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Acute Subjective and Behavioral Effects of Microdoses of Lysergic Acid Diethylamide in Healthy Human Volunteers

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ABSTRACT

BACKGROUND: Numerous anecdotal reports suggest that repeated use of very low doses of lysergic acid diethylamide (LSD), known as microdosing, improves mood and cognitive function. These effects are consistent both with the known actions of LSD on serotonin receptors and with limited evidence that higher doses of LSD (100–200 μg) positively bias emotion processing. Yet, the effects of such subthreshold doses of LSD have not been tested in a controlled laboratory setting. As a first step, we examined the effects of single very low doses of LSD (0–26 μg) on mood and behavior in healthy volunteers under double-blind conditions.

METHODS: Healthy young adults (N = 20) attended 4 laboratory sessions during which they received 0 (placebo), 6.5, 13, or 26 μg of LSD in randomized order at 1-week intervals. During expected peak drug effect, they completed mood questionnaires and behavioral tasks assessing emotion processing and cognition. Cardiovascular measures and body temperature were also assessed.

RESULTS: LSD produced dose-related subjective effects across the 3 doses (6.5, 13, and 26 μg). At the highest dose, the drug also increased ratings of vigor and slightly decreased positivity ratings of images with positive emotional content. Other mood measures, cognition, and physiological measures were unaffected.

CONCLUSIONS: Single microdoses of LSD produced orderly dose-related subjective effects in healthy volunteers. These findings indicate that a threshold dose of 13 μg of LSD might be used safely in an investigation of repeated administrations. It remains to be determined whether the drug improves mood or cognition in individuals with symptoms of depression.

Keywords: Behavior, Emotion, LSD, Microdosing, Mood, Psychopharmacology

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There has been a great deal of public interest in the phenomenon of microdosing lysergic acid diethylamide (LSD) to improve mood and cognitive function (1–3). Users claim that very low doses of LSD (5–20 μg) taken at 3- to 5-day intervals improve depressed mood and positive outlook and perhaps also improve cognitive function. The phenomenon has received widespread coverage, including reports in *The New York Times*, *The Atlantic*, and *The New Yorker* as well as in recent books (4,5). Although several naturalistic studies have been conducted to monitor users' experiences with the drug in noncontrolled settings (6), there have been few controlled studies with double-blind drug administration and placebo.

The pharmacology of LSD is fairly well documented. Like many approved medications for the treatment of depression, LSD has its primary effects on the serotonin system, specifically the 5-HT_{2A} receptors (7), although the drug also binds at several other serotonin receptors, including 5-HT_{1A}, 5-HT_{2C}, 5-HT_{5A}, and 5-HT_6 (8). LSD is of natural origin, obtained by hydrolysis of ergot alkaloids, which are produced by the ergot (*Claviceps*) fungus. Its primary psychoactive effects are thought to be related partial agonist actions at 5-HT_{2A} and 5-HT_{2C} receptors, and some behavioral actions have been linked to dopamine D_2 receptors (9,10). Although the psychedelic effects of LSD and other 5-HT_{2A} agonists are blocked by 5-HT_{2A} antagonists (11,12), less is known about the binding profiles of the very low doses. LSD remains bound to receptors for a long time, which may be responsible for its long duration of effect and may contribute to its reported therapeutic value with doses administered at 3- to 5-day intervals (13). The effects of high doses of LSD (100–200 μg) can last as long as 12 hours. There is a detectable metabolite, 2-oxo-3-hydroxy-LSD, but its pharmacological activity is not known (14). The safety of LSD has been well documented over decades of research and experience, including at doses many-fold higher than those proposed here (8).

The use of LSD as an antidepressant has a long history. During the 1950s and 1960s, more than 1000 studies were published supporting therapeutic effects of LSD in combination with psychotherapy for disorders such as depression (15,16). However, many of these early studies lacked adequate control groups and did not isolate drug effects from effects of the psychotherapy itself. More recently, preclinical studies

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have shown that LSD exerts antidepressant-like effects in animal models (17), and a small number of recent studies in humans have shown that high doses of the drug (200–800 μg) are effective in reducing psychiatric symptoms, including end-of-life anxiety in patients with terminal illness and addictive disorders in drug users (18,19). Some of the positive emotional effects of LSD, such as optimism, reportedly persist for weeks after administration of a moderately high dose (20). It should be noted that these studies are typically conducted in the safe, pleasant environment of a testing room furnished with welcoming décor, pleasant music, and an effort to create a relaxing atmosphere. In less predictable environments, LSD can produce less positive and even negative emotional effects, although there are limited data on the connection between environment and emotional experience on the drug (21).

Several recent controlled studies have described the behavioral and neural effects of high doses of LSD (100–200 μg) in healthy adults (11,12,22–26). Although such high doses would be impractical for a regularly dosed therapeutic drug used in naturalistic settings because of perceptual distortions and impaired inhibitory control, it is interesting to note that the high doses produce some possibly beneficial emotional effects, such as reduced reactivity to fearful faces, and increased feelings of trust and closeness to others.

There have also been reports that LSD improves cognitive function. This is consistent with reports that improved cognition often accompanies improved mood (2,3,6), and there is evidence that LSD can enhance learning in animal models of depression (17). 5-HT_{2A} signaling is known to be involved in learning (27), and intrahippocampal administration of LSD enhances associative learning in rabbits (28). Improvements in cognitive function would be consistent with cellular findings by Ly *et al.* (29) that LSD and other psychedelic drugs increase dendritic arbor complexity, promote growth of dendritic spines, and stimulate formation of synapses (16).

Several studies have examined the effects of low doses of psychedelic drugs in human volunteers either with single doses under controlled conditions or with repeated doses under naturalistic conditions. For example, Yanakieva *et al.* (30) used a between-subject design in a controlled setting to examine the effects of LSD (0, 5, 10, and 20 μg) on perception of time in older adults aged 55 to 75 years. Subjects overestimated time intervals of 2 seconds and longer after the 10-μg dose. Prochazkova *et al.* (31) conducted an unblinded naturalistic study using estimated doses of psilocybin or psilocin during a group social event to assess the effects of the drug on creativity-related problem-solving tasks. Participants reported that the drug increased cognitive fluency, flexibility, and originality without affecting analytic cognition. In perhaps the most comprehensive naturalistic study to date, the authors obtained extensive questionnaire data from about 350 individuals who reported microdosing, assessing both actual experiences and expected effects of using the psychedelic drugs on measures of mood, attention, mind-wandering, and well-being. Participants reported transient enhanced mood and well-being (6). Although the participants described strongly held beliefs about the beneficial effects of microdosing, these expectancies did not always align with the actual reports of beneficial effects after using the drug.

The study presented here addresses a gap in our knowledge about the acute effects of very low doses of LSD on mood, cognition, and affective responses to stimuli with emotional valence. We tested the mood-altering, physiological, and behavioral effects of 3 low doses (6–26 μg) of LSD in young adults in a double-blind, within-subject placebo-controlled laboratory. Understanding the acute effects of a drug is a first step in investigating the effects of repeated doses in clinical populations.

METHODS AND MATERIALS

Study Design

The study used a within-subject, double-blind design consisting of 4 sessions in which healthy young adults received, in counterbalanced order, 0 (placebo), 6.5, 13, or 26 μg of LSD. Subjective mood states and physiological measures were recorded at baseline before drug administration and then at 30- to 90-minute intervals after drug administration, and at the time of peak drug effect subjects completed behavioral tasks assessing cognition and affective responses to emotional stimuli. Sessions were conducted in private living room–style laboratory rooms equipped with a couch, table, and computer for testing. Between measurements, participants were allowed to relax, read, or watch movies.

Subjects

Healthy subjects (N = 20; 12 women) aged 18 to 40 years were recruited from the community. Screening consisted of a physical examination, electrocardiogram, modified Structural Clinical Interview for DSM-5, and self-reported health and drug use history. Inclusion criteria were fluency in English, at least a high school education, body mass index of 19 to 26, no current or past year DSM-5 disorders, no past year drug or alcohol dependence, not currently pregnant or nursing, no night shift work, no regular medication aside from birth control, and at least one use of a psychedelic drug that we defined as 3,4-methylenedioxymethamphetamine, LSD, psilocybin, *N,N*-dimethyltryptamine, or others considered on a case-by-case basis. Subjects were excluded if they had an adverse reaction to a psychedelic drug resulting in an unwillingness to use the drug again.

Subjects were required to abstain from drugs and medications for 48 hours before and 24 hours after each session. In addition, they were instructed to abstain from cannabis 7 days before and 24 hours after each session and to abstain from alcohol for 24 hours before and 12 hours after each session. They were permitted to consume their normal amounts of caffeine and nicotine before and after the session. Subjects were instructed to have a normal night's sleep and to fast for 12 hours before the session. A granola bar was provided at arrival, and lunch was provided 240 minutes after drug administration. They were not permitted to drive, bike, or operate machinery for 12 hours after each session. Subjects were told that they might receive a placebo, stimulant, sedative, or hallucinogen drug. All subjects provided informed consent prior to beginning the study procedures, which were approved by the University of Chicago Institutional Review Board.

Procedure

Orientation Session. Subjects attended an orientation session to review the protocol, provide informed consent, receive presession instructions, and practice study tasks and questionnaires.

Drug Sessions. Subjects attended four 8-hour experimental sessions beginning at 9:00 AM and separated by at least 7 days. Compliance to drug abstinence instructions was verified by urinalysis (Instant Drug Test Cup; CLIAwaived, San Diego, CA) and breath alcohol testing (Alco-Sensor III; Intoximeters, St. Louis, MO). Female subjects provided urine samples for pregnancy tests. After compliance was confirmed, baseline measures of subjective state and cardiovascular function were obtained. LSD (6.5, 13, or 26 μg; Organix Inc., Woburn, MA) or placebo (water) was administered sublingually at 9:30 AM. The drug was administered under double-blind conditions in a volume of 0.5 mL consisting of water and the appropriate volume of LSD solution. The subject held the solution under the tongue without swallowing for 60 seconds under observation by a research assistant. Subjective and cardiovascular measures were taken at 10:30 and 11:30 AM and at 1:00, 2:00, 3:30, and 4:30 PM. At noon, subjects completed a battery of behavioral tasks, including measures of affective responses to emotional stimuli as well as a measure of working memory. At 1:10 PM, lunch was provided. At 4:30 PM, subjects completed an end-of-session questionnaire. Subjects were also asked to complete a mood questionnaire 48 hours after each session to detect lasting alterations in mood.

Drug

The drug was manufactured by Organix and was prepared in solution with tartaric acid by the University of Chicago Investigational Pharmacy. The drug was administered sublingually. The doses were selected to be below the threshold for hallucinatory effects and within the range that is used in naturalistic settings. A recent comprehensive survey indicated that the average dose used for microdosing LSD is 13.5 μg (6). The onset of action after oral LSD is 30 minutes, with a peak plasma concentration at 1.5 to 3 hours and a half-life of 9 hours (32).

Subjective and Cardiovascular Drug Effects

Subjective and physiological measures were obtained to monitor the effects of the drug. Standardized questionnaires were used to assess mood and drug effects.

Drug Effects Questionnaire. The Drug Effects Questionnaire (33) consists of 5 questions assessing subjective drug effects using 100-mm visual analog scales: Do you feel a drug effect?, Do you like the drug effect?, Do you feel high?, Do you want more of what you received?, and Do you dislike the drug effect?

Addiction Research Center Inventory. The Addiction Research Center Inventory (ARCI) (34) consists of 49 true/false questions with 5 subscales of drug-like effects: A (amphetamine-like, stimulant effects), BG (benzedrine group, energy and intellectual efficiency), MBG (morphine-benzedrine group, euphoric effects), LSD, and PCAG (pentobarbital-chlorpromazine-alcohol group, sedative effects).

Profile of Mood States. The Profile of Mood States (POMS) (35) was originally our primary outcome measure. It was administered before drug administration and at 120 and 360 minutes. It consists of 72 mood adjectives rated on a Likert scale from 0 (not at all) to 4 (extremely), divided into subscales assessing Anxiety, Depression, Anger, Vigor, Fatigue, Confusion, Friendliness, and Elation. The POMS Depression scale with 2 distractor items (cheerful and clear-headed) was used to assess mood via e-mail 48 hours after each session.

5 Dimensions of Altered States of Consciousness Questionnaire. The 5 Dimensions of Altered States of Consciousness Questionnaire (5D-ASC) (36) was administered once each session at 12:50 PM. It consists of 94 statements describing sensations typical of a psychedelic or mystical experience. Subjects responded to statements on a 100-mm visual analog scale indicating how they felt relative to their normal waking consciousness, the degree to which they experienced each item during that day's session. Its 5 subscales measure aspects of the psychedelic experience: Oceanic Boundlessness, Dread of Ego Dissolution, Visionary Restructuralization, Acoustic Alterations, and Vigilance Reduction.

Physiological, Behavioral, and Cognitive Measures. Heart rate and blood pressure were measured repeatedly during the sessions. The following behavioral and cognitive tasks were administered once during each session: the dual *n*-back (37), a measure of working memory; the digit symbol substitution task, a measure of cognitive functioning; the cyberball task, a measure of simulated social exclusion (38); the emotional images task, in which participants rate positive, negative, and neutral emotional images from the International Affective Picture System (39) using an evaluative space grid (40); and a remote associations task measuring convergent thinking, an aspect of creativity (41). Descriptions are provided in the Supplement.

Statistical Analyses

Analyses were conducted using SPSS, version 25 (IBM Corp., Armonk, NY). Missing cases (owing to equipment malfunction or other data collection problems) were deleted listwise, which led to smaller sample sizes for some analyses. Subjective and physiological effects of the drug were assessed using repeated-measures analysis of variance with dose and time as within-subjects factors and follow-up planned contrasts comparing each dose with placebo. Behavioral data from tasks were analyzed with repeated-measures analyses of variance with dose as a within-subjects factor and similar follow-up tests.

RESULTS

Demographics

Subjects were, on average, in their mid-20s (mean = 25 years) with an average of 3 years post–high school education (Table 1). The largest proportion was Caucasian (*n* = 9) and reported moderate previous drug use experience.

Table 1. Demographics and Drug Use of the Participants

Category	*n* or Mean ± SD (Range)
N (Male/Female)	20 (8/12)
Age, Years	25 ± 3 (19–30)
Education, Years	15 ± 1 (12–16)
Body Mass Index, kg/m^2	25.1 ± 4.0 (18–31)
Race	
Caucasian	9
African American	4
Asian	1
Other/More than one race	6
Depression Anxiety Stress Scale	
Depression	2.1 ± 2.4 (0–8)
Anxiety	1.7 ± 2.0 (0–6)
Stress	3.6 ± 2.9 (0–11)
Drug Use in Past Month	
Caffeine, servings/day	1.8 ± 2.1 (0–8)
Tobacco	
Smokers/Nonsmokers	6/14
Cigarettes/day for smokers only	1.4 ± 1.0 (0.2–2)
Alcohol, drinks/week	3.4 ± 2.8 (0–13)
Alcohol, drinking days/week	2.7 ± 2.0 (0–7)
Cannabis, times/month	14.0 ± 16.2 (0–60)
Lifetime Drug Use	
Stimulant	
Never used	3
1–5 times	7
6–25 times	7
26–60 times	3
Tranquilizer	
Never used	1
1 time	1
5 times	5
6–20 times	3
21–70 times	1
Opiate	
Never used	12
1–5 times	3
6–10 times	2
11–100 times	2
MDMA, Ecstasy, or Molly	
Never used	1
1–5 times	11
6–20 times	6
21–70 times	2
LSD	
Never used	6
1–5 times	10
6–20 times	4
Psilocybin or mescaline	
Never used	6
1–5 times	11
6–20 times	3
Other psychedelics (e.g., DMT, salvia, ketamine, peyote)	
Never used	14
1–5 times	3
6–20 times	3

DMT, *N,N*-dimethyltryptamine; LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine.

Subjective Effects

Drug Effects Questionnaire. LSD (13 and 26 μg) significantly increased ratings of "feel drug" on the Drug Effects Questionnaire (Figure 1A) (dose × time, $F_{18,342}$ = 10.36, $p < .001$; 26 μg vs. placebo, $p < .001$ at 120 and 180 minutes, $p < .01$ at 240 minutes; 13 μg vs. placebo, $p < .05$ at 120 minutes). LSD (26 μg) increased ratings of "feel high" (Figure 1B) (dose × time, $F_{18,342}$ = 8.48, $p < .001$; 26 μg vs. placebo, $p < .001$ at 120 and 180 minutes) and "like drug" (Figure 1C) (dose × time, $F_{18,342}$ = 2.34, $p < .01$; 26 μg vs. placebo, $p < .01$ at 120 minutes). The 26-μg dose also significantly increased ratings of "dislike drug" (Figure 1D) (dose × time, $F_{18,342}$ = 2.30, $p < .01$; 26 μg vs. placebo, $p < .05$ at 240 minutes). There was a trend toward a dose × time interaction on "want more" (Figure 1E) ($F_{18,342}$ = 1.49, p = .09).

Addiction Research Center Inventory. LSD (26 μg) increased scores on the LSD subscale compared with placebo (Figure 1B) (dose × time, ARCI LSD subscale, $F_{18,342}$ = 4.13, $p < .001$; 26 μg vs. placebo, $p < .05$ at 120 minutes and $p < .01$ at 180 minutes). There were no significant drug effects on ARCI A, MBG, and PCAG subscales.

Profile of Mood States. On the POMS, LSD (26 μg) significantly increased ratings of Vigor relative to placebo (dose, $F_{3,57}$ = 5.14, $p < .01$; 26 μg vs. placebo, $p < .05$). On POMS ratings of Friendliness, there was a main effect of dose ($F_{3,57}$ = 2.80, $p < .05$), but follow-up tests did not reach significance. On the POMS Anxiety subscale, there was a main effect of dose and a trend for the highest dose to increase ratings ($F_{3,57}$ = 3.24, $p < .05$; 26 μg vs. placebo, p = .051). The drug did not significantly affect Elation, Depression, Anger, Fatigue, and Confusion subscales (Table 2).

5D-ASC Questionnaire. On the 5D-ASC administered at the end of each session, LSD dose-dependently increased ratings on the subscales of Experience of Unity (Figure 2B) (dose, $F_{3,57}$ = 3.53, $p < .05$; 13 μg vs. placebo, $p < .05$; 26 μg vs. placebo, $p < .05$), Blissful State (Figure 2A) (dose, $F_{3,57}$ = 6.71, $p < .01$; 13 μg vs. placebo, $p < .01$; 26 μg vs. placebo, $p < .05$), Impaired Control and Cognition (Figure 2B) (dose, $F_{3,57}$ = 2.94, $p < .05$; 26 μg vs. placebo, $p < .05$), and Changed Meanings of Percepts (Figure 2C) (dose, $F_{3,57}$ = 2.85, $p < .05$), although follow-up tests did not reveal a significant dose effect. LSD also tended to increase ratings of Spiritual Experience, Insightfulness, and Complex Imagery (dose Spiritual Experience, $F_{3,57}$ = 2.40, p = .08; dose Insightfulness, $F_{3,57}$ = 2.64, p = .06; dose Complex Imagery, $F_{3,57}$ = 2.43, p = .08). There were no significant linear drug effects on

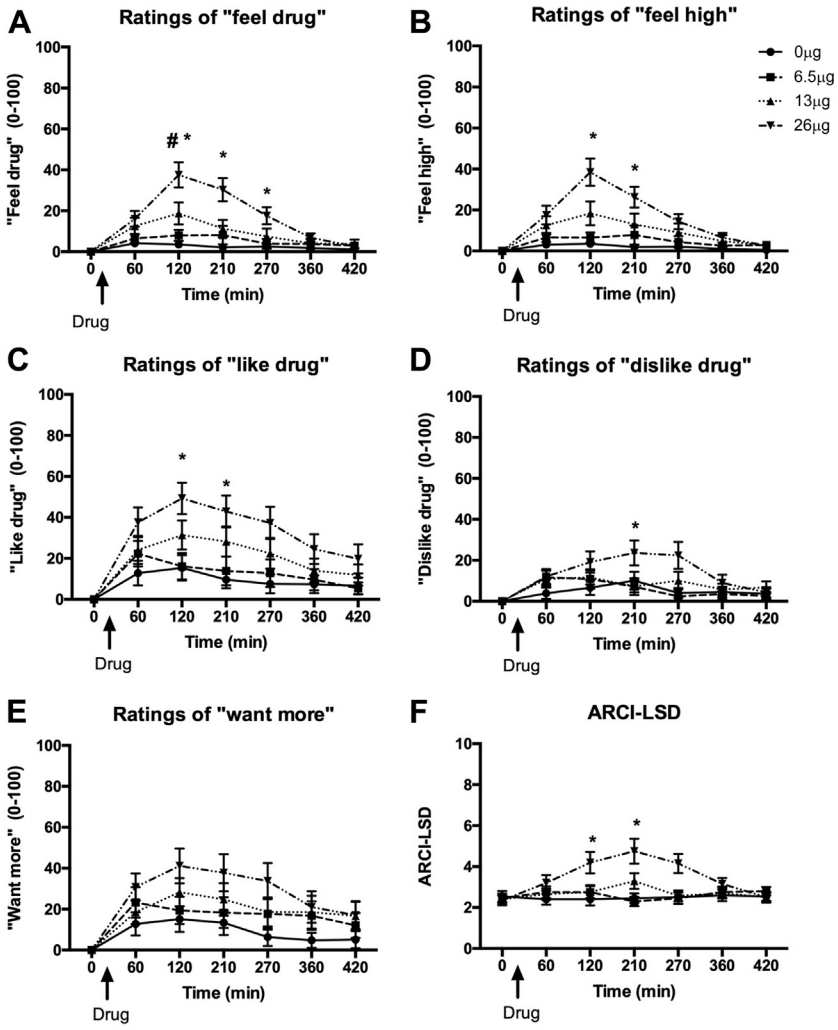

Figure 1. Effects of lysergic acid diethylamide (LSD) on subjective reports of "feel drug" **(A)**, "feel high" **(B)**, "like drug" **(C)**, "dislike drug" **(D)**, "want more" **(E)**, and Addiction Research Center Inventory (ARCI) LSD subscale **(F)**. Bars depict mean ± SEM. *Significant difference for 26 μg vs. placebo, $p < .01$; #Significant difference for 13 μg vs. placebo, $p < .05$.

Disembodiment, Anxiety, Elementary Imagery, and Audiovisual Synesthesia subscales.

Follow-up Questionnaire. On the follow-up questionnaire administered 48 hours after each session, there were no significant effects of dose. However, because these questionnaires were sent via e-mail and did not require an additional laboratory visit, only 11 of the 20 subjects completed all 4 follow-up questionnaires.

Physiological Effects

LSD (13 and 26 μg) significantly increased systolic blood pressure from 105.35 mmHg on the placebo session to a peak of 111.5 mmHg at 13 μg and 115.3 mmHg at 26 μg (dose × time, $F_{18,342} = 1.68$, $p < .05$; at 120 and 180 minutes, 26 μg vs. placebo, $p < .01$; at 120 minutes, 13 μg vs. placebo, $p < .05$), and 26 μg significantly increased diastolic blood pressure (dose × time, $F_{18,342} = 1.72$, $p < .05$; 26 μg vs. placebo at 120 minutes, $p < .01$). The drug did not significantly affect heart rate or basal body temperature.

Emotion Processing Tasks

Produced their expected effects on dimensions of emotional processing, but LSD had little effect on task performance (see Supplement). The only apparent drug effects were on the emotional images task, a marginal decrease in positivity ratings for positive pictures observed at the highest dose (Figure 3), and on the Remote Associates Test, a marginal increase in attempted trials.

Drug Identifications

During the placebo session, 14 participants correctly guessed that they had received placebo (incorrect guesses: sedative [$n = 5$] or cannabinoid [$n = 1$]). During the 6.5-μg dose session, no participants correctly guessed that they had received a hallucinogen (incorrect guesses: placebo [$n = 9$], a stimulant [$n = 4$], a sedative [$n = 4$], opioid [$n = 1$), or cannabinoid [$n = 2$]). During the 13-μg dose session, 2 of the 20 participants correctly guessed what they had received (incorrect guesses: placebo [$n = 9$], a stimulant [$n = 3$], a sedative [$n = 4$], or opioid [$n = 1$]). During the 26-μg dose session, 6 participants correctly guessed that they received a hallucinogen

Table 2. Mean (SD) for Outcomes of Subjective Ratings of Mood and Behavioral Tasks

	Placebo	6.5 μg	13 μg	26 μg
IAPS Image Ratings, 0–6				
Positive	2.0 (0.5)	2.0 (0.5)	1.9 (0.4)[a]	1.8 (0.5)
Neutral	1.1 (0.6)	1.2 (0.5)	1.1 (0.5)	1.1 (0.6)
Negative	0.3 (0.2)	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)
Face Identification, seconds to detect				
Angry	11.2 (3.2)	10.7 (2.6)	10.6 (3.5)	10.8 (2.6)
Sad	8.0 (2.3)	7.3 (1.8)	8.3 (2.5)	8.0 (1.9)
Happy	7.8 (2.4)	7.2 (2.2)	7.9 (2.8)	7.4 (1.7)
Fearful	8.4 (2.6)	7.5 (2.3)	8.7 (3.0)	8.5 (3.4)
Disgust	7.1 (2.5)	7.9 (2.6)	7.3 (2.9)	7.3 (2.6)
Surprise	7.7 (1.4)	7.8 (1.6)	7.8 (2.0)	8.0 (2.4)
Cyberball, Positive Mood Ratings 1–100				
Accept	27.4 (4.3)	27.1 (4.1)	28.0 (4.0)	28.0 (5.0)
Reject	18.8 (6.9)	19.0 (6.5)	18.8 (6.6)	18.9 (7.0)
n-Back				
Correct, *n*	19.0 (1.6)	19.2 (1.4)	19.3 (1.6)	19.6 (2.2)
RT, ms	2595.7 (132.9)	2602.9 (142.5)	2601.3 (111.5)	2601.8 (123.8)
DSST				
Correct, *n*	71.7 (14.6)	72.3 (11.4)	72.3 (12.7)	70.6 (11.5)
Attempted, *n*	71.7 (14.6)	72.4 (11.4)	72.3 (12.7)	70.4 (11.7)
Remote Associates				
Correct, *n*	7.1 (2.2)	7.5 (1.5)	7.6 (2.4)	7.6 (2.3)
Attempted, *n*	14.2 (4.2)	15.2 (3.2)	15.3 (4.0)	15.7 (4.1)
POMS, Peak Change From Baseline				
Depression	−0.2 (1.4)	0.3 (1.7)	−0.3 (2.5)	1.1 (2.7)
Anxiety	−0.5 (2.1)	−1.3 (4.7)	0 (4.8)	1.7 (4.7)
Friendliness	−2.8 (4.0)	−0.9 (6.1)	−1.8 (5.3)	−0.5 (6.7)
Vigor	−4.1 (5.8)	−2.4 (6.7)	−2.5 (6.3)	−1.4 (11.1)
Anger	−0.2 (1.0)	−0.5 (1.6)	0.4 (2.3)	0.2 (2.8)
Fatigue	1.1 (3.6)	0.2 (3.5)	0.4 (3.5)	1.1 (4.8)
Confusion	−0.2 (1.8)	−0.1 (1.4)	0.4 (2.3)	1.5 (3.1)
Elation	−1.9 (4.6)	−1.7 (4.5)	−0.4 (5.0)	−0.8 (5.2)
POMS Depression Follow-up (*n* = 11)	7.4 (7.6)	6.7 (7.3)	7.4 (11.8)	7.4 (11.5)

DSST, digit symbol substitution task; POMS, Profile of Mood States; RT, response time.
[a]Significant difference from placebo, $p < .05$.

(incorrect guesses: stimulant [*n* = 6], sedative [*n* = 2], cannabinoid [*n* = 3], opioid [*n* = 1], or placebo [*n* = 2]).

DISCUSSION

In this study, we investigated the acute effects of very low microdoses of LSD on mood, cognition, and behavior in healthy young adult volunteers and identified the threshold doses at which LSD produces detectable subjective effects. We report that at doses 1/10th to 1/20th those used recreationally (and more recently in therapeutic settings), LSD produces measurable modest increases in ratings of drug effect scales. At these doses, LSD also had subtle effects on behavioral tasks, tending to increase the number of attempted trials on a creativity task (the Remote Associates Test). This is the first controlled study to investigate the acute subjective and behavioral effects of microdoses of LSD using a placebo-controlled within-subjects design in healthy young adult volunteers.

Doses of 13 and 26 μg LSD produced measurable subjective and physiological effects. The effects were linearly dose related across all 3 doses, and 26 μg of LSD significantly increased ratings of "feel drug," "like drug," "feel high," and "dislike drug" on the Drug Effects Questionnaire as well as scores on the ARCI LSD subscale and the POMS Vigor subscale. Interestingly, the drug also produced dose-dependent alterations of consciousness as measured by the 5D-ASC, which had previously been shown only at 100- to 200-μg doses (42). Physiologically, the 26-μg dose increased blood pressure but did not significantly affect temperature or heart rate. Previous studies have shown that 200 μg of LSD increases heart rate, blood pressure, and body temperature (23), but the current findings reveal the threshold dose at which LSD produces these effects. This profile of responses to very low doses of LSD extends our understanding of the basic pharmacology of the drug and sets the stage for future studies on the behavioral and physiological effects of repeated doses of LSD.

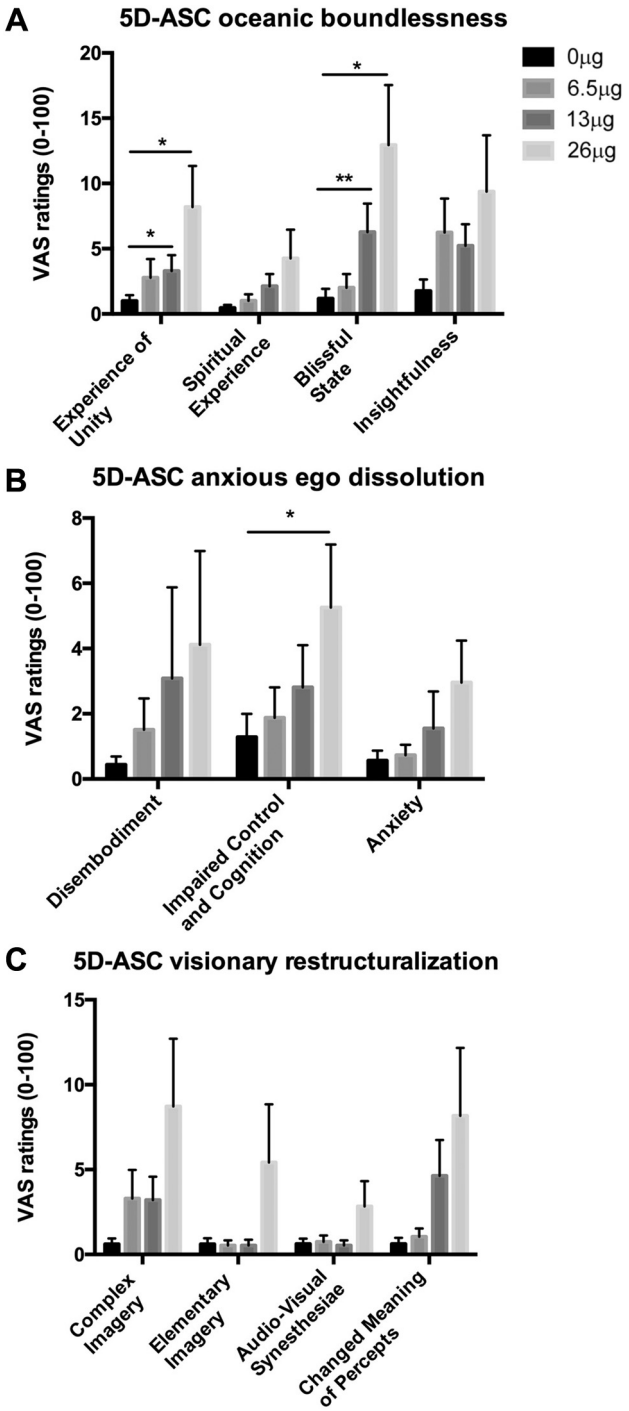

Figure 2. Effect of lysergic acid diethylamide on the 5 Dimensions of Altered States of Consciousness Questionnaire (5D-ASC) ratings on domains of **(A)** oceanic boundlessness, **(B)** anxious ego dissolution, and **(C)** visionary restructuralization. Bars depict mean ± SEM. *Significant difference from placebo, $p < .05$; **Significant difference from placebo, $p < .01$. VAS, visual analog scale.

There is some evidence that higher doses of LSD combined with psychotherapy can have beneficial effects on mood. Case reports and studies from the 1950s and 1960s suggest that LSD

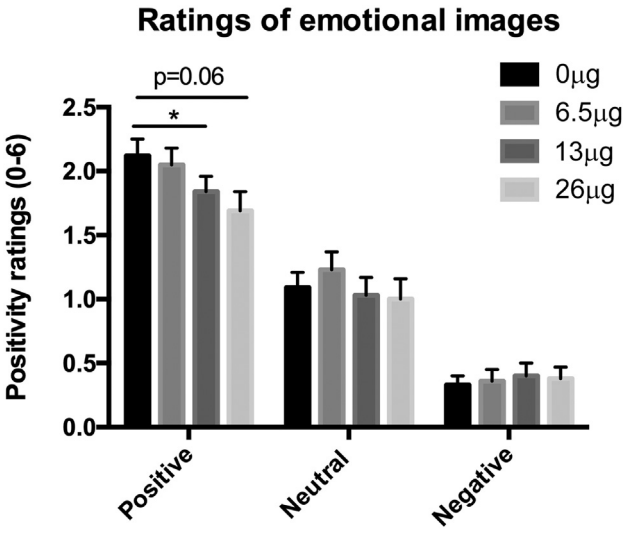

Figure 3. Effects of lysergic acid diethylamide on ratings of emotional images. Bars depict mean ± SEM. *Significant difference from placebo, $p < .05$.

may be effective in a clinical context [reviewed in (43)], and recent studies are investigating 100 to 200 μg of LSD in combination with psychotherapy for anxiety associated with life-threatening illnesses (18). Our participants were healthy and without mood disturbances. It is possible that their increased ratings of Vigor after 26 μg could contribute to beneficial effects for patients in a psychotherapy setting, but this remains to be established in patient samples. The items on the Vigor subscale of the POMS include adjectives such as the following: lively, active, energetic, cheerful, alert, full of pep, carefree, and vigorous. Although some of these effects may fit with the reported mood effects of microdosers in the community setting, the effects of repeated microdoses of LSD in clinical populations of symptomatic volunteers remain to be determined.

While single larger doses of LSD have been shown to have beneficial effects on mood, few studies have examined smaller doses administered at regular intervals. In rodents, repeated low doses of psilocin and ketamine reduce anxiety-like behavior (44,45) and enhance learning in animal models of depression (17). Anecdotal reports in humans suggest that repeated (every 3 days) ingestion of microdoses of LSD enhance mood and reduce ratings of depression (1). A recent survey of 98 regular microdosers suggested that the drug improved psychological functioning, including reductions in depression and stress and lower distractibility (6). Although we did not detect effects of single doses on mood or depression, it remains to be determined whether antidepressant effects would be detected in individuals who report significant levels of depression.

Although some previous studies have suggested improvements in cognition, these were not detected here on the digit symbol substitution task or the *n*-back task. Few studies have assessed acute effects of LSD on cognition. In one recent study LSD (100 μg) significantly increased cognitive bizarreness (46), and in another study LSD (10 μg) altered time perception, resulting in the overreproduction of temporal intervals longer than 2 seconds (30). In one recent naturalistic, open-label (pre-post) study, microdosing psilocybin-containing truffles improved convergent and divergent

thinking without affecting analytic cognition on two creativity tasks (31). Although we found that LSD marginally increased the number of attempted trials on a measure of creativity, overall we detected minimal effects on cognitive function.

Several previous studies using higher doses of LSD have shown acute effects on emotion processing. One study showed that LSD (100–200 μg) impaired recognition of fearful facial expressions (25), and in a functional magnetic resonance imaging study LSD (100 μg) dampened amygdala and medial prefrontal cortex reactivity to fearful faces (47). Interestingly, greater reduction in amygdala response was related to greater subjective drug effects. In another recent study, the $5HT_{1A/2A}$ agonist, psilocybin, at a relatively higher dose (0.215 mg/kg), reduced feelings of social rejection during cyberball (48). We did not observe similar results in our sample, perhaps because of drug or dose differences. Finally, we showed that microdoses of LSD decrease positivity ratings of positive images. This finding was surprising and went against our hypothesis that the drug, in light of reports of antidepressant effects, may positively bias responses to affective stimuli. One possible explanation for our results is that LSD reportedly enhances global connectivity in the brain, giving rise to the phenomenon of ego dissolution or a weakening of the boundary between the self and the universe (49). This increased connectivity between normally distinct networks (default mode, salience, and frontoparietal attention networks) may affect perception of valenced stimuli, leading subjects to rate positive images as less positive.

Our study had a number of strengths. Most notably, we tested 3 doses of the drug, compared with placebo, under double-blind conditions in a controlled laboratory setting. The participants included men and women who were free of other drugs or alcohol at the time of testing. We allowed 7 days for drug clearance between the sessions. We used standardized self-report questionnaires and emotion and cognitive tests, and we obtained physiological measures at regular intervals. Until now, the effects of these very low doses of LSD have been investigated mainly in naturalistic, open-label studies and through surveys (6,31,50). Here, we presented a profile of the full range of responses to the acute doses of the drug—including subjective, behavioral, affective, and cognitive—in healthy young adults. In line with the conclusions of Polito and Stevenson (6), we conclude that the 13-μg dose would be optimal for a repeated dosing study because it produced minimal subjective, behavioral, or physiological effects that might interfere with normal function. The findings form a basis for future studies investigating repeated doses, and doses in clinical populations, to determine the empirical basis of the purported therapeutic effects reported by regular users of these drugs.

The effects of low doses of LSD should be investigated when the drug is administered repeatedly and in individuals who report negative affect. Individuals who report microdosing in their everyday lives take the drug every 3 to 5 days, and it is possible that the beneficial effects emerge only after repeated administration. This could be because of subtle pharmacokinetic accumulation of the drug, or it could be because of pharmacodynamic neural adaptations that occur over days. An important aim for future research will be to collect pharmacokinetic data, extending existing data with higher doses (32). Regular users claim that the drug improves mood and cognition, which raises the possibility that their normal mood and cognitive function were less than optimal before using the drug. Therefore, it is important to examine the effect of LSD, either in single doses or in repeated dosing regimens, in populations reporting clinical mood symptoms such as anxiety and depression. Studies such as this, investigating the mood and cognitive effects of low doses of psychedelic drugs under controlled conditions, will advance our understanding of the neural and behavioral processes underlying depressed mood and could lead to new treatments.

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ClinicalTrials.gov: Mood Effects of Serotonin Agonists; https://clinicaltrials.gov/ct2/show/NCT03790358; NCT03790358.

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