EFFECTS OF SETTING ON THE SUBJECTIVE AND BEHAVIORAL EFFECTS OF d-AMPHETAMINE IN HUMANS

JAMES P. ZACNY, BETSY K. BODKER, and HARRIET DE WIT
The University of Chicago

Abstract — The effects of setting on the subjective and behavioral effects of 20 mg oral d-amphetamine were studied in eight healthy volunteers. A within-subjects design was used in which subjects ingested either amphetamine or placebo capsules in either an inpatient (isolated laboratory room) or an outpatient (normal daily environment) setting. The order of the four experimental conditions was randomized across subjects. Subjective drug effects were assessed using the Profile of Mood States, the Addiction Research Center Inventory, a Visual Analogue Scale, and a Drug Effects/Liking questionnaire, completed prior to and 1, 3, and 6 h after capsule ingestion. In addition, an End-of-Session questionnaire measuring overall drug liking and drug identification was completed at the 6-h timepoint. Subjects wore wrist monitors to record their physical activity levels during the 6-h post-ingestion period. Amphetamine produced typical stimulant-like subjective effects such as elation, euphoria, and friendliness, but the setting neither quantitatively nor qualitatively altered the drug response.

The effects of mood-altering drugs are thought to depend upon the environment in which they are experienced. Both anecdotal evidence and data from laboratory studies suggest that subjective effects of drugs can vary both quantitatively and qualitatively, depending on the context in which the drugs are administered. Marijuana and alcohol, for example, have been shown to produce greater euphorigenic effects when they are administered in a naturalistic or social setting (i.e., a group) compared to when they are administered under socially isolated laboratory conditions (Carlin, Bakker, Halpern, & Post, 1972; del Porto & Masur, 1984; Lindman, 1982; Pliner & Cappell, 1974; Sher, 1985). The setting can also produce a qualitative change in the subjective effects of a drug. For example, in a marijuana study (Jones, 1971), the drug produced sedation in the isolated setting but not in the social setting.

Observations in our laboratory have also suggested that environmental setting may play a role in the subjective effects of the stimulant, amphetamine (AMPH). In a series of studies with normal healthy volunteers (e.g., college students), low-to-moderate doses of AMPH reliably produce a characteristic profile of subjective effects, including increases in vigor, elation, and friendliness (Chait, Uhlenhuth, & Johanson, 1986; de Wit, Uhlenhuth, & Johanson, 1985, 1987; Johanson, Kilgore, & Uhlenhuth, 1983; Johanson & Uhlenhuth, 1980; Zacny & de Wit, 1989). Most of these studies have investigated the drug's effects while subjects were in their normal daily environments: Subjects came to the laboratory to ingest capsules but were then free to leave and engage in their normal activities. In one recent study (unpublished), however, AMPH was administered to subjects who remained isolated in a hospital room for the duration of the drug's effects, and under these conditions the drug failed to produce any of its typical stimulant-like effects. We speculated that the mood effects of AMPH may depend on a
minimum level of ambient activity and stimulation and that the restricted environment of the hospital room was not conducive to observing stimulant-like effects.

The present study was designed to systematically investigate this notion, using a within-subjects, placebo-controlled design. Normal healthy volunteers received \(d\)-amphetamine (20 mg) and placebo under each of two conditions: remaining in the laboratory under socially isolated conditions, and returning to their normal daily environments to experience the drug's effects. It was hypothesized that the effects of AMPH would be greater in the nonlaboratory environment.

METHOD

Subjects

Eight normal healthy adults participated in the study. They were recruited from the university and surrounding community through local newspaper advertisements, posters, and word-of-mouth referrals. Candidates who met initial screening criteria (e.g., age range 21–35 and consumption of at least one alcoholic drink per week) were scheduled for a screening interview. At the interview, candidates completed the SCL-90 (Derogatis, 1983) and a health questionnaire to determine their psychiatric and medical status. They were interviewed by a psychiatric social worker and were given a physical examination (including an electrocardiogram) by a physician. Subjects with any significant medical or psychiatric problems (including any history of drug- or alcohol-related problems or Axis I psychiatric disorder; American Psychiatric Association, 1987) were excluded from participating.

Prior to participation, subjects read and signed a consent form which explained the nature and procedure of the study and listed the drugs they might receive (appetite suppressants/stimulants, sedatives/tranquilizers, antihistamines, alcohol, or placebo) and their possible side effects. The protocol was approved by the Institutional Review Board. Subjects were paid during a final debriefing session.

Procedure

Each subject participated in six sessions, conducted twice a week, from 0900 h to 1500 h. During each session, subjects ingested a capsule containing either placebo (PLC), 10 mg of AMPH, or 20 mg of AMPH, and they either remained in the laboratory for the following 6 h ("inpatient" [LAB condition]) or returned to their normal daily environment and activities ("outpatient" [NONLAB condition]). For each subject, the order of the six conditions (PLC-LAB, PLC-NONLAB, AMPH(10)-LAB, AMPH(10)-NONLAB, AMPH(20)-LAB, AMPH(20)-NONLAB) was randomly determined. Subjects were told a few days beforehand whether their next session would be LAB or NONLAB. Sessions were conducted on two weekdays per week separated by at least three days, that is, Monday and Thursday, Monday and Friday, or Tuesday and Friday.

During each session, subjects were instructed to finish eating breakfast by 0800 h and to arrive at the laboratory at 0900 h. At this time, they filled out 0 h (baseline) mood forms (see next page). They were also given an activity-monitoring device (Motor Activity Displaying Monitor; Verona, PA) to put on their nondominant wrist. When all mood forms had been completed, subjects were given a capsule (size 00) with 130 ml of water. The capsules contained either PLC (dextrose powder) or 10 or 20 mg \(d\)-amphetamine sulfate with dextrose filler.
LAB sessions. After filling out mood forms and taking the capsule, subjects spent the next 6 h by themselves in a comfortable room (10 × 13 m) equipped with a TV/VCR and a recliner chair and/or sofa. They were allowed to bring work- or study-related materials (i.e., homework) and/or recreational materials (i.e., VCR tapes) with them to the session. They were not allowed to leave the room, except to go to the bathroom, and they were not permitted to have any social contact (including telephone calls) for the 6-h session. The technician came into the room briefly at 1, 3, and 6 h after capsule ingestion to remind subjects to fill out mood forms, and at 1200 h to give them lunch.

NONLAB sessions. After filling out mood forms and taking the capsule, subjects were free to leave the laboratory and carry out their normal daily activities. They were given mood forms to fill out 1, 3, and 6 h after capsule ingestion. They were instructed to refrain from eating until 1200 h and were asked to consume their normal amount of food for lunch. Subjects returned to the laboratory at 1500 h to turn in completed forms and activity monitors.

Dependent measures:
Subjects filled out six questionnaires:

1. The Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1971), which consists of 72 adjectives commonly used to describe momentary mood states. Subjects indicate how they feel at the moment in relation to each of the 72 adjectives on a 5-point scale ranging from “not at all” (0) to “extremely” (4). There are eight clusters of items (scales) which have been separated using factor analysis (Anxiety, Depression, Anger, Vigor, Fatigue, Confusion, Friendliness, and Elation), and two additional unvalidated scales, Arousal and Positive Mood.

2. A version of the Addiction Research Center Inventory (ARCI; Martin, Sloan, Sapira, & Jasinski, 1971), which consists of 49 true-false questions which are sensitive to the effects of a variety of abused drugs. The items have been separated empirically into five scales: the MBG scale, a general measure of drug-induced euphoria, BG and A scales, sensitive to stimulant effects, the LSD scale, which reflects somatic and/or dysphoric effects, and the PCAG scale, which measures sedative-like effects.

3. The Visual Analogue Scale (VAS), a form which has horizontal 100-mm lines corresponding to six adjectives (“stimulated,” “high,” “anxious,” “sedated,” “down,” and “hungry”). Subjects were instructed to make a vertical mark along each line indicating how they feel at that moment, from “not at all” to “extremely.”

4. The Drug Effects/Liking questionnaire, on which subjects were asked to categorize “the effect of the drug as you are currently feeling it” (FEEL) and to rate “how much you like or dislike the effects of the capsule you ingested” (LIKE). On the FEEL question, subjects were asked to rate the extent to which they currently felt a drug effect on a scale of 1 to 5 (1 = “I feel no effect from it at all,” to 5 = “I feel a very strong effect”). The LIKE question was answered by making a vertical mark along a 100-mm line labeled “Disliked a lot” at one end, “Neutral” in the middle, and “Liked a lot” at the other.

5. The Conversation Diary, on which subjects in the NONLAB setting estimated how many of the last 30 min they had spent in conversation (talking and/or listening) with another person(s).

6. The End-of-Session Questionnaire, on which subjects were asked to first rate along a 100-mm line how much they liked the drug’s effects overall from “Disliked a lot” to “Neutral” to “Liked a lot.” Next, the questionnaire asked (yes/no) if they thought
they received an active drug; if yes, subjects were asked whether they would label it as a stimulant ("upper") or a sedative ("downer").

The first four subjective effects questionnaires were filled out immediately before and 1, 3, and 6 h after capsule ingestion. The Conversation Diary was filled out every 30 min beginning at 0.5 h after capsule ingestion, while the End-of-Session questionnaire was filled out 6 h after capsule ingestion.

The measure of subjects' physical activity was obtained for each session. The technician recorded the reading on the monitor at the beginning and at the end of each session.

Data analysis

Subjective effects data were analyzed with univariate analysis of variance (ANOVA) for repeated measures. Separate three-way ANOVAs (Setting × Drug × Hour) were used for measuring each scale from the POMS, ARCI, VAS, and Drug Effects/Liking forms. A two-way ANOVA (Setting × Drug) was used to analyze activity levels and the End-of-Session LIKE question. F-values were considered significant for \( p < 0.05 \), with adjustments of within-factors degrees of freedom (Huynh-Feldt) to protect against violations of symmetry. Because of the relatively small sample size in our study, we will also report those effects which approached significance (i.e., \( p \leq 0.10 \)).

RESULTS AND DISCUSSION

Five males and three females (average age, 25; range, 21–31) participated in the study. Most of the subjects were white, never-married, and full-time students (Table 1). They were, on average, light alcohol users, and none were smokers. Their lifetime recreational drug use was minimal.

We will only be reporting data from the 0 and 20 mg AMPH conditions in this paper, because preliminary data analysis indicated that the 10 mg AMPH dose produced negligible effects on all dependent measures in both settings.

Table 1. Subject characteristics (N = 8)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean and SD)</td>
<td>25 (4.0)</td>
</tr>
<tr>
<td>Race: White/Other</td>
<td>7/1</td>
</tr>
<tr>
<td>Marital Status: Never married/Married or Divorced</td>
<td>7/1</td>
</tr>
<tr>
<td>Full time student: yes/no</td>
<td>7/1</td>
</tr>
<tr>
<td>Education (n; highest level achieved)</td>
<td></td>
</tr>
<tr>
<td>Partial college</td>
<td>2</td>
</tr>
<tr>
<td>College degree</td>
<td>1</td>
</tr>
<tr>
<td>Advanced degree</td>
<td>5</td>
</tr>
<tr>
<td>SCL-90 scores (mean and SD)</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.28 (.24)</td>
</tr>
<tr>
<td>Depression</td>
<td>0.34 (.33)</td>
</tr>
<tr>
<td>Current recreational drug use</td>
<td></td>
</tr>
<tr>
<td>Alcohol (mean drinks per week)</td>
<td>5.1 (range: 1–17)</td>
</tr>
<tr>
<td>Caffeine (mean drinks per week)</td>
<td>13.1</td>
</tr>
<tr>
<td>Cigarettes (n)</td>
<td>0</td>
</tr>
<tr>
<td>Marijuana (n; regular use)</td>
<td>0</td>
</tr>
<tr>
<td>Lifetime drug use (n; ever used)</td>
<td></td>
</tr>
<tr>
<td>Tranquilizers</td>
<td>0</td>
</tr>
<tr>
<td>Stimulants</td>
<td>0</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>0</td>
</tr>
<tr>
<td>Marijuana</td>
<td>2</td>
</tr>
</tbody>
</table>
Activity was significantly higher in the NONLAB relative to the LAB setting \( [F(1,7) = 8.2, p < 0.05] \). All eight subjects had higher activity readings (as measured by the activity monitor) in the NONLAB than in the LAB setting (mean activity count [SEM in parentheses] in NONLAB setting: 145.4 (23.5); mean activity count in LAB setting: 54.2 (7.2)). However, AMPH had no effect on the activity measure in either setting. Subjects, on average, rated themselves as spending 132 min of the 360-min postingestion period in social conversation in the NONLAB setting (averaged across drug conditions), but AMPH did not affect conversation levels.

AMPH produced typical stimulant-like subjective effects on mood and drug effects ratings. Significant or near significant Drug \( \times \) Hour interactions were obtained on the Elation, Friendliness, and Positive Mood scales of the POMS, the A and MBG scales of the ARCI, the “high” rating on the VAS, and the FEEL question on the Drug Effects/Liking questionnaire. Relative to PLC, AMPH increased scores on the Elation \( [F(3, 21) = 6.4, p < 0.005] \) (Fig. 1, top left frame), Friendliness \( [F(3, 21) = 7.4, p < 0.005] \) (Fig. 1, top right frame), Positive Mood \( [F(3, 21) = 6.9, p < 0.005] \), and MBG scales \( [F(3, 21) = 4.1, p < 0.05] \) (Fig. 1, bottom left frame). Relative to PLC, AMPH also tended to increase scores on the A \( [F(3, 21) = 3.2, p < 0.06] \) (Fig. 1, bottom right frame) scale and ratings of “high” \( [F(3, 21) = 3.1, p = 0.10] \). As shown in Figure 1, subjective effects of AMPH peaked at 3 h postinjection. On the Drug Effects/Liking Questionnaire, sub-

![Graph](image-url)
naire, subjects reported feeling greater drug effects when they received the active drug than when they got PLC \( F(3, 21) = 8.1, p < 0.001 \), but there were no significant drug effects on the “Like” question, or on the overall liking question on the End-of-Session questionnaire. In the End-of-Session questionnaire, a majority of subjects (six out of eight in the LAB sessions and five out of eight in the NONLAB sessions) correctly identified AMPH as a stimulant. PLC capsules were correctly identified by four of the subjects in the LAB sessions and by five of the subjects in the NONLAB sessions. When misidentifying PLC capsules, subjects were just as likely to label them as having stimulant-like effects as having sedative-like effects.

Contrary to expectations, the effects of AMPH were similar whether subjects remained in the laboratory (LAB) or whether they returned to their normal activities (NONLAB). No significant interactions between setting and drug were obtained on any of the subjective effects questionnaires. Figure 2 shows scores from the Elation scale of the POMS as a function of setting and drug: little difference existed in the magnitude of effects in Elation scores after ingestion of AMPH across setting conditions. The only setting effect was on “hungry” scores from the VAS \( F(1, 7) = 6.9, p < 0.05 \), but the differences across setting conditions were clinically minimal (i.e., mean “hungry” scores in the LAB setting was 22.5 and 27.8 in the NONLAB setting). The absence of interactions between the setting and subjective drug effects was unexpected in view of our previous observations with AMPH and the results of several studies using other drugs. One reason for the lack of setting effects in this study may be that the settings were not sufficiently different. It is conceivable that subjects, for whatever reason, may have been just as isolated in the NONLAB setting (e.g., going to the library to study) as in the LAB setting. Unsystematic reports from the debriefing interviews, for example,
revealed that indeed three out of the eight subjects in the study spent most of their time in the library after capsule ingestion during NONLAB sessions. Alternatively, the LAB setting may have contained sufficient stimulation (e.g., TV, study materials) to produce typical AMPH effects.

In conclusion, prototypic subjective effects of AMPH were obtained in both the LAB and the NONLAB settings. The fact that subjective effects were not more robust or qualitatively different in the NONLAB than in the LAB setting stands in contrast to a number of studies in which isolated settings attenuated or changed the quality of drug effects (Carlin et al., 1972; del Porto & Masur, 1984; Jones, 1971; Lindman, 1982; Pliner & Cappell, 1974; Sher, 1985), although other studies have reported prototypic subjective drug effects even in isolated laboratory settings (de Wit, Metz, Wagner, & Cooper, 1990; Hollister, Overall, & Gerber, 1975; Lukas, Mendelson, Amass, & Benedikt, 1990). Further research needs to be conducted to delineate those variables (e.g., drug type and dose, route of administration, subject population) that determine under what conditions setting modulates drug effects.

REFERENCES


