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Amphetamine-induced place preference in humans

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Abstract

Background—The conditioned place preference procedure is a widely used animal model of rewarding drug effects that, to date, has not been tested in humans. In this study, we sought to demonstrate that humans, like non-humans, would exhibit a preference for a place previously associated with amphetamine. Further, we investigated the relationship between conditioned place preference and the mood-altering effects of the drug.

Methods—Thirty-one healthy individuals participated in a five-session procedure during which they experienced the effects of d-amphetamine (20mg) or placebo on two occasions in two distinctive environments (sessions 1 to 4). One group of subjects (paired group, N=19) received amphetamine consistently in one room and placebo in another room, while a second group (unpaired group, N=12) received amphetamine and placebo without regard to the rooms. During the sessions, participants completed questionnaires to rate their mood. On the fifth session, they rated their preference for the two rooms.

Results—Individuals in the paired group rated their liking of the amphetamine-paired room significantly higher than the placebo-associated room, while there was no difference between ratings of the two rooms for individuals in the unpaired group. In the paired group, drug liking ratings during the conditioning sessions positively predicted preference for the drug-associated room, whereas reports of amphetamine-induced anxiety and dysphoria negatively predicted room liking scores.

Conclusions—This study demonstrates that humans, like non-humans, prefer a place associated with amphetamine administration. These findings support the idea that subjective responses to a drug contribute to its ability to establish place conditioning.

Keywords

amphetamine; human; conditioned place preference; subjective effects

Introduction

The place preference procedure is a widely accepted animal model of the motivational or rewarding effects of drugs (1,2). In these experiments, animals undergo several conditioning sessions in which they receive a drug and saline in distinct environments. Subsequently, they are allowed to move freely between the two environments. Typically animals will spend

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significantly more time in the environment paired with a rewarding drug i.e., a conditioned place preference. Conversely, if the drug produces aversive effects, they will spend less time in the drug-paired environment i.e., a conditioned place aversion. The place preference procedure has been used to investigate several aspects of addictive behaviors, including tolerance and sensitization (3,4) and the neural substrates underlying the reinforcing effects of psychoactive drugs (5-7). However despite the fact that its use with animals has grown considerably in recent years (8), the model has never been validated in humans (9).

Procedures designed to assess drug preferences in nonhumans rely on certain implicit assumptions regarding the positive interoceptive effects of drugs. Most notably, it is assumed that drugs produce similar subjective states in non-humans as they do in humans. Thus, when an animal spends more time in the previously drug-paired compartment of the place preference chamber, it is inferred that the environment has acquired “rewarding” properties through association with “pleasurable” drug effects. There is a good empirical basis for the assumption that humans and nonhumans respond similarly to drugs of abuse. For example, in operant drug self-administration studies, animals and humans will self-administer the same drugs, and in humans these drugs produce pleasurable subjective effects (10-15). Thus, despite some exceptions e.g., (16), reinforcing effects of drugs are usually associated with positive subjective effects. To date, the conditioned place preference procedure has not been tested in humans and thus the assumption that a conditioned place preference is based upon the subjectively positive effects of a drug has not been tested directly.

In this study, we aimed to validate a procedure in humans based upon the place preference procedure in animals. One goal was to demonstrate that humans, like nonhumans, prefer a place previously associated with amphetamine, a drug with known reinforcing effects (17). A second goal was to examine the correspondence between place preference and the subjective, mood-altering effects of the drug. We examined measures of preference for a room associated with a moderate dose of d-amphetamine (20 mg), compared to a room associated with placebo, in healthy adults. Subjects experienced the drug and placebo on two occasions each in two rooms (Room 1 and 2). One group (paired, N=19) consistently received the drug in one room and the placebo in another room, whereas a control group (unpaired, N=12) experienced the drug and placebo in both rooms. During each conditioning session, participants reported upon subjective effects of the drugs. Notably, we assessed both positive subjective effects and also negative effects such as anxiety or depression. After the four conditioning sessions, on a test day, participants were asked to indicate how much they liked each of the testing rooms and which room they preferred. We obtained subjective ratings of room preference because it was physically impractical to obtain objective measures of spontaneous exploration between the rooms. We hypothesized that among individuals in the paired group, ratings of room liking would be greater for the room which had previously been associated with amphetamine, compared to the room that had been associated with placebo. In addition, we assessed the relationship between ratings of liking for each room and subjective drug responses. We hypothesized that there would be a logical relationship between the mood-altering effects of the drug during conditioning, and measures of preference on the test day i.e., more positive (elation and positive mood) and less negative (anxiety and dysphoria) subjective drug effects would predict liking of the drug-associated room.

Materials and Methods

Subjects

Healthy male (n=17) and female (n=14) volunteers aged 18 to 40 were recruited. Eligible candidates were screened for psychiatric and physical health, including an electrocardiogram. Exclusion criteria included a current or prior diagnosis of a Major Axis I DSM-IV disorder (18) including drug abuse or dependence, a serious medical condition, high blood pressure,

abnormal electrocardiogram, daily use of medications, a body mass index outside of 19-26 kg/m^2, less than high school education or lack of fluency in English, night shift work, and pregnancy or lactation in women. Qualifying participants signed a Consent Form that detailed the study procedures. They were told that the study was designed to investigate the effects of drugs upon mood and physiology. For blinding purposes, they were told that they might receive a stimulant (appetite suppressant), sedative (tranquilizer) or placebo (sugar).

Study Design

The study was comprised of five sessions; four drug administration sessions and one testing session, each conducted at least two days apart. Drug administration sessions lasted for four hours and always began at 9 am. During the four drug administration sessions, subjects received two doses of d-amphetamine (20 mg) and two doses of placebo separately in randomised order under double-blind conditions. The fifth testing session lasted approximately one hour during which subjects completed questionnaires indicating their liking of the testing rooms, and which room they preferred. At the end of the study, they were debriefed about the study aims and received payment ($200).

Experimental Procedure

The University of Chicago Hospital's Institutional Review Committee for the use of human subjects approved the experimental protocol. Drug administration sessions were conducted in comfortably furnished rooms with a television/VCR, magazines, and a computer for administering questionnaires. Two rooms of similar size were used for the drug administration sessions; room 1 had south facing windows and a sofa, room 2 had north facing windows and a comfortable chair. Individuals in the paired condition (N=19) always received d-amphetamine in one room and placebo in the other room in a counterbalanced design; paired group 1 (N=9) received d-amphetamine in room 1 and placebo in room 2, whereas paired group 2 (N=10) received placebo in room 1 and d-amphetamine in room 2. A second group of individuals (N=12) received d-amphetamine and placebo once in each room (unpaired condition).

On arrival at the laboratory for each of the four conditioning sessions, subjects provided breath and urine samples to test for recent drug and alcohol use, and for pregnancy in females; no subjects tested positive. They were then shown to their assigned testing room for that session. Subjects relaxed for 30 min before baseline measures of blood pressure, heart rate and subjective state were obtained. They then consumed a capsule that contained either placebo or 20 mg d-amphetamine. During the following three hours, participants remained in their assigned room. They completed mood questionnaires and their blood pressure and heart rate were recorded every 30 min. In-between the measurements, participants were allowed to watch television, movies, or read. At the end of the session, participants completed a questionnaire to rate their overall experience and were then allowed to leave the laboratory.

When subjects returned to the lab for the fifth session they were escorted to a separate room from the ones where they had received drug or placebo. At this session they completed a Room Preference questionnaire, on which they rated Rooms 1 and 2 (see Dependent Measures section). Subjects were told that the laboratory was undergoing renovation and that we wanted to consider their comments in the design of the new testing rooms. At the end of this session, they were debriefed about the aims of the study and received payment.

Dependent Measures

Subjective effects of drugs were assessed using an experimental version of the Profile of Mood States (POMS, 19), the Addiction Research Centre Inventory (ARCI, 20), and the Drug Effects

Questionnaire (DEQ, 21). Heart rate and blood pressure were measured at repeated intervals using a digital monitor (Dinamap 1846SX, Critikon, Tampa, FL).

A paper and pencil questionnaire was used to assess room preference. Participants were first asked to rate how much they liked each room; two 100-mm horizontal lines, labeled Room 1 and Room 2, were anchored at the left end with “Dislike” (0), in the centre with “Neutral” (50), and at the right end with “Like very much” (100). Participants were asked to place a vertical mark along each line to indicate how much they liked each room. They were also asked to describe why they liked or disliked each room. Finally, subjects were asked to indicate which room (1 or 2) they would prefer to be in if they had to participate in a further four hour experimental session.

Drugs

D-amphetamine sulfate (four 5 mg tablets; Dexedrine, Mallinckrodt, St Louis, MO) was administered in opaque gelatin capsules (size 00) with dextrose filler. Placebo capsules contained only dextrose.

Data Analysis

Demographic characteristics of the paired and unpaired groups were assessed using Independent Samples t-test or Pearson's Chi-squared test. Initial analyses from the unpaired group indicated that Room 1 was preferred over Room 2, regardless of drug administration. Therefore, analyses for the paired group were controlled for the room in which subjects received d-amphetamine. Thus, VAS Room Liking of the drug- and placebo-associated rooms within the paired group was examined using two-factor (Drug × Paired Group; 1 or 2) repeated measures ANCOVA. For individuals in the unpaired group, differences in VAS Room Liking between the two rooms was assessed using Student's Paired *t*-test.

Subjective responses to amphetamine and placebo did not differ between the first and second administration sessions and thus were expressed as the mean peak change from pre-drug baseline for drug and placebo sessions. Relationships between subjective responses (mean peak change amphetamine – placebo) were explored using multiple linear regression models to find significant predictors of VAS Room Liking (drug Room Liking – placebo Room Liking). Five measures of positive and negative subjective drug effects (ARCI MBG “euphoria”, POMS Positive Mood, ARCI LSD “dysphoria”, POMS Anxiety) and overall drug liking (DEQ) were entered into a direct model. Differences were considered to be significant if $p<0.05$. All analyses were performed using SPSS version 16.0 for Windows.

Results

Demographic Characteristics

Most participants were white in their early twenties (Table 1). The paired and unpaired groups differed only in age [$t(29)=2.4$ $p<0.05$]; participants in the paired group were older. No demographic characteristics were significantly related to subjective responses to amphetamine.

Room Liking and Preference

VAS Room Liking ratings of room 1 and 2 did not differ among individuals in the unpaired group [$t(11)=0.7$, Figure 1]. However, on the measure of “Which room would you prefer to be in for a further testing session?”, 67% preferred room 1 over room 2.

Subjects in the paired condition rated the amphetamine-associated room significantly higher than the placebo-associated room [Room $F(1,17)=4.3$ $p=0.05$, Figure 1]. Notably, there was a trend to a difference between group in the paired condition [Room*Paired Group $F(1,17)=3.3$

p=0.086]; the difference in VAS Room Liking scores was greater among individuals who received amphetamine in room 1 than among those who received amphetamine in room 2. On the measure of "Which room would you prefer to be in?", 67% of those who received amphetamine in room 1 preferred that room, and 50% of those who received amphetamine in room 2 preferred that room.

Subjective Effects of Amphetamine

Amphetamine produced a typical profile of stimulant-like effects in both the paired and the unpaired groups. In comparison to placebo, 20 mg *d*-amphetamine significantly increased subjective stimulation (ARCI A, BG; POMS Arousal, Vigor) and decreased tiredness (POMS Fatigue). Amphetamine also significantly increased ratings of positive mood (POMS Positive mood, Friendliness) and elation (ARCI MBG, POMS Elation).

Four subjective effects predictor variables (ARCI MBG, Positive Mood, ARCI LSD, POMS Anxiety) that represented both positive and negative subjective drug effects, and DEQ Drug Liking were selected to be entered into a multiple linear regression model to predict VAS Room Liking. First, simple correlations were performed between the measures and with VAS Room Liking. Room Liking was marginally negatively correlated with POMS Anxiety (r^2=-.45 p=0.06). ARCI MBG was highly correlated with POMS Positive Mood (r^2=0.71 p=0.001) and thus this measure was removed from the model to avoid redundancy. The four remaining variables produced an adjusted R^2 of 0.34 [$F(4,13)=3.2$ $p<0.05$] for the prediction of Room Liking. That is, together these variables accounted for 34% of the variance in Room Liking (Table 2). POMS Anxiety and DEQ Drug Liking significantly predicted Room Liking (Figure 2) and there was also a non-significant trend for ARCI LSD. POMS Positive Mood did not significantly predict Room Liking scores.

Discussion

In this study, we aimed to validate the place preference procedure in humans. Specifically, we sought to establish that healthy human volunteers would exhibit a preference for a room previously associated with amphetamine. Further, we examined the relationship between room liking and the subjective effects of amphetamine. As predicted, subjects in the paired group liked the room associated with d-amphetamine significantly more than the room associated with placebo. Moreover, we demonstrated an orderly relationship between the subjective effects of d-amphetamine and ratings of liking the room in which they experienced the drug. Across individuals, both drug liking and negative (unpleasant) subjective effects of amphetamine significantly predicted how much they liked the drug-associated room. This preliminary study is the first demonstration that humans, like nonhumans, exhibit a preference for a place previously associated with drug administration.

This study raises questions about the methods and interpretation of the place preference procedure in humans. One methodological issue relates to the potential influence of pre-existing place preferences and their influence on drug conditioning. Another relates to the relationship between quantitative ratings of liking of a room and categorical preferences for a room, and whether either of these corresponds to the behavioral measure of time spent in one or the other chamber that is obtained in animals. A final issue relates to individual differences in subjective drug effects and how an individual's relative liking or disliking of the drug may influence conditioning.

As is commonly observed in studies with nonhumans, individuals in this study appeared to prefer one room over the other (Room 1 over Room 2) regardless of drug administration. Pre-existing preferences have been a continuing and controversial issue in place preference experiments in animals. Thus, experiments can use either a "biased" (unbalanced) design to

adjust for pre-existing preferences (22,23) or an “unbiased” (balanced) design, in which the stimulus conditions in each environment are carefully controlled to produce equal preference (1). In the present study we did not pre-test subjects to establish individual room preferences and assumed a balanced design since there were no obvious differences between the two rooms. However, individuals in the unpaired group appeared to prefer Room 1 over Room 2, and the room that was associated with drug administration appeared to influence room preference among individuals in the paired groups i.e., 67% and 50% for paired groups 1 and 2 respectively. Thus, in our study, as in the animal lab (24-28), pairing the non-preferred room with amphetamine i.e., in paired group 2, increased preference for that room in comparison to the control group. Conversely, pairing the preferred room with amphetamine i.e., in paired group 1, did not produce an increase in preference for that room in comparison to the control group presumably due to ceiling effects. Likewise, on the other measure of preference i.e., quantitative ratings of room liking, we observed an interaction between drug and room conditioning. Subjects who received amphetamine in Room 1 tended to rate their subjective liking of the drug room higher than subjects who received the drug in Room 2, suggesting that amphetamine increased subjective “liking” of an affectively salient room more than that of a neutral room. Thus, in humans, as in animals, pre-existing preferences for one place over another may interact with drug-induced place conditioning.

A second methodological issue relates to the specific outcome measures used as a measure of place preference. In animal studies, the dependent variable is usually the time spent in the drug-paired vs. placebo-paired compartment. In this initial study with humans it was impractical to measure actual time spent in either room in a free choice procedure, and instead we obtained answers to two questions: i. how much did they like each room from memory, and ii. which room they would rather be in for another study session. One problem in the present results was that the answers to these questions were sometimes inconsistent i.e., individuals in paired group 2 rated the drug room higher than the placebo room, yet only 50% of individuals indicated a preference for this room, which suggests that they measure different dimensions. A second, more important problem is the verbal report format for assessing preference. Although verbal reports of liking and preferences are usually a good indicator of subjects' drug preference behavior in other procedures (29,30), it is possible that the subjects behavior, if they were given the option to spend time in the two rooms, would yield different results. Physiological measures e.g., heart rate, may also be a more sensitive indicator of preference in a test involving re-exposure to the two rooms. Thus, the subjective vs. objective nature of the outcome measure is an important methodological difference between the animal and human procedures, which should be addressed in future studies.

A third issue relates to the variability in subjective responses to d-amphetamine in humans. In studies with animals, it is commonly assumed that the animals are fairly homogeneous in their responses to the drug. However, many studies have shown that human volunteers vary in their responses to amphetamine, including the magnitude of effects, their liking of effects and in the quality of effects e.g., anxiety vs. positive mood (13,31-33). Thus, it is not surprising that place preference for the drug would depend on the nature of the drug effects experienced by the individual, and this variability adds an interesting dimension to the studies with humans. The results of multiple linear regression analyses confirmed our hypothesis that positive subjective effects of amphetamine would positively predict room liking, and negative subjective effects would negatively predict room liking. Specifically, we found that how much subjects liked the drug effect predicted room liking scores, and drug-induced anxiety and dysphoria negatively predicted room liking. That is, the more subjects liked the drug, and the less anxiety and dysphoria they experienced after drug administration, the more they liked the room associated with amphetamine.

This preliminary study raises many questions that will only be answered with additional research. The influence of initial room preferences on drug conditioning is not known, and might be addressed by obtaining initial room preference scores for each individual, as is done in animal studies. It is not known whether more conditioning sessions, or higher doses of the drug would lead to a stronger place preference. Finally, the nature of the outcome measures i.e., self-reported room preference and ratings of room liking, and their relationship to the actual time spent in a behavioural free choice test remain to be explored. This first demonstration that pairing an environment with drug administration can selectively alter ratings of preference for that environment is important for several reasons. It provides an important validation of a procedure commonly used in animals. It supports the assumption that place preference is related to subjective experience of the drug effect, and provides the added information that individual differences in subjective experience can influence preference. It provides a basis for further studies examining the relationships between self-report measures to behavioral indices of preference. Finally, it may have clinical applications if it is demonstrated that drug-associated places acquire conditioned incentive value.

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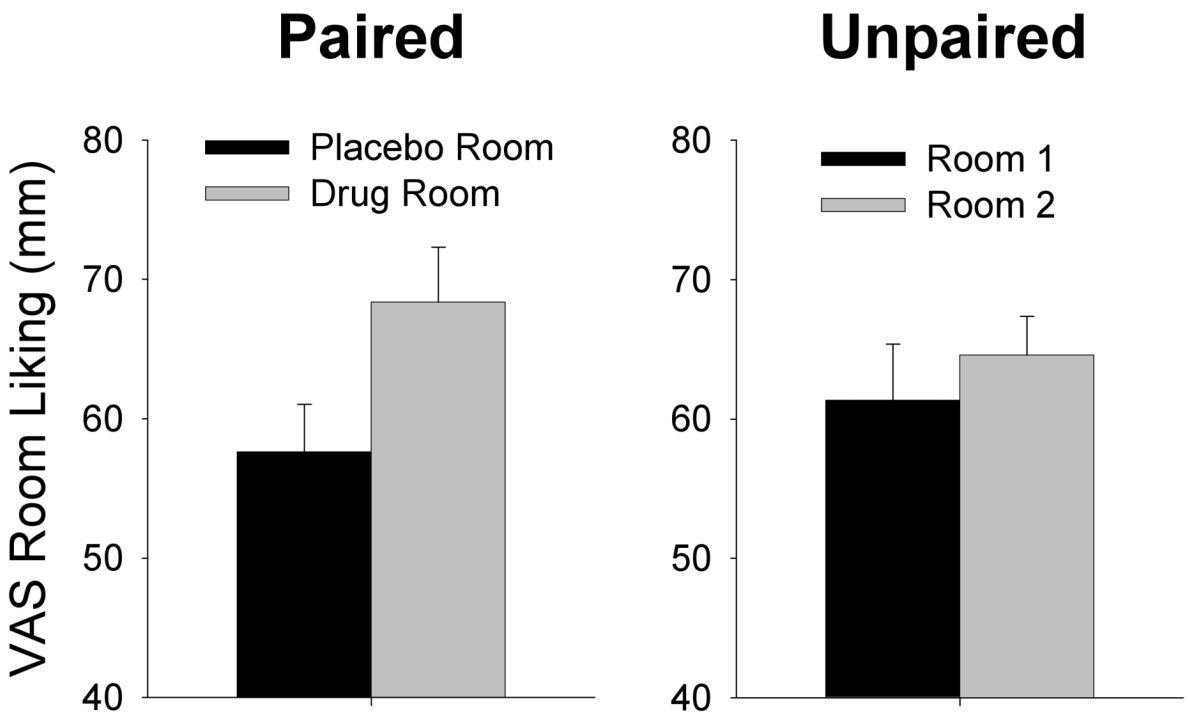

Figure 1.
Effects of conditioning upon VAS Room Liking scores. Data represent mean ± SEM room liking for (1) placebo- and drug-paired rooms among individuals in the paired conditioning groups and (2) Room 1 and Room 2 among individuals in the unpaired conditioning group.

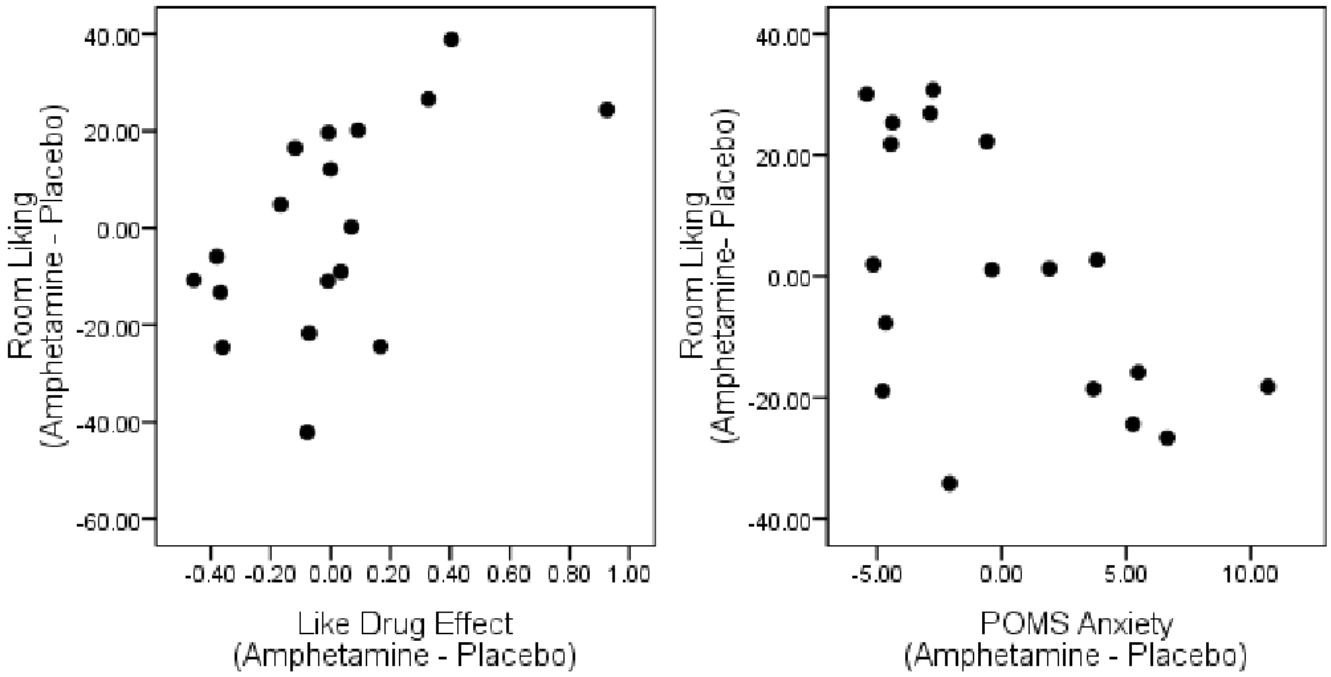

Figure 2.
Partial regression plots showing correlations between room liking and subjective responses to amphetamine among individuals in the paired groups.

Table 1

Demographic characteristics of participants. Data represent mean ± SEM for individuals in the paired and unpaired conditioning groups.

	Paired (N=19)	Unpaired (N=12)
Sex (male/female)	11/8	6/6
Age	25.1±0.5	21.5±0.6
Body Mass Index (kg/m^2)	22.7±0.5	22.9±0.6
Caffeine consumption (cups/week)	6.0±1.0	5.1±1.7
Alcohol consumption (drinks/week)	2.7±0.5	4.5±1.2
Smoking status (cigarettes per week)	1.4±1.1	2.5±1.8
Race (%)		
White	63	50
Black	11	17
Asian	16	25
Other	10	8
Drug Use (% ever used)		
Cannabis	74	67
Stimulants	26	17
Opiates	11	0
Tranquilizers	5	0
Hallucinogens	32	17

Table 2

Multiple linear regression analysis of subjective effects (amphetamine – placebo) that predicted room liking (amphetamine – placebo) among individuals in the paired condition.

Variables	Room Liking	POMS Anxiety	DEQ Drug Liking	ARCI LSD	β	t	*p*
POMS Anxiety	-0.45				-0.49	-2.40	0.03
Drug Liking	0.18	0.26			0.56	2.41	0.03
ARCI LSD	-0.33	0.18	0.36		-0.43	-2.02	0.065
Positive Mood	-0.12	0.09	0.35	0.03	-0.26	-1.21	0.25