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ARTICLE
Low doses of lysergic acid diethylamide (LSD) increase reward-related brain activity

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Renewed interest in classic psychedelics as treatments for psychiatric disorders warrants a deeper understanding of their neural mechanisms. Single, high doses of psychedelic drugs have shown promise in treating depressive disorders, perhaps by reversing deficits in reward processing in the brain. In addition, there are anecdotal reports that repeated ingestion of low doses of LSD, or "microdosing", improve mood, cognition, and feelings of wellbeing. However, the effects of low doses of classic psychedelics on reward processing have not been studied. The current study examined the effects of two single, low doses of LSD compared to placebo on measures of reward processing. Eighteen healthy adults completed three sessions in which they received placebo (LSD-0), 13 µg LSD (LSD-13) and 26 µg LSD (LSD-26) in a within-subject, double-blind design. Neural activity was recorded while participants completed the electrophysiological monetary incentive delay task. Event-related potentials were measured during feedback processing (Reward-Positivity: RewP, Feedback-P3: FB-P3, and Late-Positive Potential: LPP). Compared to placebo, LSD-13 increased RewP and LPP amplitudes for reward (vs. neutral) feedback, and LSD-13 and LSD-26 increased FB-P3 amplitudes for positive (vs. negative) feedback. These effects were unassociated with most subjective measures of drug effects. Thus, single, low doses of LSD (vs. placebo) increased three reward-related ERP components reflecting increased hedonic (RewP), motivational (FB-P3), and affective processing of feedback (LPP). These results constitute the first evidence that low doses of LSD increase reward-related brain activity in humans. These findings may have important implications for the treatment of depressive disorders.

INTRODUCTION
The last decade has witnessed renewed interest in classic psychedelics as therapeutic agents for psychiatric disorders. Psychedelics are serotonin agonists that act predominantly but not exclusively on 5-HT$_{2A}$ receptors [1, 2]. LSD, in particular, also acts on dopamine systems that are involved in reward processing [3–5]. Clinical trials suggest single, relatively high doses of psychedelic drugs (e.g., 100–200 µg LSD or 35 mg psilocybin) have potential in the treatment of mood and anxiety disorders [6–8]. Interestingly, there are also widespread anecdotal reports that repeated, very low doses of LSD (e.g., 10–15 µg), can improve mood, cognition, and wellbeing [9, 10]. Although this phenomenon of repeated ingestion of low doses of LSD (about 1/10th of a high dose), known as "microdosing" [10], has received much public attention, its beneficial effects have yet to be demonstrated, and the neurobiological and behavioral effects of either single or repeated low doses of LSD remain poorly understood. Initial studies in humans suggest single, low doses of LSD (up to 26 µg sublingual), like higher doses (75 µg intravenous), alter connectivity between distant brain networks [11, 12]. Some of these neural effects are observed at doses (5–20 µg) that produce only modest subjective or cognitive effect [13, 14] and do not impair proprioception [15–17]. This raises the possibility that repeated low doses of LSD may produce beneficial effects by altering brain function, even in the absence of strong perceptual effects. One important target of antidepressant drug effects is on neural activity related to reward processing. Deficits in reward processing are a characteristic feature of depression and can be detected by a dampened neural response to reward, using electrophysiological measures [18, 19]. As a first step to studying the profile of repeated low doses of LSD on reward processing, the current study used electrophysiological measures to examine neural responses to two single doses of LSD (13 and 26 µg) versus placebo.

Functional magnetic resonance imaging (fMRI) studies indicate that high doses of LSD or psilocybin alter connectivity among reward processing regions [8, 20–22], and there is limited evidence that similar effects occur at very low doses. High doses of LSD (100 µg) increase resting-state connectivity between core reward regions in the striatum and numerous resting-state networks [22], and reduce effective control over the thalamus by the ventral striatum [20], a key reward region associated with depression [23, 24]. LSD (100–200 µg) [25] and psilocybin (.16 mg/kg) [26] also reportedly alter amygdala-frontal cortex connectivity in ways that correlate with decreased symptoms in patients with treatment-resistant depression (10–25 mg) [7, 8]. Few studies have examined connectivity at very low doses of LSD. However, we recently reported that LSD (13 µg) altered amygdala-middle frontal gyrus connectivity and this alteration was correlated with increased positive mood [27].

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It remains to be determined whether very low doses of LSD, after either single or repeated administration, alter core reward processing networks associated with depression.

The current study utilized scalp electroencephalogram (EEG) to examine the effects of single, low doses of LSD on event-related potentials (ERPs) during reward processing in healthy young adults. We examined reward-related ERPs using the electrophysiological monetary incentive delay (eMID) task [28], measuring neural activity across several stages of reward processing. The eMID is sensitive to symptoms of depression [18, 29]. In the present study, we focused mainly on ERPs during processing of feedback of positive or negative feedback.

Reward feedback elicits a rapid cascade of neuropsychological processes that can be decomposed by the temporal resolution of ERPs. Three main feedback-related ERPs display a distinct time-course, separate scalp topographies, and covary with different neuroanatomical correlates [30]. First, the Reward-Positivity (RewP) is a frontocentral ERP that encodes the hedonic impact of positive (vs. negative) feedback [31] and is attenuated in depressive disorders [32]. It is believed that the RewP reflects reward prediction errors [33], which track unexpected outcomes via phasic mesencephalic dopamine pathways within the frontostriatal circuit [34], including the ventral striatum [35]. Next, the Feedback-P3 (FB-P3) is a parietal ERP that encodes the motivational salience of feedback and updates predictive models to maximize future rewards [36]. Several studies indicate the FB-P3 covaries with activation in the thalamus, amygdala, and hippocampus [37], regions also impacted by low doses (13 μg) of LSD [27]. Finally, the Late-Positive Potential (LPP) encodes the affective value of feedback [38]. The LPP covaries with activation in the visual cortex and amygdala [39], regions also linked to depressive disorders [40] and impacted by high (100–200 μg) and low (13 μg) doses of LSD [25, 27].

Together, the RewP, FB-P3, and LPP reflect the temporal progression of psychological processes that index the hedonic, motivational, and affective impact of reward feedback. We hypothesized that single, low doses of LSD (13 or 26 μg) would increase reward-related ERP amplitudes during feedback processing, consistent with a potential anti-depressant-like effect.

MATERIALS AND METHODS
Study design
This study used a within-subject, double-blind design to test the effects of single, low doses of LSD on mood and neural responses to reward using EEG. Healthy young adults participated in three 5-h sessions in which they received, in randomized order, placebo (LSD-0), 13 (LSD-13), or 26 (LSD-26) μg of LSD sublingually. EEG recordings were obtained using the eMID from 120 to 180 min after drug administration.

Participants
Participants were healthy young adults ($N = 18$, 6 women) aged 18 to 35 (see Table 1 for details). They underwent screening for physical and psychiatric health with a physical examination, electrocardiogram, modified Structural Clinical Interview for DSM-5, and self-reported health and drug-use history. Inclusion criteria were English fluency, right-handedness, at least a high school education, body mass index of 18 to 29 kg/m², and at least one prior use of a classic psychedelic drug (e.g., LSD, psilocybin, N,N-dimethyl-tryptamine [DMT]) or 3,4-methylene-diox-ymethamphetamine (MDMA)). They were excluded if they had a history of psychosis, severe posttraumatic stress disorder or panic disorder, past-year substance use disorder (except nicotine), pregnant or nursing, working night shifts, regular medication aside from birth control, adverse reaction to a psychedelic drug, or unwillingness to use this type of drug again. None of the participants met criteria for major depressive disorder although this was not an exclusion criterion. Participants provided written, informed consent prior to beginning the study, which was approved by the Institutional Review Board of the Biological Sciences Division of The University of Chicago. Additional measures collected on the same sample are described in

Table 1. Demographics and drug use characteristics.

Category	n or Mean ± SD (Range)
Participants (Male/Female)	18 (12/6)
Age, Years	24.5 ± 4 (19–30)
Education, Years	15.3 ± 1.5 (14–18)
Body mass index, kg/m²	22.4 ± 2.9 (18–28.2)
Race	
Caucasian	15
African American	1
Asian	2
Current drug use in past month	
Cannabis, times/month ($n = 11$)	5.7 ± 8.5 (0–25)
Alcohol, drinks/week ($n = 17$)	3.5 ± 2.3 (0–7.5)
Alcohol, drinking days/week	2.2 ± 1.5 (0–4.5)
Caffeine, servings/day ($n = 18$)	2.1 ± 1.3 (0–3.5)
Tobacco, times/day ($n = 2$)	0.5 ± 2.1 (0–8.5)
Total lifetime drug use, nonmedical	
Psychedelic ($n = 18$)	12.4 ± 22.9 (1–100)
MDMA ($n = 6$)	0.6 ± 0.9 (0–3)
Stimulant ($n = 7$)	37 ± 141 (0–500)
Opiate ($n = 5$)	2.8 ± 8.8 (0–30)
Tranquilizer ($n = 3$)	0.3 ± 0.9 (0–4)
Drug dose administration order	
Placebo, LSD-13, LSD-26	4
Placebo, LSD-26, LSD-13	5
LSD-13, Placebo, LSD-26	3
LSD-13, LSD-26, Placebo	2
LSD-26, Placebo, LSD-13	2
LSD-26, LSD-13, Placebo	2

Murray et al., 2021 [12]. See Supplementary Materials for additional participant exclusion information.

Procedure
Orientation session. During a pre-study orientation session, participants received instructions about the study. They were told to abstain from drugs and medications for 48 h before and 24 h after each session, from cannabis for 7 days before and 24 h after each session, and from alcohol for 24 h before and 12 h after each session. They were permitted to consume their normal amounts of caffeine and nicotine up to 3 h before sessions. Participants were instructed to have a normal night's sleep and fast for 12 h before the sessions. To minimize drug-specific expectancies, participants were told they might receive a placebo, stimulant, sedative, or hallucinogenic drug.

Experimental sessions. Participants attended three 5-h sessions from 8 am to 1 pm, separated by at least 7 days. Compliance to drug abstention was verified by urinalysis (CLIAwaived Instant Drug Test Cup, San Diego, CA; amphetamine, cocaine, oxycodone, THC, PCP, MDMA, opiates, benzodiazepines, barbiturates, methadone, methamphetamine, buprenorphine) and breath alcohol testing (Alcosensor III, Intoximeters, St. Louis, MO). Females provided urine samples for pregnancy tests. Participants received a granola bar as a standardized breakfast. Pre-drug measures of subjective state and cardiovascular function were obtained, and the drug (LSD-0, LSD-13, LSD-26) was administered sublingually under double-blind conditions. EEG recordings began 120 min after drug administration when effects are at their peak [12] and lasted about 60 min.

Drug. The drug was manufactured by Organix and was prepared in solution with tartaric acid by the University of Chicago Investigational Pharmacy. Drug solution (or water) was administered in a volume of 0.5 mL. The doses were selected to be below the threshold for
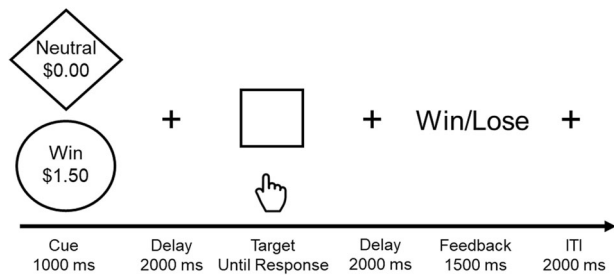
Fig. 1 Task structure and stimulus presentation for the modified eMID displaying an example trial. Each trial begins with a reward or neutral cue stimulus (reward condition: bottom left, neutral condition: top left), then a target white square stimulus requiring a quick response (middle), and finally positive and negative feedback stimuli are presented consisting of the words "Win" or "Lose" (right). Fixation crosses are displayed between each stimulus. The presentation duration of each stimulus is displayed below.

hallucinatory effect [14] and within the range that is used in naturalistic settings [41].

Subjective measures
All descriptions and statistical analyses of subjective measures are described at-length in the Supplementary Materials and in Murray et al., 2021 [12].

EEG measures
Electrophysiological monetary incentive delay (eMID) Task. The eMID task was administered using E-Prime software (Psychology Software Tools, Pittsburgh, PA) (see Fig. 1). During the eMID task, participants first viewed reward or neutral cues, then responded as quickly as possible to a target stimulus, and finally received positive or negative feedback based on their performance [28]. On each trial, a fixation cross was displayed for 2000 ms followed by a reward or neutral cue for 1000 ms. Reward cues indicated participants could gain $1.50 while neutral cues indicated no money could be gained on that trial. Next, a fixation cross was randomly jittered between 2000 and 2500 ms followed by a white square. Participants then responded as quickly as possible to the white square using a single response box button with their right index finger. Quick responses executed while the white square remained on the screen resulted in positive feedback while slower responses executed after the white square disappeared resulted in negative feedback. A fixation cross was then displayed for 2000 ms after each response.

Finally, a positive or negative feedback stimulus was presented for 1500 ms consisting of the words "Win" or "Lose" indicating quick enough, or too slow, responses. On reward trials, positive feedback (e.g., "Win") indicated monetary gains of $1.50 while negative feedback (e.g., "Lose") indicated no-gains (e.g., $0.00). Positive and negative feedback were also presented on neutral trials although monetary rewards were not possible. Unbeknownst to participants, positive and negative feedback were presented approximately 50% of the time in reward and neutral conditions using an adaptive algorithm that decreased or increased the duration of the white square by 20 ms, consistent with prior studies [18, 28, 42, 43]. Several feedback-related ERP components are influenced by the frequency of feedback stimuli [36], including the RewP and FB-P3 [44]. To control for such effects, this task keeps positive and negative feedback equiprobable in reward and neutral feedback conditions [42]. We note, however, one limitation of this approach is that the adaptive algorithm complicates interpretation of any task-related behavioral data. Participants were informed of their own total monetary earnings following each experimental session. The eMID task took approximately 45 min to complete and may have induced fatigue.

At each session, participants completed 32 practice trials and the initial white square duration in the eMID task was matched to practice trial reaction times. Including punishment cues, not analyzed here, each block contained 30 trials with 10 instances of each cue stimulus presented randomly without replacement. There were 6 blocks for a total of 180 trials, resulting in 30 trials for each type of feedback: Reward "Win", Reward "Lose", Neutral "Win", and Neutral "Lose". For clarity, we refer to reward and neutral conditions as "feedback condition" and positive and negative feedback as "feedback valence".

Electrophysiological acquisition. Complete electrophysiological acquisition details are described at-length in the Supplementary Materials.

Electrophysiological preprocessing. All offline processing was performed using EEGLAB [45] and ERPLAB [46] in MATLAB (The Math Works, Inc.). Raw EEG data were resampled at 250 Hz, re-referenced to the average of both mastoids, and 64 channels were retained consistent with the 10–20 system. Next, line noise [47] and noisy channels were removed. Unfiltered data were then saved. Independent component analysis (ICA) was used to correct for blink and muscle artifacts. Before ICA, data were high pass filtered at 1.0 Hz and continuous time segments were removed if any scalp electrode exceeded a voltage threshold of 500 μV in a 500 ms time window that slid across the full continuous data every 250 ms. Next, ICA was performed, and the resulting ICA weights were applied to the unfiltered data saved before artifact rejection. ICA components corresponding to ocular and muscular artifacts were identified and removed using visual inspection.

Data were then bandpass filtered from 0.1 to 30 Hz, segmented into epochs from −200 to 1000 ms time-locked to feedback onset, and baseline corrected using the 200 ms pre-stimulus interval. Epochs were then removed if any scalp electrode exceeded a 100 μV threshold in a 200 ms time window that slid across the entire epoch in steps of 100 ms. Remaining epochs were then averaged together separately resulting in four feedback bins: Reward "Win", Reward "Lose", Neutral "Win", Neutral "Lose". Participants with less than 20 trials in each feedback condition were excluded from statistical analysis (see Supplementary Materials for details). A total of 18 participants were retained with an average of 28.577 (SD: 2.970) trials per feedback bin.

ERP measurement. The RewP was measured as the average activity from 250–350 ms at electrode FCz where the difference between positive and negative feedback (e.g., "Win" and "Lose") was maximal [33]. The FB-P3 was measured as the average activity from 350–550 ms at electrode POz where positivity was maximal [36]. Finally, the LPP was measured as the average activity from 700–1000 ms at electrode Cz where differences between feedback conditions were maximal.

Statistical analysis. The primary outcome measures were the RewP, FB-P3, and LPP measured after feedback presentation. A 3-way repeated measures ANOVA (drug dose: LSD-0, LSD-13, and LSD-26) x 2 (feedback condition: reward and neutral feedback) x 2 (feedback valence: positive and negative feedback) was performed separately for each ERP component. Fisher's protected t-tests [48] were employed to minimize familywise error rate, which requires a significant omnibus ANOVA F test in order to proceed to pairwise comparisons. Follow-up t-tests were only performed to examine significant effects involving drug dose. To further reduce multiple comparisons, t-tests following significant interaction effects with drug dose were limited to ERP difference waves calculated as the difference between feedback condition (e.g., reward – neutral) or feedback valence (e.g., positive – negative). Difference wave approaches are also important to isolate feedback-related variance in each component from surrounding activity that may be unspecific to reward processing, increasing the statistical power at the cost of slightly decreased signal-to-noise ratio [49]. Greenhouse–Geisser correction was used for all ANOVA analyses and Cohen's d was used to calculate all t-test effect sizes. No additional variables were included. Related analyses were performed on ERPs measured after cue stimuli and before motor responses during reward anticipation. These analyses revealed no significant associations between LSD dose and ERP amplitudes (see Supplementary Materials). The drug produced moderate subjective effects including increased energy, positive mood, elation, anxiety, and intellectual efficiency, and ratings of "bliss" [12]. These subjective reports were mostly unassociated with ERP amplitudes (see Supplementary Materials).

RESULTS
RewP
Results revealed a significant main effect of feedback condition ($F_{(1, 17)} = 17.344$, $p = .001$, $\eta_p^2 = 0.505$) and feedback valence ($F_{(1, 17)} = 20.266$, $p < 0.001$, $\eta_p^2 = 0.544$). RewP amplitudes were increased for reward (M: 8.510, SD: 5.653) compared to neutral feedback conditions (M: 5.711, SD: 3.932) and for positive (M: 8.068, SD: 4.749) compared to negative valence feedback

(*M*: 6.153, *SD*: 4.736). Results also revealed a significant drug dose x feedback condition x feedback valence interaction ($F(2, 34) = 3.631$, $p = 0.047$, $\eta_p^2 = 0.176$). To unpack the interaction, positive – negative feedback difference waves were calculated separately for reward and neutral feedback conditions and for each drug dose. In the reward feedback condition, follow-up t-tests revealed that LSD-13 significantly increased RewP difference wave amplitudes compared to LSD-0 ($t(17) = 2.127$, $p = 0.048$, $d = 0.490$) and LSD-26 ($t(17) = 2.548$, $p = 0.021$, $d = 0.587$). No other significant effects emerged ($ps > 0.136$).

FB-P3
Results revealed a significant main effect of feedback condition ($F(1, 17) = 11.630$, $p = 0.003$, $\eta_p^2 = 0.406$) and feedback valence ($F(1, 17) = 4.686$, $p = 0.045$, $\eta_p^2 = 0.216$). FB-P3 amplitudes were increased for reward (*M*: 8.076, *SD*: 3.273) compared to neutral feedback conditions (*M*: 6.321, *SD*: 3.308) and for positive (*M*: 7.593, *SD*: 3.117) compared to negative valence feedback (*M*: 6.804, *SD*: 3.279). Results also revealed a significant drug dose x feedback valence interaction ($F(2, 34) = 4.259$, $p = 0.035$, $\eta_p^2 = 0.200$). To unpack the interaction, positive – negative feedback difference waves were calculated separately for each drug dose. Follow-up t-tests revealed, compared to LSD-0, both LSD-13 and LSD-26 increased FB-P3 difference wave amplitudes [LSD-13 ($t(17) = 2.121$, $p = 0.049$, $d = 0.489$) and LSD-26 ($t(17) = 2.884$, $p = 0.010$, $d = 0.665$)]. No other significant effects emerged ($ps > 0.349$).

LPP
Results revealed a significant main effect of feedback condition ($F(1, 17) = 5.791$, $p = 0.028$, $\eta_p^2 = 0.254$). LPP amplitudes were increased for reward (*M*: 4.195, *SD*: 3.175) compared to neutral feedback conditions (*M*: 2.646, *SD*: 3.187). Results also revealed a significant drug dose x feedback condition interaction ($F(2, 34) = 3.691$, $p = 0.038$, $\eta_p^2 = 0.178$). To unpack the interaction, reward – neutral feedback condition difference waves were calculated separately for each drug dose. Follow-up t-tests revealed that LSD-13 significantly increased LPP difference wave amplitudes compared to LSD-0 ($t(17) = 2.913$, $p = 0.010$, $d = 0.671$). No other significant effects emerged ($ps > 0.072$).

Subjective ratings
LSD-13 and LSD-26 increased ratings of energy, positive mood, elation, anxiety, and intellectual efficiency, as well as "bliss" [12].

DISCUSSION
The current study examined the effects of single, low doses of LSD (13 and 26 μg) versus placebo (LSD-0) on neural activity during reward processing in healthy adults. Compared to LSD-0, LSD-13 enhanced the hedonic and affective impact of reward (vs. neutral) feedback, reflected by increased RewP and LPP amplitudes, while both LSD-13 and LSD-26 increased the motivational salience of positive (vs. negative) feedback, reflected by increased FB-P3 amplitudes. Of note, these doses produce subjective effects that are comparable to low doses of amphetamine [50], including increases in energy, positive mood, elation, anxiety, and intellectual efficiency [12]. The ERP amplitudes in the current study were unrelated to most of these subjective effects (see Supplementary Materials). These results suggest single, low doses of LSD broadly increased neural sensitivity to reward feedback, particularly at doses that produce few perceptible subjective effects. If these findings extend to repeated doses in symptomatic participants, they may have important implications for the treatment of depressive disorders.

The current results provide the first evidence that a single, low dose of LSD may increase reward-related brain activity on measures that are hypoactive in depressive disorders. Compared

to LSD-0, LSD-13 increased the hedonic impact of positive (vs. negative) feedback in reward conditions (e.g., for monetary gains compared to no-gains), as indexed by increased RewP difference wave amplitudes (see Fig. 2). Prior research indicates that the RewP reflects reward prediction errors [33], which are powerful bottom-up reinforcement learning signals that encode better- (vs. worse-) than-expected outcomes. Consistent with enhanced reward prediction error encoding, behavioral studies have shown high doses of LSD (e.g., 100 μg) may accelerate reinforcement learning behaviors in humans [51] and associative learning rates in mice [52]. By contrast, blunted RewP amplitudes may constitute a biomarker for depressive disorders that prospectively predict risk, onset, and treatment outcomes [32]. Using related monetary incentive delay tasks, neuroimaging studies of depressive disorders have reported similar neural profiles of hypoactivation in the ventral striatum after reward feedback [29], a likely neural generator of the RewP [35]. The present results are the first to show that a single, low dose of LSD (e.g., LSD-13) increased the RewP. This observation raises the possibility that repeated low doses of LSD may be able to alleviate certain symptoms of depression by reversing deficits in neural sensitivity to rewards.

Beyond the RewP, LSD-13 and LSD-26 increased the motivational salience of positive (vs. negative) feedback compared to LSD-0 regardless of reward or neutral conditions (see Fig. 3), as indexed by increased FB-P3 amplitudes. Although the P300 ERP component is studied in a variety of experimental contexts, the FB-P3 is specific to feedback processing and is thought to update predictive models with motivationally salient feedback information to maximize future rewards [37]. In the eMID task, neutral feedback still delivered positive and negative performance information that can be used to update predictive models and improve future performance despite being unassociated with monetary rewards [36]. However, previous eMID studies have reported negative (vs. positive) feedback increased FB-P3 amplitudes. Strikingly, this pattern is consistent with present results: in the LSD-0 condition, negative feedback slightly increased FB-P3 amplitudes, but this pattern was reversed by LSD-13 and LSD-26, suggesting the drug enhanced the motivational processing of positive feedback.

Finally, LSD-13 (vs. LSD-0) increased the affective value of reward (vs. neutral) feedback regardless of positive or negative feedback valence, as indexed by increased LPP amplitudes (see Fig. 4). These results suggest a single, low dose of LSD may alter emotional processing in the brain. Consistent with this, it was recently reported that LSD (13 μg) altered connectivity between the amygdala and prefrontal cortex, in a manner that correlated with positive mood [27]. These regions also covary with the LPP [39]. Our results suggest a single, low dose of LSD may increase the affective value of reward-related stimuli. Although few studies have examined the LPP during reward processing, negative stimuli increase the LPP during emotional processing tasks [53], reflecting a "negativity bias" linked to depressive disorders [40, 54]. Interestingly, high doses (30–35 mg) of psilocybin have shown promise in patients diagnosed with treatment-resistant depression, perhaps by reversing this hypersensitivity to negative stimuli [7, 8, 55–57 however, see 58]. Although speculative, it is possible that single, low doses of LSD may increase emotional sensitivity to reward feedback in a similar fashion while only producing modest subjective drug effects [however, see 59]. Investigating whether low doses of LSD may decrease neural sensitivity to negative stimuli and increase neural sensitivity to reward feedback is a promising area for future research.

The current study found that only LSD-13 increased RewP and LPP amplitudes. Further, although most LSD effects were dose-dependent [12], one subjective measure related to energy and intellectual efficiency (ARCI-BG) was increased after LSD-13, but not LSD-26, relative to LSD-0. Anecdotal reports of microdosing refer to finding a "sweet spot" that is neither too low nor too high
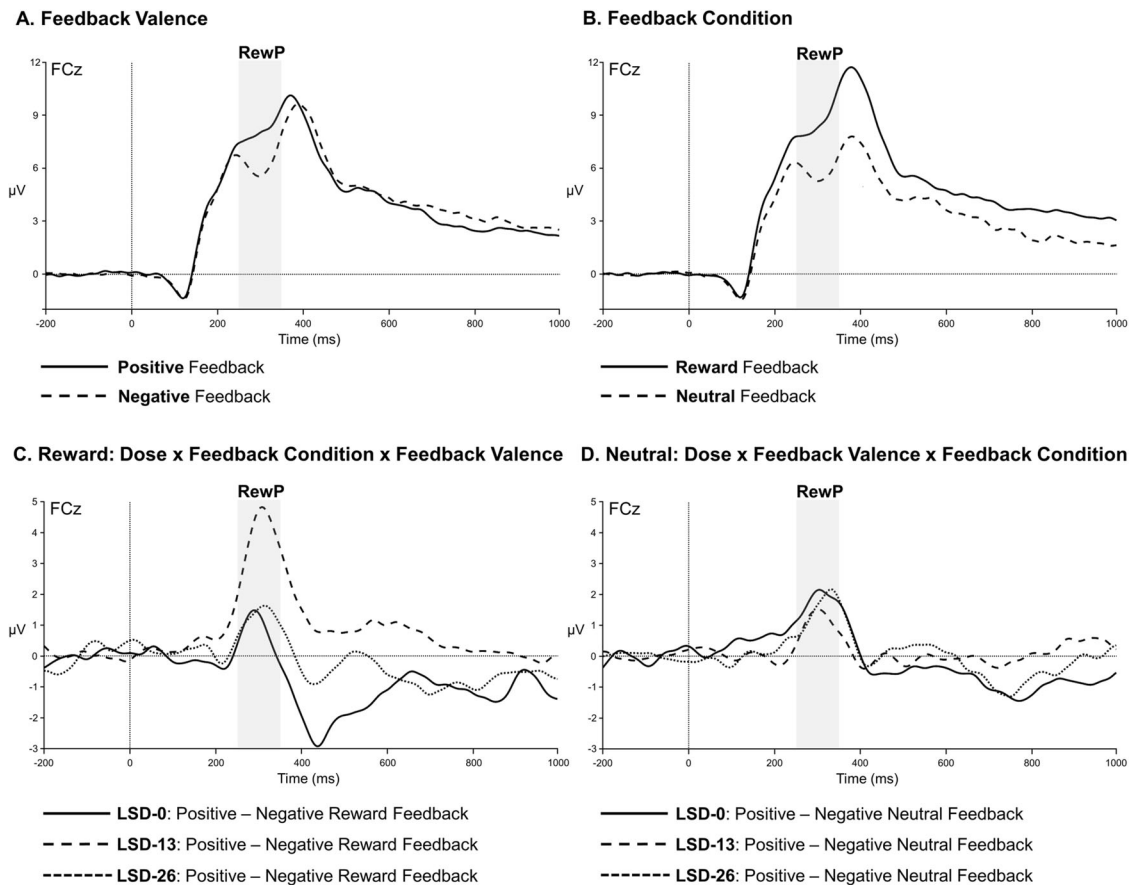
A. Feedback Valence

B. Feedback Condition

C. Reward: Dose x Feedback Condition x Feedback Valence

D. Neutral: Dose x Feedback Valence x Feedback Condition

Fig. 2 Waveforms displaying the RewP at electrode FCz. Top panels display the main effect of feedback valence (**A** Top left) showing positive "Win" feedback (solid) and negative "Lose" feedback (dashed) and the main effect of feedback condition (**B** Top right) showing reward feedback (solid) and neutral feedback (dashed) conditions. Bottom panels display positive – negative feedback difference waves separately in reward feedback conditions (**C** Bottom left) and in neutral feedback condition (**D** Bottom right) for LSD-0 (solid), LSD-13 (lightly dashed), and LSD-26 (heavily dashed).

for the desired effect [60]. It is possible that LSD, like other psychoactive drugs, induces non-linear dose effects [61, 62]. Alternatively, the absence of dose-dependent increases in neural responses to reward may be due to our small sample size. Future studies using the eMID with a wider range of doses and a larger sample will be needed to determine the full effect of low-dose LSD on reward-related neural activity.

Growing evidence indicates LSD may influence reward processing via both direct and indirect action on dopamine receptors. In mice, doses of LSD ranging from 30–160 µg directly affected frontostriatal dopamine [63, 64]. Convergent animal and human studies suggest the effects of LSD on dopamine may be independent of its primary action on 5-HT$_{2A}$ receptors [19, 65]. There is also evidence that very low doses of LSD (5–20 µg) indirectly affect striatal dopamine receptors via 5-HT pathways [63, 64]. The role of 5-HT receptors in reward processing remains unclear. However, emerging evidence from optogenetics and imaging techniques suggests 5-HT receptors are deeply implicated in hedonic experiences of "liking" [66] and 5-HT$_{2A}$ antagonism may play a specific role in the etiology of treatment-resistant depressive disorders [67, 68]. It is therefore possible that dopamine and serotonin receptor systems may act in concert to affect reward processing, beyond their individual effects [69].

If our findings with single low doses of LSD extend to repeated low doses, they suggest that low-dose LSD may have potential for the treatment of depressive disorders, especially for treatment-resistant individuals who do not respond to selective serotonin reuptake inhibitors (SSRIs). SSRIs produce antidepressant effects by desensitizing 5-HT$_{1A}$ receptors over several weeks [70]. However, SSRIs are ineffective for up to 30% of depressed patients [71] and often do not treat symptoms associated with dopaminergic reward systems, such as loss of motivation and pleasure [72]. By contrast, the direct and indirect effects on dopamine receptors raises the possibility that low doses of LSD may act in part via frontostriatal reward systems that are associated with depression but often left untreated by SSRIs. In fact, several measures of reward hyposensitivity that predict SSRI treatment outcomes in depression are attenuated or reversed by single doses of LSD in healthy adults [73, 74]. These include behavioral learning, cortico-striatal connectivity [20, 22, 51] and RewP amplitudes [75] as reported in the current study. Interestingly, SSRIs can also attenuate subjective psychedelic effects [76], leading some to suggest 5-HT$_{1A}$ and 5-HT$_{2A}$ may constitute competitive and mutually exclusive serotonergic pathways to similar antidepressant effects [77]. Looking at more lasting effects of LSD treatments, there is some evidence that 5-HT$_{2A}$ hyperactivation influences genetic expression and engenders longer term synaptic plasticity and neurochemical changes [78]. If true, this may support the feasibility of clinical trials for repeated, low doses of LSD.

Notably, the single low doses of LSD used in the current study (13 and 26 µg) produced few perceptive subjective effects. There is controversy about the role of subjective effects in the treatment of depression with psychedelic drugs: Some argue that the strong cognitive and emotional states observed with high doses of LSD and psilocybin are essential for the beneficial clinical outcome [79] while
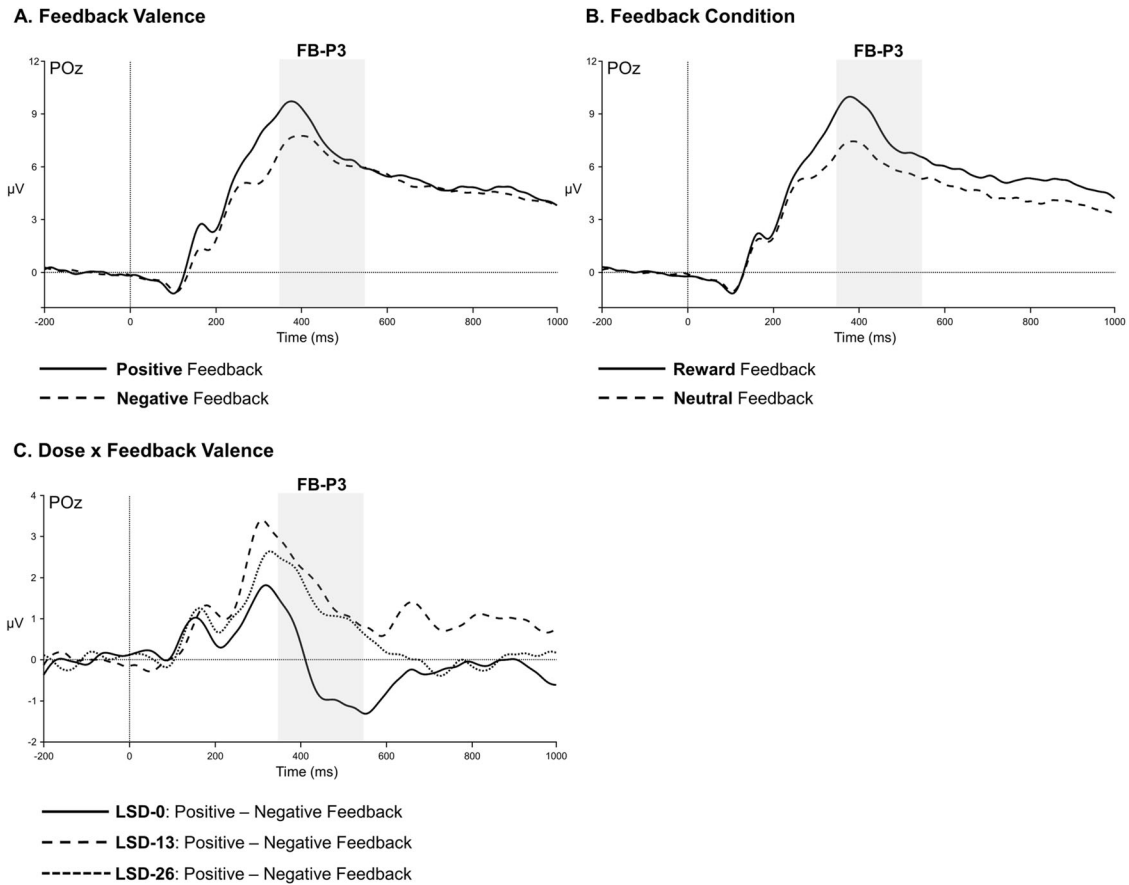
A. Feedback Valence

B. Feedback Condition

C. Dose x Feedback Valence

Fig. 3 Waveforms displaying the FB-P3 at electrode POz. Top panels display the main effect of feedback valence (**A** Top left) showing positive "Win" feedback (solid) and negative "Lose" feedback (dashed) and the main effect of feedback condition (**B** Top right) showing reward feedback (solid) and neutral feedback (dashed) conditions. **C** (bottom left) displays positive – negative feedback difference waves for LSD-0 (solid), LSD-13 (lightly dashed), and LSD-26 (heavily dashed).

A. Feedback Condition

B. Dose x Feedback Condition
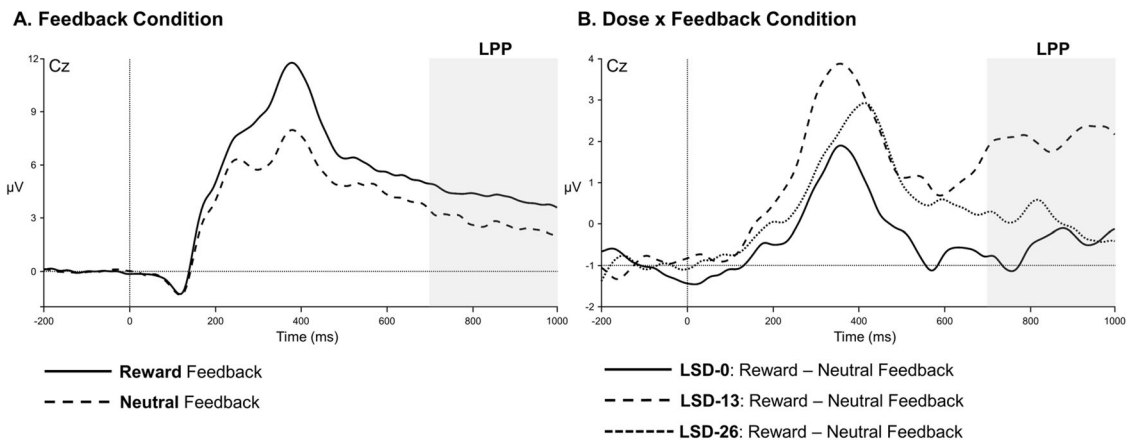
Fig. 4 Waveforms displaying the LPP at electrode Cz. A (left side) displays the main effect of feedback condition showing reward feedback (solid) and neutral feedback (dashed) conditions. **B** (right side) displays the drug dose x feedback condition interaction showing reward – neutral feedback condition difference waves for LSD-0 (solid), LSD-13 (lightly dashed), and LSD-26 (heavily dashed).

others [80] argue that the antidepressant effects may be dissociable from the perceptual experience. It is intriguing to speculate that very low doses of LSD (single or repeated), which produce negligible subjective effects, may nevertheless increase reward-related brain activity, supporting the potential of this approach for developing new antidepressant treatments. To make progress, future studies are needed to address outstanding questions related to tolerance,

optimal dosage, drug-by-drug interactions, how many sessions are needed for change, durability of the effects, and potential side effects and risks of treatment, among others.

This study had several limitations. The participants were relatively homogeneous with regard to mental health, body weight and education, and all had some prior experience with a psychedelic drug. We did not control for menstrual cycle phase in

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female participants. This is an important future research direction because cycle phase has been linked to reward-related brain activity. During the study, we did not assess the time between the last use of a psychedelic drug and the sessions, and, although participants were instructed to refrain from use of all drugs for 48 h before the sessions, we did not test urine specifically for recent psychedelic use. EEG measures were obtained at a time during the session when the drug effects were expected to have reached their peak, but the full time course of effects, relative to drug administration, is not known. Our sample was small, which limited the power of the sample and limited our ability to examine sources of individual differences, including sex. Moreover, the participants' depression scores were too low to conduct meaningful analyses. Finally, it is possible that a larger sample would reveal clearer dose-related effects, or effects of the drug on other ERPs including during anticipation (see Supplementary Materials). It will be important to investigate these effects in a larger, and perhaps more heterogeneous sample of participants.

CONCLUSION

The present study provides the first evidence that single, low doses of LSD increase reward-related brain activity in humans. Compared to LSD-0, LSD-13, and LSD-26 increased neural sensitivity to reward feedback, affecting the same ERP components that are attenuated in depressive disorders. By contrast, these doses of LSD did not impact ERPs during reward anticipation and produced only modest subjective effects (see Supplementary Materials). Importantly, most subjective effects of the drug were not related to its effects on neural activity during reward processing (see Supplementary Materials). If these findings with single doses are extended to repeated low doses of LSD, and if they are associated with beneficial psychological outcomes, they may support popular claims about the benefits of microdosing. Future studies should examine the neural and psychiatric effects of repeated administration of low doses and investigate the duration of any beneficial effects that are detected. Studies should also investigate sources of variability in response to the drug, using larger samples and a broader array of outcome measures.

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AUTHOR CONTRIBUTIONS

FUNDING

COMPETING INTERESTS

HdW serves on the Board of Directors of PharmAla Biotech and has served as Scientific Advisor to Awakn Life Sciences, Gilgamesh Pharmaceuticals and Mind

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41386-022-01479-y.

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