking"						
S1	0†	0	0	0	0	0	0	0	0	0	0	0
S2	2	12	12	3	8	3	−2	−2	8	8	−2	−7
S3	13	8	13	−10	−10	−25	20	15	25	5	0	5
S4	35	−45	0	0	0	0	35	−45	0	0	0	0
S5	27	−13	7	20	−50	0	−10	−10	−10	0	0	0
S6	0	0	−5	−2	−2	−2	0	−5	0	−5	0	0
Mean	13	−6	4 5	2	−9	−4	7	−8	4	1	0	0
						"Potency"						
S1	0	0	0	0	0	0	0	0	0	0	0	0
S2	−10	−10	0	−8	−18	−18	2	−8	12	−13	−13	2
S3	37	−3	37	3	−2	−2	17	−3	17	0	0	0
S4	50	25	0	0	0	5	15	50	0	0	0	0
S5	−7	−17	−52	25	55	15	−13	2	−43	33	23	33
S6	20	−45	5	0	0	0	20	0	0	0	0	0
Mean	15	−8	−2	3	6	0	7	7	−2	3	2	6
						"Anxious"						
S1	0	0	0	0	0	0	0	0	0	0	0	0
S2	0	0	0	−2	−2	−2	0	0	0	0	0	0
S3	97	7	−3	5	0	0	55	5	0	0	0	0
S4	50	0	0	0	0	0	0	15	0	0	0	0
S5	0	−15	−30	33	−27	23	0	0	−5	5	−5	30
S6	63	3	−2	0	0	0	80	55	5	0	0	0
Mean	35	−1	−6	6	−5	3 5	22 5	12 5	0	1	−1	5
						Composite ("Liking" + "Stimulated" + "Potency" + "Anxious" − "Sedated")						
S1	2	2	2	0	0	0	0	0	0	0	0	0
S2	−8	2	12	−7	−12	−12	0	−10	20	−5	−15	−5
S3	155	20	45	3	−12	−27	97	17	42	5	0	5
S4	202	−3	17	0	0	−5	50	−10	0	0	0	0
S5	36	−89	−74	148	−72	58	−53	−78	−118	38	18	63
S6	153	−42	−6	−3	−23	22	165	120	0	−5	−30	0
Mean	90	−18	−1	23 5	−20	6	43	6 5	−9	5 5	−4 5	10 5

*Day within each 3-day active dose phase
†Change, in mm

Subjects were required to participate on one of four tasks for six hours per day over fifteen consecutive days. No contingencies on task rate or accuracy were programmed Under these conditions amphetamine decreased error rates on the DSST task and increased the proportion of hits on a vigilance task, although the improvement in vigilance performance across time limited the reliability of this result. Previous reports of amphetamine's effects on behavior indicate that the drug generally improves suboptimal performance resulting from fatigue or boredom, but does not enhance optimal performance [e.g., (32)]. The results of the present study are consistent with these reports in that amphetamine's effects were likely determined under conditions in which less than optimal performance was observed as a result of the repetitive nature of the tasks and the absence of any programmed contingencies maintaining performance accuracy.

Four subjects in the present study smoked tobacco cigarettes. Amphetamine increased the number of smoking bouts per day in two subjects. No other changes in smoking topography were observed Previous nonresidential studies have similarly reported selective increases in the number of cigarettes smoked during 90-minute sessions in some, but not all tobacco cigarette smokers following amphetamine doses up to 25 mg (4,21). In combination, these results indicate that amphetamine increases tobacco cigarette smoking in some, but not all tobacco cigarette smokers, and that these effects are observed under highly controlled conditions in a smoking laboratory during 90-minute sessions as well as in a less restrictive residential laboratory over longer (i.e., three-day) intervals.

Previous studies have reported increases in social and verbal behavior following amphetamine administration [e.g , (18,31)],

as well as increases in choices of social over nonsocial options in subjects presented with mutually exclusive options (20,22). In the above studies, all subjects were physically isolated from their speaking partners. Griffiths and co-workers (18) also demonstrated amphetamine-induced increases in social interaction, defined as "behavior which required the presence of or involved another person," in subjects residing on a residential research ward. In the present study, amphetamine had no effect on the amount of time subjects spent in social contact, but increased the percentage of social time spent in verbal interaction. However, this effect was observed only in the absence of restrictions on use of the social area. When social access was restricted, amphetamine had no effect on social behavior. These results indicate that amphetamine produces differential effects on social and verbal behavior The relationship between amphetamine and social/verbal behavior can be influenced by contextual factors, including availability of social stimuli, alternative nonsocial options, and preestablished social interaction patterns [e.g., (29,30)].

The difference in time allocation between instrumental and contingent activities during baseline conditions was greater during the social period than during the private period, as described in previous studies incorporating time-allocation contingencies (14,15). When the behavioral contingency was operative, decreases in time spent on the contingent activities and increases in time spent on the instrumental activities, relative to baseline, were observed during both the private and social periods. Amphetamine produced no effect on the distribution of time to these activities. These results are in contrast to previous studies in which marijuana increased time allocated for instrumental activities to a greater extent than placebo during the work period and decreased time allocated for instrumental activities, relative to placebo, during the social period (14,15). These studies indicated that marijuana's "amotivational" effects were related to the contextual factors under which the effects were determined. The absence of amphetamine effects in the present study are not likely the result of an insensitive procedural manipulation. Rather, it appears that amphetamine, at the dose used in the present study, had little effect on time allocation.

At 2330, subjects rated the interoceptive effects produced by the two doses that were administered earlier in the day. These ratings were based on subject's recollection of drug effects. Peak drug effects, even following the second daily dose, had likely dissipated well before the ratings were completed. The advantage of this procedure was that subject activities during the day were not influenced by their own verbal reports of drug effect, and the ratings were based on effects observed at all times following drug administration (i.e., amphetamine's time-course of behavioral effects are not equal across measures, and ratings completed at times closer to dose administration may have been heavily influenced by a subset of the behavioral measures). The obvious disadvantage of the procedure, however, was that the accuracy and sensitivity with which subjects recalled drug effects was potentially diminished. Under these conditions, the VAS ratings must be interpreted with caution.

When subjects were initially exposed to the 10 mg dose of d-amphetamine, they rated the interoceptive cues related to "Stimulated" and "Anxious," as well as the "Potency" and "Liking" of the dose, as increased from placebo, and "sedation" as decreased from placebo. No changes on the "High" scale were reported, otherwise the initial changes in VAS ratings were similar to those reported in other studies [e.g., (5,6)].

The VAS changes were observed primarily during the first active day of the first exposure to amphetamine, or occasionally during the first day of the second three-day drug phase Tolerance to the "subjective" effects of drugs have previously been reported during daily amphetamine administration [e.g., (19)] but not when doses are administered three times per week [e.g , (6,25)]. A lack of tolerance to the reinforcing effects of stimulant drugs has been previously reported [e.g., (11,24)], suggesting that the tolerance to the interoceptive effects of amphetamine, indicated by changes in VAS ratings, may not be reflective of change in other functional effects of the drug. No tolerance to amphetamine's effects on task performance, verbal interaction, tobacco cigarette smoking or food intake was observed Clearly, additional research comparing ratings of the interoceptive effects of the drug with the reinforcing functions and behavioral effects are necessary to separate these complex but potentially important factors operating during exposure to amphetamine

These results provide a profile of amphetamine effects indicating minimal behavioral disruption at doses that significantly decreased food intake. This behavioral profile is clearly distinct from that obtained when subjects are required to smoke marijuana cigarettes under the same conditions Marijuana increased food intake [e.g., (16)] and decreased tobacco cigarette smoking (26) and verbal interaction (13). Marijuana also produced differential effects on allocation of time to low- and high-probability activities during the private and social period without affecting task performance (14,15) These results demonstrate that drugs from different pharmacological classes produce markedly different profiles of effects across a range of behavioral measures, indicating the utility of the simultaneous measurement of multiple dimensions of behavior in the analysis of the behavioral effects of drugs

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