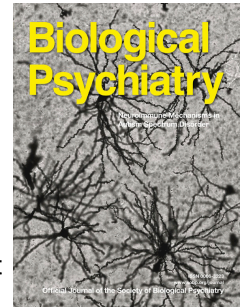


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Acute subjective and behavioral effects of microdoses of LSD in healthy human volunteers

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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 sub-threshold 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 - 26µg) on mood and behavior in healthy volunteers under double-blind conditions.

Methods: Healthy young adults (N=20) attended four laboratory sessions during which they received placebo, 6.5µg, 13µg, or 26µg LSD in randomized order at one-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 three doses (6.5µg, 13µg, or 26µg). 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 13µg 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.

The study is registered on clinicaltrials.gov as “Mood effects of serotonin agonists,” NCT03790358, <https://clinicaltrials.gov/ct2/show/NCT03790358>.

Introduction

There has been a great deal of public interest in the phenomenon of “microdosing” LSD to improve mood and cognitive function (1-3). Users claim that very low doses of LSD (5-20 µg) taken at 3-5-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 non-controlled 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 5HT_{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-HT₆ (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 D2 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 3-5 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 (O-H-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. In the 1950s and 1960s, over 1,000 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 show 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 μ g) are effective in reducing psychiatric symptoms, including end-of-life anxiety in terminally ill patients 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, though 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 μ g) 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 increase 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). 5HT_{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 (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 in single doses under controlled conditions or with repeated doses under naturalistic conditions. For

example, (30) used a between-subject design in a controlled setting to examine the effects of LSD (0, 5, 10 and 20 micrograms) on perception of time in older adults, aged 55 to 75. Subjects over-estimated time intervals of 2 seconds and longer after the 10 microgram 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 wellbeing. Participants reported transient enhanced mood and wellbeing (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 three low doses (6-26 micrograms) 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 to investigating the effects of repeated doses in clinical populations.

Methods

Study Design

The study used a within-subject, double blind design consisting of four sessions wherein healthy young adults received, in counterbalanced order, 0 (placebo), 6.5, 13, or 26 micrograms (μg) of LSD. Subjective mood states and physiological measures were recorded at baseline before drug administration and then at 30-90 min 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) ages 18 - 40 were recruited from the community. Screening consisted of a physical examination, electrocardiogram, modified Structural Clinical Interview for DSM-V and self-reported health and drug-use history. Inclusion criteria were: English fluency, at least a high school education, BMI of 19–26, no current or past year DSM-V 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 which we defined as MDMA, LSD, psilocybin, DMT, 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 seven 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 fast for 12 hours before the sessions. 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 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 pre-session 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 (CLIAwaived Instant Drug Test Cup, San Diego, CA) and breath alcohol testing (Alcosensor 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, and 26 μ g; Organix, Inc.) 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 the research assistant. Subjective and cardiovascular measures were taken at 10:30 and 11:30 AM, and 1, 2, 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, Inc. (MA), and 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 μ g (6). The onset of action after oral LSD is 30 minutes, with a peak plasma concentration at 1.5-3 hours and 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 (DEQ; 33): The DEQ consists of five questions assessing subjective drug effects using 100mm Visual Analog Scales: do you feel a drug effect, like the drug effect, feel high, want more of what you received, or dislike the drug effect.

Addiction Research Center Inventory (ARCI; 34): The ARCI consists of 49 "True-False" questionnaires 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 (lysergic acid diethylamide), and PCAG (pentobarbital-chlorpromazine-alcohol group, sedative effects).

Profile of Mood States (POMS; 35): The POMS was originally our primary outcome measure. It was administered before drug administration and at 120 and 360 minutes. It consists 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 two distractor items (*cheerful* and *clear-headed*) was used to assess mood via email, 48 hours after each session.

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

Physiological, behavioral and cognitive measures (described in Supplementary Materials).

Heart rate and blood pressure were measured repeatedly during the sessions. The following behavioral and cognitive tasks were administered once during the session: the Dual N-Back (37) a measure of working memory, the Digit Symbol Substitution Task (DSST) a measure of cognitive functioning,

“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 (RAT) measuring convergent thinking, an aspect of creativity (41).

Statistical Analyses

Analyses were conducted using SPSS. Missing cases (due to equipment malfunction or other data collection problems) were deleted list-wise, which led to smaller sample sizes for some analyses. Subjective and physiologic effects of the drug were assessed using repeated measures analysis of variance (ANOVA), with dose and time as within-subjects factors and follow-up planned contrasts comparing each dose to placebo. Behavioral data from tasks were analyzed with repeated measures ANOVAs with dose as a within-subject factor and similar follow-up tests.

Results

Demographics

Subjects were in their mid-20's (mean= 25 years) with an average of 3 years post-high school education (Table 1). They were mostly Caucasian (N=9), and reported moderate previous drug use experience.

TABLE 1 here

Subjective effects

DEQ

LSD (13µg and 26µg) significantly increased ratings of “feel drug” on the Drug Effects Questionnaire [Figure 1a: Dose x Time $F(18,342)=10.36$, $p<0.001$; 26µg vs. placebo $p<0.001$ at 120min and 180min, $p<0.01$ at 240min and 13µg vs. placebo $p<0.05$ at 120min]. LSD (26µg) increased ratings of “feel high” [Figure 1b: Dose x Time $F(18,342)=8.48$, $p<0.001$; 26µg vs. placebo $p<0.001$ at 120min and 180min] and “like drug” [Figure 1c: Dose x Time $F(18,342)=2.34$, $p<0.01$; 26µg vs. placebo $p<0.01$ at 120min]. The 26µg dose also significantly increased ratings of “dislike drug” [Figure 1d: Dose x Time

$F(18,342)=2.30, p<0.01$; $26\mu\text{g}$ vs. placebo $p<0.05$ at 240min]. There was a trend toward a dose x time interaction on “Want More” [Figure 1e: $F(18,342)=1.49, p=0.09$].

ARCI

LSD ($26\mu\text{g}$) increased scores on the LSD scale, compared to placebo [Figure 1b: Dose x time; ARCI-LSD $F(18,342)=4.13, p<0.001$; $26\mu\text{g}$ vs. placebo $p<0.05$ at 120min and $p<0.01$ at 180min]. There were no significant drug effects on ARCI A, MBG, BG, or PCAG scales.

POMS

On the POMS, LSD ($26\mu\text{g}$) significantly increased ratings of Vigor, relative to placebo [Dose $F(3,57)=5.14, p<0.01$; $26\mu\text{g}$ vs. placebo $p<0.05$]. On POMS ratings of Friendliness, there was a main effect of dose [$F(3,57)=2.80, p<0.05$] but follow up tests did not reach significance. On the POMS Anxiety scale there was a main effect of dose and a trend for the highest dose to increase ratings [$F(3,57)=3.24, p<0.05$; $26\mu\text{g}$ vs. placebo $p=0.051$]. The drug did not significantly affect Elation, Depression, Anger, Fatigue, or Confusion scales (Table 2).

[TABLE 2]

5D-ASC

On the 5D-ASC administered at the end of each session, LSD dose-dependently increased ratings on the scales of Experience of Unity [Figure 3a: Dose $F(3,57)=3.53, p<0.05$; $13\mu\text{g}$ vs. placebo $p<0.05$ and $26\mu\text{g}$ vs. placebo $p<0.05$], Blissful State [Figure 3a: Dose $F(3,57)=6.71, p<0.01$; $13\mu\text{g}$ vs. placebo $p<0.01$ and $26\mu\text{g}$ vs. placebo $p<0.05$], Impaired Control and Cognition [Figure 3b: Dose $F(3,57)=2.94, p<0.05$; $26\mu\text{g}$ vs. placebo $p<0.05$], and Changed Meanings of Percepts [Figure 3c: Dose $F(3,57)=2.85, p<0.05$], though follow up tests did not reveal a significant dose effect. LSD also tended to increase ratings of Spiritual Experience, Insightfulness, Complex Imagery [Dose SE $F(3,57)=2.40, p=0.08$, I $F(3,57)=2.64, p=0.06$, CI $F(3,57)=2.43, p=0.08$]. There were no significant linear drug effects on Disembodiment, Anxiety, Elementary Imagery, Audiovisual Synesthesiae.

Follow-up questionnaire

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

Physiological effects

LSD (13 μ g and 26 μ g) significantly increased systolic blood pressure from 105.35 mm Hg on the placebo session to a peak of 111.5 at 13 μ g and 115.3 at 26 μ g [Dose x Time $F(18,342)=1.68$, $p<0.05$; at 120min and 180min 26 μ g vs. placebo $p<0.01$, at 120min 13 μ g vs. placebo $p<0.05$] and 26 μ g significantly increased diastolic blood pressure [Dose x Time $F(18,342)=1.72$, $p<0.05$; 26 μ g vs. placebo at 120min $p<0.01$]. The drug did not significantly affect heart rate or basal body temperature.

Emotion processing tasks. The tasks produced their expected effects on dimensions of emotional processing, but LSD had little effect on task performance (see Supplementary Materials). 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 2), and on the Remote Associates task a marginal increase in attempted trials.

Drug Identifications

During the placebo session, 14 participants correctly guessed they had received placebo [incorrect guesses sedative (N=5) or cannabinoid (N=1)]. During the 6.5 μ g dose session, no participants correctly guessed 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 μ g dose session 2 out of the 20 participants correctly guessed what they received [incorrect guesses placebo (N=9), a stimulant (N=3), a sedative (N=4), or opioid (N=1)]. During the 26 μ g dose session 6 participants correctly guessed they received a hallucinogen [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 one tenth to one twentieth those used recreationally (and more recently in therapeutic settings), LSD produces measurable modest increases in ratings of drug effects 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 μ g LSD produced measurable subjective and physiological effects. The effects were linearly dose-related across all three doses, and 26 μ g LSD significantly increased ratings of “feel drug,” “like drug,” “feel high,” and “dislike drug,” and scores on the ARCI-LSD scale and the Vigor scale on the POMS. Interestingly, the drug also produced dose-dependent alterations of consciousness as measured by the 5D-ASC, which had previously only been shown at 100-200 μ g doses (42).

Physiologically, the 26 μ g dose increased blood pressure, but did not significantly affect temperature or heart rate. Previous studies have shown that 200 μ g LSD increase heart rate, blood pressure, and body temperature (23), but the present findings reveal the threshold dose at which LSD produces these effects. This profile of responses to very low doses of LSD extend our understanding of the basic pharmacology of the drug, and set the stage for future studies on the behavioral and physiological effects of repeated doses of LSD.

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 may be effective in a clinical context (reviewed in 43), and recent studies are investigating 100-200 μ g 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 μ g 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 such adjectives as “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 anti-depressant 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 DSST or N-back tasks. 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 over-reproduction of temporal intervals greater than 2 seconds (30). 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 (100-200µg) impaired recognition of fearful facial expressions (25), and in an fMRI 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 (0.215mg/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 three doses of the drug, compared to 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, emotion and cognitive tests and 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 present 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 (6), we conclude that the 13 μ g dose would be optimal for a repeated dosing study, as 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 affects 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 3-5 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 or 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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Figure Legends:

Figure 1: Effects of LSD on subjective reports of a) “feel drug,” b) “feel high,” c) “like drug,” d) “dislike drug,” e) “want more,” and f) ARCI-LSD scale. Bars depict mean \pm SEM.

*signifies significant difference 26ug vs. placebo $p<0.01$, # signifies significant difference 13ug vs. placebo $p<0.05$.

Figure 2: Effects of LSD on ratings of emotional images. Bars depict mean \pm SEM. * indicates significant different from placebo $p<0.05$.

Figure 3: Effect of LSD on the 5D-ASC ratings on domains of a) oceanic boundlessness, b) anxious ego dissolution, and c) visionary restructuralization. Bars depict mean \pm SEM. * indicates significant different from placebo $p<0.05$. ** indicates significant different from placebo $p<0.01$.

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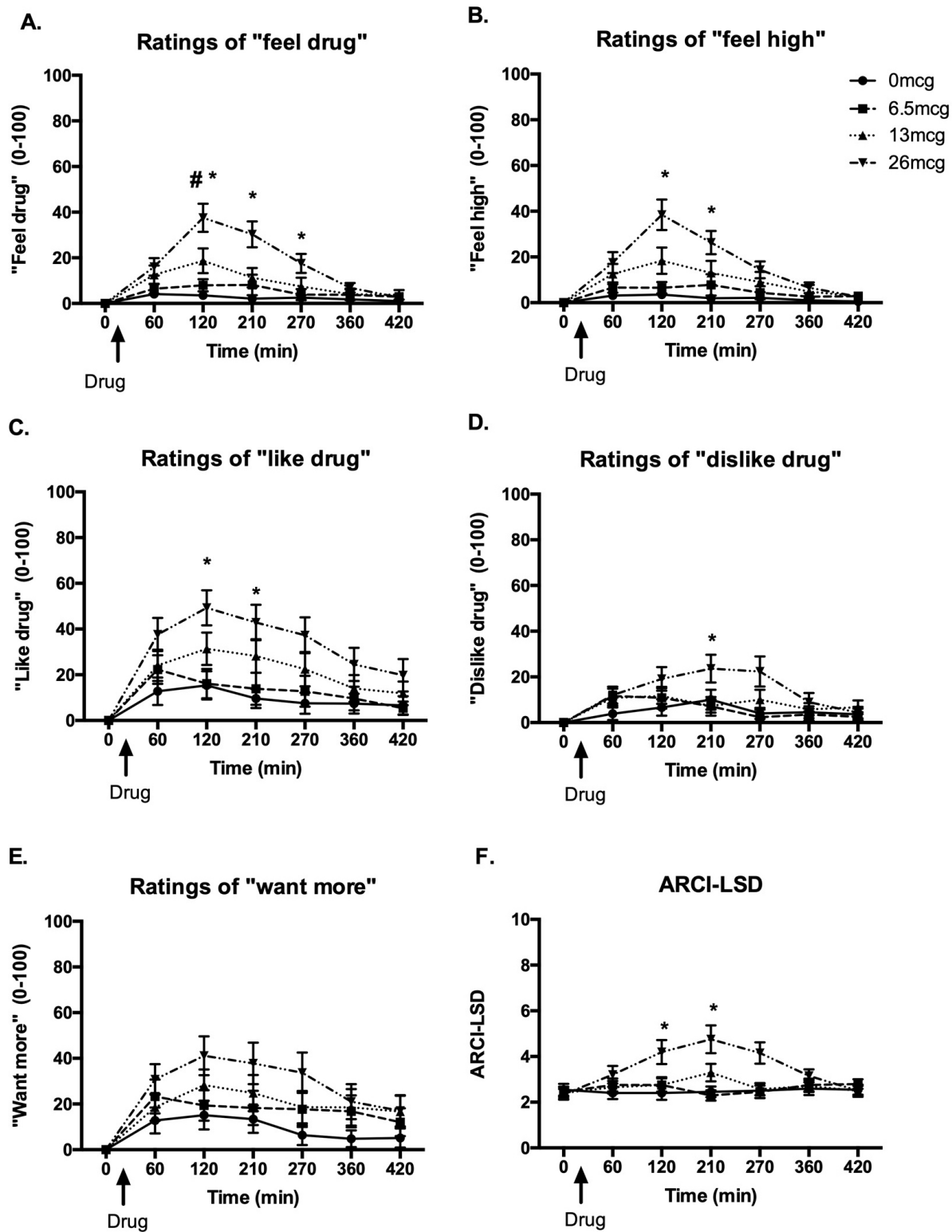
Table 1. Demographic and drug use of the participants (N=20).

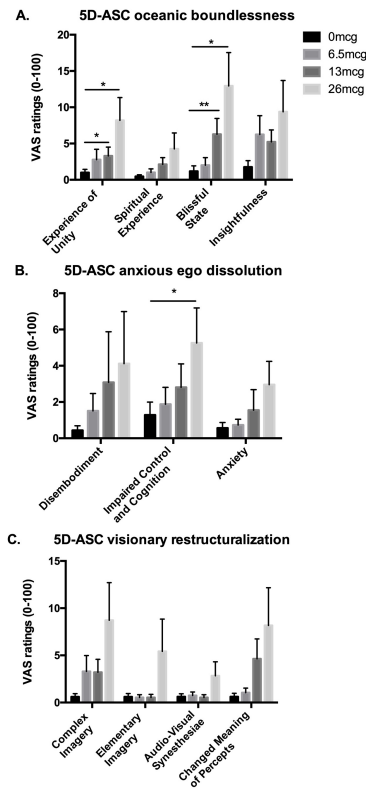
Category	Count or Mean \pm SD (Range)
N (male/female)	20 (8/12)
Age (years)	25 \pm 3 (19 - 30)
Education (years)	15 \pm 1 (12 - 16)
Body Mass Index (kg/m²)	25.1 \pm 4.0 (18.0 - 31.3)
Race	
Caucasian	9
African-American	4
Asian	1
Other/ More than One Race	6
DASS	
Depression	2.1 \pm 2.4 (0 - 8.0)
Anxiety	1.7 \pm 2.0 (0 - 6.0)
Stress	3.6 \pm 2.9 (0 - 11.0)
Current Drug Use (past month)	
Caffeine (servings/ day)	1.8 \pm 2.1 (0 - 7.9)
Tobacco	
Smokers/non-smokers	6/14
Cigarettes/ day (smokers only)	1.4 \pm 1.0 (0.2 - 2.5)
Alcohol (drinks/ week)	3.4 \pm 2.8 (0 - 13.0)
Alcohol (drinking days/ week)	2.7 \pm 2.0 (0 - 7.0)
Cannabis (times/ month)	14.0 \pm 16.2 (0 - 60.0)
Lifetime Drug Use	
Stimulant	14.1 \pm 18.7 (0 - 60.0)
Tranquilizer	12.0 \pm 44.4 (0 - 200.0)
Opiate	8.1 \pm 22.1 (0 - 93.0)
MDMA, Ecstasy, 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 Psychedelic (DMT, Salvia, Ketamine, Peyote)	
Never used	14
1 – 5 times	3
6 – 20 times	3

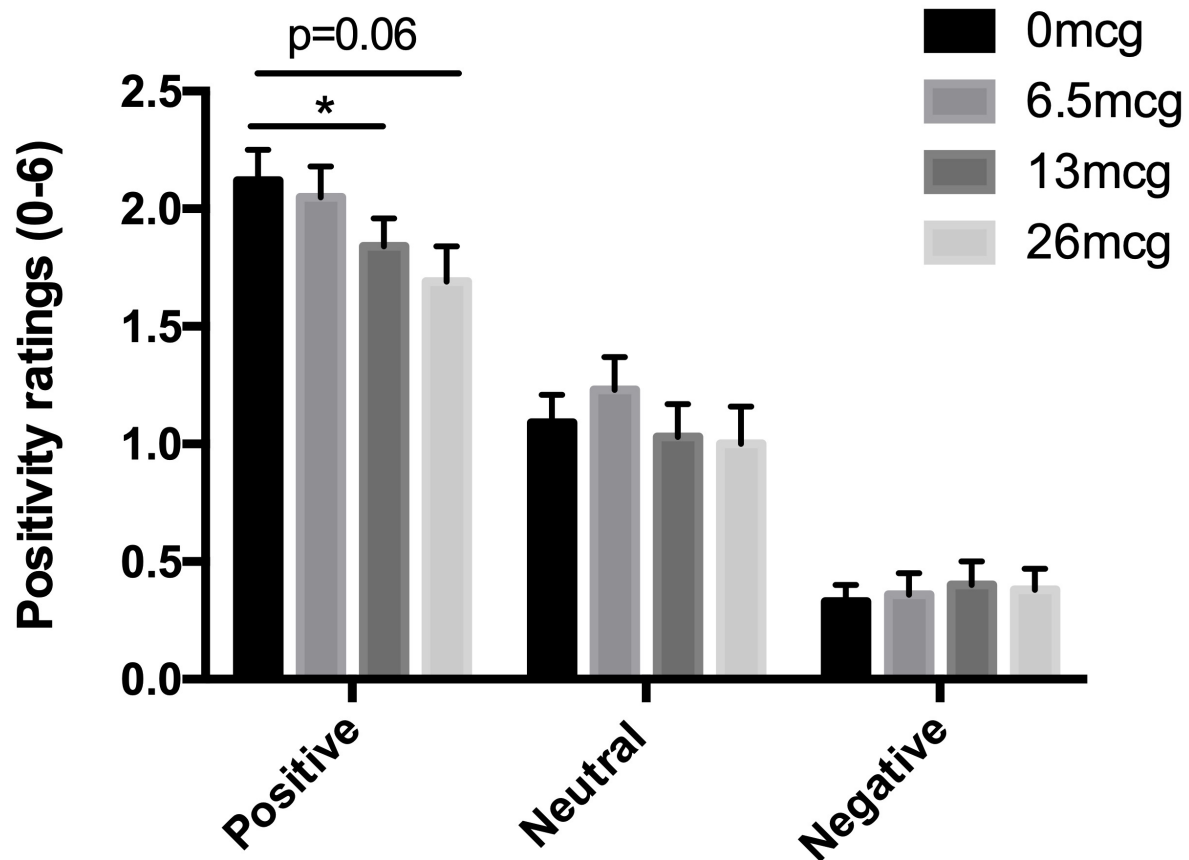
Table 2. Means and SDs for outcomes of subjective ratings of mood and behavioral tasks. * indicates a significant difference from placebo, $p < 0.05$.

	Placebo	6.5 μ g	13 μ g	26 μ g
Image Rating (1-6)				
Positive	2.00(0.5)	2.02(0.48)	1.86(0.43)*	1.78(0.53)
Neutral	1.10(0.57)	1.20(0.54)	1.14(0.50)	1.06(0.56)
Negative	0.32(0.24)	0.35(0.29)	0.38(0.32)	0.39(0.31)
Face Identification (s)				
Angry	11.18(3.17)	10.67(2.58)	10.56(3.53)	10.83(2.63)
Sad	8.03(2.31)	7.30(1.81)	8.29(2.55)	7.97(1.94)
Happy	7.76(2.41)	7.24(2.25)	7.89(2.84)	7.38(1.68)
Fearful	8.39(2.58)	7.51(2.29)	8.72(3.01)	8.53(3.42)
Disgust	7.07(2.47)	7.90(2.60)	7.32(2.89)	7.31(2.61)
Surprise	7.66(1.38)	7.76(1.65)	7.82(1.98)	7.96(2.43)
Cyberball (Positive mood 1-100)				
Accept	27.4(4.32)	27.10(4.15)	28.05(4.00)	28.00(5.05)
Reject	18.80(6.89)	19.05(6.50)	18.80(6.57)	18.95(7.03)
N-Back				
Correct (N)	19.00(1.6)	19.17(1.4)	19.35(1.60)	19.6(2.2)
RT (ms)	2595.72 (132.93)	2602.91 (142.48)	2601.27 (111.48)	2601.47 (123.81)
DSST				
Correct (N)	71.74(14.64)	72.30(11.36)	72.30(12.71)	70.65(11.46)
Attempted (N)	71.74(14.64)	72.40(11.37)	72.35(12.70)	70.40(11.75)
Remote Associates				
Correct (N)	7.10(2.22)	7.55(1.54)	7.60(2.40)	7.6(2.28)
Attempted (N)	14.20(4.25)	15.20(3.19)	15.35(4.02)	15.70(4.08)
POMS (peak change from baseline)				
Depression	-0.20(1.40)	0.30(1.71)	-0.35(2.50)	1.15(2.71)
Anxiety	-0.55(2.11)	-1.35(4.73)	0.00(4.78)	1.70(4.75)
Friendliness	-2.80(3.97)	-0.95(6.14)	-1.80(5.26)	-0.50(6.72)
Vigor	-4.13(5.80)	-2.40(6.73)	-2.55(6.30)	-1.45(11.08)
Anger	-0.25(0.97)	-0.50(1.61)	0.40(2.34)	0.20(2.83)
Fatigue	1.13(3.56)	0.25(3.47)	0.40(3.46)	1.10(4.81)
Confusion	-0.20(1.82)	-0.10(1.41)	0.45(2.26)	1.50(3.12)
Elation	-1.88(4.62)	-1.75(4.47)	-0.40(4.99)	-0.80(5.18)
POMS Depression Follow-Up (N=11)	7.45(7.59)	6.73(7.32)	7.45(11.79)	7.36(11.54)





Ratings of emotional images



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Key Resource Table

The journals of the Society of Biological Psychiatry support efforts in the biomedical research community to improve transparency and reproducibility in published research. Thus, *Biological Psychiatry* and *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* are pleased to participate in the initiative to include a Key Resources Table in published articles.

Authors are asked to submit this table at first revision, which may be uploaded using the "Key Resources Table" item type. This table will then be published as supplemental information.

The Key Resources Table is designed to promote reproducibility and thus, should include the resources and relevant details necessary to reproduce the study's results. It does not need to be exhaustive. Extensive lists (e.g., oligonucleotides, etc.) may be supplied in a supplementary table and the table referenced here. We strongly encourage the use of RRID identifiers that provide persistent, unique identifiers to key study resources. Search for RRDs at <https://scicrunch.org/resources>.

Resource categories

Note: For all categories, indicate sex and species when applicable

- **Antibody** - include host organism common name and clonality (e.g., "mouse monoclonal")
- **Biological sample** - any other biological entity, ranging from isolated tissue to defined population
- **Cell line** - if a primary cell line, describe in Additional Information
- **Chemical compound, drug** - commercially available reagents
- **Commercial assay/kit** - detection assays; labeling and sample preparation kits
- **Deposited data or public database** - include both raw data from this paper deposited into a repository and public repository databases (postmortem tissue; genetic consortia data; etc.)
- **Genetic reagent** - applies to mutations and variants in whole organism, including transgenically introduced constructs
- **Peptide, recombinant protein** - commercially available reagents
- **Recombinant DNA reagent** - traditional cultured clones, plasmids, cDNAs, etc., including recombinant DNA libraries
- **Sequence-based reagent** - oligonucleotides, primers, etc.; indicate sequence

- **Software, algorithm** - include version number and URL for download
- **Organism/Strain** - applies to whole organism
- **Transfected construct** - in cell line; indicate species of cell line or construct component
- **Other** - miscellaneous other categories, including histological stains

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

Supplementary Information

Details of Methods

Physiological Measures

Heart rate and blood pressure were obtained with a monitor (Critikon Dinamap Plus; GE Healthcare Technologies, Waukesha, WI, USA) at regular intervals throughout the session. Body temperature was also recording using a tympanic thermometer (Braun Thermoscan 5 Digital Ear Thermometer, Braun, Kronberg, Germany).

Behavioral and Cognitive Tasks

Dual N-Back. We used an N-back task adapted from (1) used to measure fluid intelligence, or the ability to adapt thinking to a new cognitive problem or working memory. In the task, stimuli (shapes or letters) are presented for 3 seconds, and subjects must respond on a keyboard when they see the same audiovisual stimulus that they saw n stimuli previously. They complete a series of four blocks of 20 trials that increase in difficulty, and only the data from the last block was used here. Subjects respond when the location of a square in a nine square grid matches the location they saw 2-back or when the letter presented matches the previously presented letter. They respond with the left shift key for the visuo-spatial dimension, and the right shift key for the visuo-auditory letter dimension.

Digit Symbol Substitution Task (DSST). The DSST is a widely used measure of cognitive functioning. In this task, subjects are given a key with 9 symbols corresponding to the numbers 1 – 9, followed by a series of numbers with blanks to enter symbols. They are instructed to fill in the symbol that matches each number as quickly as they can, over a 90 second period. The outcome measure is the number of symbols correctly entered.

Simulated Social Rejection Task. The “Cyberball” task is widely used in simulating social acceptance and exclusion (2). Subjects play “catch” with two virtual players in two phases, with an acceptance phase followed by a rejection phase. During the acceptance phase subjects are included in the game ($60 \pm 3\%$ of the tosses were to him/her) and in the rejection phase they are excluded ($15 \pm 3\%$ of the tosses were to him/her). After the task subjects rated their mood and estimated the percentage of tosses (0–100%) they received.

Emotional Images Task. In this task, subjects rated the positivity and negativity of images with emotional content. Positive, negative, and neutral emotional images from the International Affective Picture System (3) were presented in randomized order as described in (4). No more than two pictures of consistent valence appeared consecutively, and images were presented for 6 seconds, preceded and followed by 3 seconds of a fixation mark. Subjects rated each image immediately after its presentation using an evaluative space grid (5), consisting of both positive and negative valence (“0”: not at all; “4” extreme), and evaluations of arousal.

Remote Associations Task (RAT). This task, measures convergent thinking, an aspect of creativity (6). Subjects are given three words, and then have thirty seconds to type in a fourth word that relates to each of the given words individually. An example would be: *flower, scout, friend*, with the correct answer being: *girl*. Each of the 20 word sets is designed with one correct solution in mind, and the outcome measures were the number of trials attempted and the number of correct responses out of 20.

Details of Task Results

Emotional Images Task

The emotional images task produced its expected effects on affective ratings. That is, subjects rated positive pictures as being more positive [$F(2,38)=194.28, p<0.001$; negative v. neutral, negative vs. positive and positive vs. neutral, all $p<0.001$]. The higher doses of LSD seemed to decrease positivity ratings for

positive pictures [Figure 2: Dose x Emotion $F(6,114)=2.35$, $p<0.05$; 13 μ g vs. placebo $p<0.05$, 26 μ g vs. placebo $p=0.06$], with no significant effects on ratings of arousal.

Dynamic Affect Recognition Task

On the emotion recognition task, there was a main effect of emotion on identification speed [$F(5,8)=21.6$, $p<0.001$], such that participants were significantly slower to identify anger than the other emotions on placebo and all doses of LSD. There were no significant main effects or interactions of drug dose.

Cyberball

The task produced its expected effects on participants' perception of the number of throws they received, and the extent to which they were included in the game. That is, participants correctly perceived that they received fewer throws during rejection and were included in the game to a lesser degree [Perceived throws, main effect of condition: $F(1,19)=221.10$, $p<0.001$; sense of inclusion, main effect of condition $F(1,19)=599.20$, $p<0.001$]. Rejection also, as expected, decreased ratings of positive mood [$F(1,19)=43.10$, $p<0.001$]. LSD did not significantly affect mood responses to rejection.

Cognitive Tasks

On the N-back and DSST tasks LSD did not significantly affect the number of trials attempted [Table 2; DSST $F(3,54)=0.55$, $p=0.65$], correct trials [DSST $F(3,54)=0.41$, $p=0.75$, N-back $F(3,54)=0.39$, $p=0.76$] or reaction time for correct trials [N-back $F(3,54)=0.10$, $p=0.96$] at any dose. On the RAT, LSD tended to increase the number of attempted trials in a linear fashion [$F(1,19)=3.67$, $p=0.07$], though the effect did not reach significance. The drug did not significantly influence the number of correct trials.

Supplemental References

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