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Neural complexity is increased after low doses of LSD, but not moderate to high doses of oral THC or methamphetamine

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Neural complexity correlates with one's level of consciousness. During coma, anesthesia, and sleep, complexity is reduced. During altered states, including after lysergic acid diethylamide (LSD), complexity is increased. In the present analysis, we examined whether low doses of LSD (13 and 26 µg) were sufficient to increase neural complexity in the absence of altered states of consciousness. In addition, neural complexity was assessed after doses of two other drugs that significantly altered consciousness and mood: delta-9-tetrahydrocannabinol (THC; 7.5 and 15 mg) and methamphetamine (MA; 10 and 20 mg). In three separate studies ($N = 73$; 21, LSD; 23, THC; 29, MA), healthy volunteers received placebo or drug in a within-subjects design over three laboratory visits. During anticipated peak drug effects, resting state electroencephalography (EEG) recorded Limpel-Ziv complexity and spectral power. LSD, but not THC or MA, dose-dependently increased neural complexity. LSD also reduced delta and theta power. THC reduced, and MA increased, alpha power, primarily in frontal regions. Neural complexity was not associated with any subjective drug effect; however, LSD-induced reductions in delta and theta were associated with elation, and THC-induced reductions in alpha were associated with altered states. These data inform relationships between neural complexity, spectral power, and subjective states, demonstrating that increased neural complexity is not necessary or sufficient for altered states of consciousness. Future studies should address whether greater complexity after low doses of LSD is related to cognitive, behavioral, or therapeutic outcomes, and further examine the role of alpha desynchronization in mediating altered states of consciousness.

Neuropsychopharmacology; https://doi.org/10.1038/s41386-024-01809-2

INTRODUCTION

The use of very low doses of psychedelics every few days, a practice known as microdosing, has gained widespread public attention in the past decade. Several books have detailed transformative anecdotal reports touting wide-ranging benefits for both healthy and patient populations [1, 2], including improvements in mood, cognition, energy, creativity, and interpersonal connectedness [3–10]. In response, the medical and scientific community has begun to investigate safety and therapeutic efficacy [11]. Low doses provide an attractive therapeutic model if beneficial effects of high doses are retained without safety and ethical concerns related to altered states of consciousness [12]. Randomized controlled trials (RCTs) in healthy populations have confirmed that low doses acutely increase ratings for well-being, even when participants have no expectation for these effects [13–22]. However, no published RCT has examined patient populations and only one RCT to date has assessed outcomes after repeated use [19]. In that RCT in healthy men, 10 µg of lysergic acid diethylamide (LSD) taken every three days did not affect mood or cognition after a 6-week protocol. However, the dose acutely increased ratings of energy, creativity, connectedness, happiness, and wellness relative to placebo. The authors described the regimen as relatively safe, with some anxiety-related adverse effects and reduced cognitive processing speed after 6 weeks, which did not reach significance after correcting for multiple comparisons. Since different effects may occur in patient populations, future RCTs are planned to further examine clinical potential. Together, although placebo-controlled studies have demonstrated acute improvements in mood, more work is needed to determine health outcomes related to low dose regimens or microdosing practices for both healthy and patient populations.

In addition to safety and efficacy, researchers are working to identify objective markers and potential mechanisms that may be driving therapeutic reports. Increased plasma levels of brain-derived neurotrophic factor (BDNF) [23], a key mediator of neuroplasticity [24–28] were reported after low doses of LSD. In addition, we have reported functional brain changes at both rest and during cognitive tasks using fMRI [13] and EEG [20, 29]. In the brain, LSD and other psychedelics are characterized by their activity at serotonin (5-HT) 2 A receptors [30–32]. Upon activation, 5-HT2A modulates neuronal sensitivity and facilitates neurotransmitter release [33–35], contributing to complex patterns of brain activity [36, 37]. According to the "entropic brain hypothesis" [38, 39], increases of neural complexity are a key mechanism for therapeutic efficacy, destabilizing maladaptive patterns of

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Received: 10 December 2023 Revised: 7 January 2024 Accepted: 17 January 2024
Published online: 29 January 2024

thinking and behavior, while reflecting the "richness" of one's experience [40–43]. However, whether such complexity extends to low doses of LSD is unknown.

Neural complexity has garnered scientific interest in the fields of psychedelics and consciousness [44, 45]. When consciousness is lost or diminished, such as during sleep, neural complexity is reduced [43, 46–49]. Measures of electroencephalography (EEG) complexity are superior to other EEG measures in discriminating conscious states, including spectral analyses of neural oscillations [50]. Thus, neural complexity has gained traction as a reliable marker of consciousness, with the potential to consolidate existing theories in the science of consciousness [51]. One apparent contradiction between the fields has been that for consciousness science, complexity follows linear increases in conscious awareness, whereas for psychedelics, increased complexity is thought to indicate a multifaceted altered state that may interfere with such awareness [52].

To clarify the roles of neural complexity and other brain signals after psychedelics, analyses across drug classes and doses are required. We have previously shown that low doses of LSD (13 and 26 µg) do not induce psychedelic-like altered states [20], unlike tetrahydrocannabinol (THC; 7.5 and 15 mg) [53], a psychedelic-like drug [54–57]. Low doses of LSD did however increase methamphetamine-like stimulant responses. Here, we examine whether neural complexity is linked to psychedelic-like altered states or to other drug effect and mood states using resting state Limpel-Ziv complexity after LSD (13 and 26 µg), THC (7.5 and 15 mg), and methamphetamine (MA, 10 and 20 mg). Limpel Ziv-complexity measures repetitive strings in finite sequences to quantify the temporal signal diversity in EEG and is a leading measure of neural complexity in both humans [58] and rodents [59].

MATERIALS AND METHODS

Study design

Three separate studies, conducted from 2020 to 2022 in the Human Behavioral Pharmacology Laboratory at the University of Chicago, compared two doses of a drug (LSD, THC, or MA) against placebo in a within-subjects design. In each study, healthy adults participated in three 5 h sessions in which they received placebo or one of two drug doses under double blind and randomized conditions separated by at least 7 days. Dependent measures included self-reported drug effects and mood states in addition to EEG measures. Drug effects were recorded before drug administration and at one hour or half-hour intervals after drug administration. Altered states of consciousness were assessed retrospectively at session end in relation to the time of peak drug effects. At 90–120 min after drug administration, during the period of anticipated peak drug effects, EEG recordings (19 scalp electrode 10–20 placement; ActiveTwo™ system, BioSemi B.V., Amsterdam) were conducted. We have previously reported on task-based EEG data from the same participants after LSD [20] and THC [60] alongside a broader assessment of mood states and drug effects. The current report presents a new analysis of EEG resting state under 10–20 electrodes across the LSD, THC, and MA studies using neural complexity as the primary outcome measure.

Subjects

Healthy adults ($N = 73$, 33 women) 18–35 years of age participated in one of three studies involving LSD ($N = 21$), THC ($N = 23$), or MA ($N = 29$). All participants were screened with a physical examination, electrocardiogram, modified Structural Clinical Interview for DSM-5, and self-reported health and drug use history. Inclusion criteria across all studies included a body mass index of 18–32 kg/m^2, English fluency, and at least a high school education. Exclusion criteria across all studies included a history of psychosis, severe posttraumatic stress disorder or panic disorder, past year substance use disorder (except nicotine), pregnant or nursing, working night shifts, and current medication aside from birth control. Exclusionary criteria specific to the LSD study included no prior use of a classical psychedelic drug (e.g., LSD or psilocybin), an adverse reaction to a psychedelic drug, or unwillingness to use this type of drug again. Exclusionary criteria specific to the THC study included reporting over 20 lifetime uses of THC-containing products, 0 uses of a THC-containing product within the last 30 days, and a negative urine test for THC at screening. After screening, participants attended an orientation session to review study procedures and were instructed to abstain from drugs and medications for 24 h before sessions. Participant compliance to drug abstention was verified by urinalysis (CLIAwaived Instant Drug Test Cup) and breath alcohol testing (Alcosensor III, Intoximeters, St. Louis, MO). Female participants provided urine samples for pregnancy tests and were tested at any phase of the menstrual cycle. To minimize drug-specific expectancies, participants were told they might receive a placebo, stimulant, or sedative, and either a hallucinogenic or cannabinoid drug, in the LSD and THC studies, respectively. Participants provided informed consent prior to beginning the study procedures, which were approved by the University of Chicago Institutional Review Board.

Drugs

LSD was manufactured by Organix and prepared in solution with tartaric acid by the University of Chicago Investigational Pharmacy. LSD (13 or 26 µg, tartate solution in water) or placebo (water) was administered sublingually in a volume of 0.5 mL. Participants held the solution under the tongue without swallowing for 60 s, under observation. These doses were selected to be below the threshold for hallucinatory effects [14] and within the range that is used in naturalistic settings. A recent survey indicated that 13.5 µg is the average dose used for microdosing LSD (range 1.4–50 µg) [61]. In contrast, 100–200 µg LSD reflects a "macrodose" range, inducing comparable subjective effects to 30 mg psilocybin, a dose used in studies of psilocybin-assisted therapy [62].

THC (Marinol® [dronabinol]; Solvay Pharmaceuticals; 7.5 mg and 15 mg) was placed in opaque capsules with dextrose filler. Placebo capsules contained only dextrose. These doses of THC produce subjective intoxication and performance impairments [63, 64]. Prior studies have shown that oral and smoked doses of THC produce similar peak levels of self-reported intoxication, although the duration of effects is longer with oral administration [65]. The 7.5 and 15 mg doses reflect the amount of THC in one-quarter and one-half of a 0.2 g cannabis cigarette containing 15% THC, which is the average THC potency observed in legal dispensaries [66].

MA (10 and 20 mg; Desoxyn; Mylan Inc) was placed in opaque capsules with dextrose filler. Placebo capsules contained only dextrose. MA doses were based on previous studies showing that these doses reliably produce subjective, behavioral and neural effects in healthy volunteers [67, 68].

Self-report measures

Subjective drug effects and mood states were assessed with the Drug Effects Questionnaire (DEQ) [69, 70], and Profile of Mood States (POMS) [71] during each session. Specifically, three dependent measures from the DEQ and POMS were selected a priori based on previous findings in the LSD study [20]. These measures included the DEQ question, "Do you feel a drug effect?" answered via 100-mm visual analog scale from 0 (not at all) to 100 (extremely), and the POMS subscales anxiety and elation, each of which are comprised of mood adjectives rated on a Likert scale from 0 (not at all) to 4 (extremely). Due to reported relationships between LSD and THC and altered states of consciousness [72], at the end of each LSD and THC session, subjects also completed the 5 Dimensions of Altered States of Consciousness (5D-ASC) questionnaire, which we used to operationalize altered states of consciousness, described as marked deviations in normal waking consciousness [73]. The 5D-ASC was completed retrospectively at session end in relation to peak drug effects. The five dimensions, or subscales, of the 5D-ASC are oceanic boundlessness (OBM), dread of ego dissolution (DED), visionary restructuralization (VRS), auditory alteration (A) and vigilance reduction (VR).

EEG measures

Resting state EEG measures were obtained identically between the THC, LSD, and MA studies. We previously reported an analysis of spectral power under electrodes specifically placed over default mode network regions after the low doses of LSD [20]. Here, EEG recorded 5 min of continuous brain activity while participants sat comfortably with eyes closed in a state of rest 90–120 min after drug administration, during the period of anticipated peak drug effects. Limpel-Ziv complexity [58] quantified temporal signal diversity of single channels with a custom script adapted from open source code (https://github.com/jfrohlich/angelman-consciousness/tree/main/CodeFromJacoSitt), and selected based on the reliability and validity of this measure in detecting

neural complexity relative to other measures of signal diversity [50]. The Limpel-Ziv (LZ76) algorithm determines signal complexity by the number of patterns found after binarizing each data point in the signal to either above, "1," or below, "0," its mean. Raw Limpel-Ziv values for each channel were normalized to the overall entropy rate, such that the normalized value indicates the level of signal diversity on a scale from 0 to 1, using the following formula: % = C*log2(length(X))/length(X) [74]. Oscillatory power across five frequency bands was assessed using a custom script [20] (delta, 1–4 Hz; theta, 4–8 Hz; alpha 8–13 Hz; beta 13–30 Hz; gamma 30–80 Hz). Information on EEG data acquisition and processing can be found in supplemental information.

Statistical analysis

All statistical analyses were conducted with SPSS (version 25; SPSS Inc, Chicago, IL). Self-report measures were analyzed using repeated measures analysis of variance (RM-ANOVA) with dose as a within-subjects factor and follow-up contrasts comparing each dose with placebo. Specifically, we examined linear effects of dose in each RM-ANOVA to assess dose-dependent effects. Then, if significant linear effects of dose were found, follow-up planned contrasts compared each dose to placebo. For DEQ, we examined the time course of drug effects using a two-way RM-ANOVA (dose, time). For POMS, peak change from baseline scores were calculated for each subject using the pre-dose baseline and the highest or lowest value during the session.

EEG measures were analyzed using RM-ANOVA with dose as a within-subjects factor as described above for self-report measures, here taking the mean value (oscillatory power or Limpel-Ziv complexity) across all 10–20 scalp electrodes for each dose condition. Follow-up contrasts compared each dose with placebo. Follow-up analyses of individual electrodes were corrected for multiple-comparisons using an FDR correction with a false discovery rate of 0.05.

Pearson correlations were used to assess relationships between measures that resulted in significant linear effects RM-ANOVA. The correlations assessed relationships between the values obtained from the highest dose condition (26 µg LSD, 15 mg THC, or 20 mg MA).

RESULTS

Demographic characteristics

The mean age of participants across studies was in the mid-twenties. Similar proportions of males and females were included, except for the LSD study, which consisted of twice as many males than females. Demographics across ethnicity and current drug use were similar, with participants reporting close to two alcohol drinking days/week, one caffeine serving/day, and close to no tobacco use. Because the THC study was designed to exclude individuals with over 20 total lifetime uses of cannabis, participants in the THC study reported 12.6 lifetime uses, relative to the ~250 lifetime uses reported in the LSD and MA groups (Table 1).

Self-report measures

On subjective ratings (Fig. 1), LSD (13 and 26 µg), THC (7.5 and 15 mg), and MA (10 and 20 mg) each dose-dependently increased ratings for feeling a drug effect (LSD: dose x time, $F_{1,20} = 11.00$, $p = 0.003$; THC: dose x time, $F_{1,22} = 82.96$, $p < 0.001$; MA: dose x time $F_{1,28} = 8.87$, $p = 0.006$). Notably, there was no significant difference between placebo and 13 µg LSD on ratings for feeling a drug effect (dose x time, $F_{1,20} = 2.80$, $p = 0.110$), indicating that the 13 µg dose in our study reflects a "sub-perceptual" dose described by individuals in naturalistic settings [61]. On mood ratings, both LSD and THC increased anxiety (LSD: dose, $F_{1,20} = 4.97$, $p = 0.038$; THC: $F_{1,22} = 22.01$, $p < 0.001$), while both LSD and MA increased elation (LSD: dose, $F_{1,19} = 4.68$, $p = 0.043$; MA: dose, $F_{1,28} = 13.29$, $p < 0.001$) during sessions. On retrospective ratings of altered states of consciousness, the low doses of LSD did not affect any of the five subscales of the 5D-ASC, however, THC increased responding to all five of the 5D-ASC subscales (OBM: dose, $F_{1,22} = 12.77$, $p = 0.002$; DED: dose, $F_{1,22} = 25.41$, $p < 0.001$; VRS: dose, $F_{1,22} = 23.16$, $p < 0.001$; A: dose, $F_{1,22} = 10.57$, $p = 0.004$; VR: dose, $F_{1,22} = 70.38$, $p < 0.001$).

EEG measures

In resting state, the low doses of LSD dose-dependently increased measures of Limpel-Ziv complexity (dose, $F_{1,20} = 19.49$, $p < 0.001$) with no significant effect of THC or MA (Fig. 2). After LSD, the distribution of significant electrodes appeared globally, but with increases of complexity absent over midline electrodes, including

Table 1. Demographic and drug use information across the lysergic acid diethylamide (LSD), tetrahydrocannabinol (THC), and methamphetamine (MA) studies.

Demographics	LSD	THC	MA
Category	***N* or Mean ± SD (Range)**	***N* or Mean ± SD (Range)**	***N* or Mean ± SD (Range)**
Subjects (Male/Female)	21 (14/7)	23 (12/11)	29 (14/15)
Age, Years	25 ± 5 (19–33)	26 ± 7 (18–34)	24 ± 4 (19–33)
Body Mass Index, kg/m^2	22.2 ± 2.6 (18–28.2)	22.9 ± 2.4 (19.5–26.6)	22.3 ± 2.1 (17.4–26.1)
Race/Ethnicity			
Caucasian	17	12	18
African American	1	1	2
Asian	1	1	3
Other/>1 Race	2	9	6
Current Drug Use in Past Month			
Alcohol, drinks/week	4.9 ± 4.1 (0–17)	3.2 ± 0.7 (0–11)	2.1 ± 1.4 (0–6)
Alcohol, drinking days/week	2.3 ± 1.4 (0–5)	2.2 ± 1.5 (0–5)	1.6 ± 1.2 (0–5)
Caffeine, servings/day	1.4 ± 1.1 (0–3.5)	1.0 ± 0.2 (0–4)	1.4 ± 1.2 (0–4)
Tobacco, times/day	0.4 ± 1.8 (0–8.5)	0.3 ± 0.2 (0–5)	0.1 ± 0.5 (0–2.5)
Total Lifetime Drug Use, Nonmedical			
Psychedelic	10.5 ± 21.3 (1–100)	0.9 ± 0.4 (0–6)	3.9 ± 10.6 (1–56)
Cannabis	241.9 ± 453.5 (5–2000)	12.6 ± 1.4 (1–20)	269.2 ± 931.4 (0–5000)
MDMA	1.6 ± 3.9 (0–16)	0.2 ± 0.1 (0–2)	0.5 ± 1.2 (0–5)
Stimulant	25.7 ± 108.8 (0–500)	0.4 ± 1.1 (0–5)	2.0 ± 4.1 (0–20)
Opiate	3.5 ± 6.6 (0–30)	0 ± 0 (0–0)	3.5 ± 8.1 (0–40)

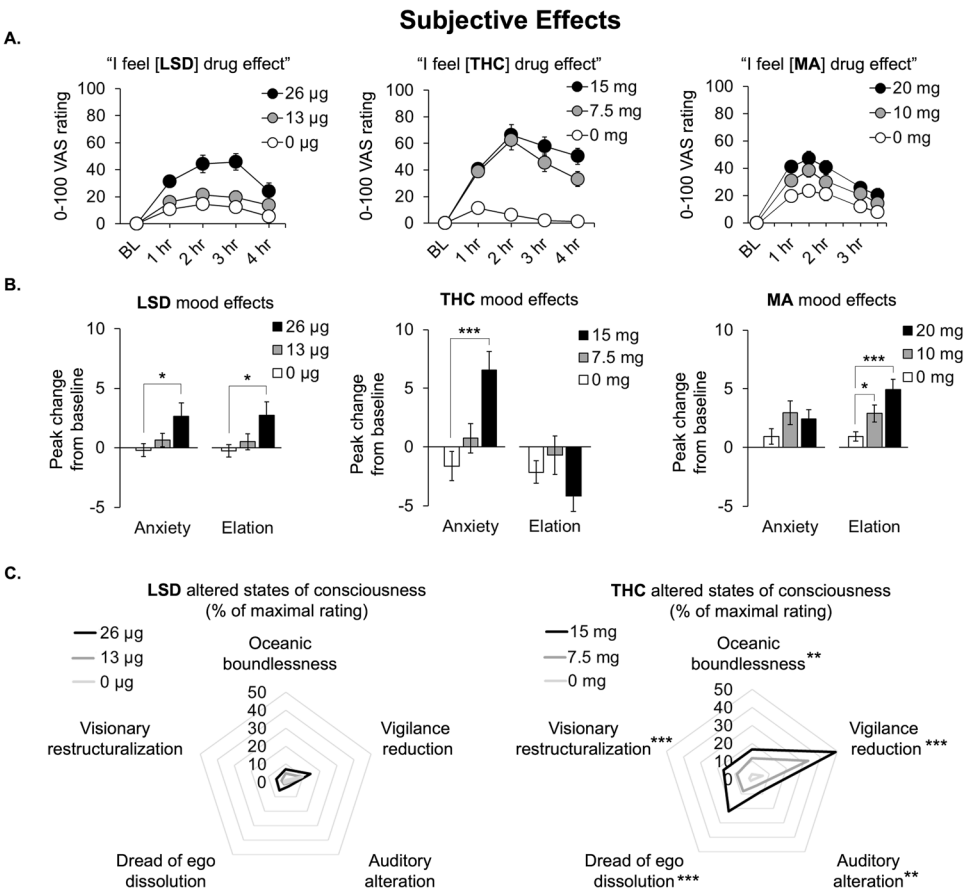

Fig. 1 Subjective drug effects across LSD, THC, and MA studies. A Drug Effects Questionnaire measure of Feel Drug Effect over sessions. **B** Profile of Mood States measures of Anxiety and Elation, peak response minus baseline. **C** 5-Dimensions of Altered States of Consciousness rated retrospectively at session end in relation to peak drug effects. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Pz. In spectral power across frequency bands (RM-ANOVA results in Supplementary Table 1), the low doses of LSD, but not THC or MA, desynchronized, or reduced, spectral power in the low frequency delta and theta bands (Fig. 3). In addition to reducing low frequency power, LSD increased high frequency gamma power. While LSD showed no effect on alpha power, THC and MA affected alpha bidirectionally, with THC reducing, and MA increasing alpha power relative to placebo conditions, particularly over frontal electrodes. MA also increased beta and gamma power.

Relationships between self-report and EEG measures

Given that the low doses of LSD affected both self-report and EEG measures, including feeling a drug effect and increasing Limpel-Ziv complexity, our next step was to determine whether the changes in EEG predict the self-reported effects across the LSD, THC, and MA studies. Surprisingly, greater limpel-Ziv complexity after 26 µg LSD was not associated with any subjective ratings, including feeling a drug effect, anxiety, or elation (Fig. 4), nor for any of the five altered states of consciousness measures on the 5D-ASC (not shown). Whereas Limpel-Ziv complexity did not predict self-reported effects after LSD, the low frequency desynchronization induced by LSD did predict self-reported mood states, with reductions in EEG delta and theta power associated with increases in elation. Participants that reported more elation after the 26 µg dose also reported more anxiety. After 15 mg THC, alpha power, but not Limpel-Ziv complexity, was related to two of the five 5D-ASC subscales, specifically DED and VR. After 20 mg MA, no EEG measures were related to self-report measures.

Examination of age-related effects

In supplemental analysis of age-related effects, we examined neural complexity and neural oscillations under placebo conditions of the THC study (30–35 relative to 18–20 years of age; Fig. S1). Adult relative to adolescent-aged participants showed global reductions in low frequency oscillations and increases in neural complexity, similar to the low doses of LSD relative to placebo.

DISCUSSION

We addressed whether low doses of LSD (13, 26 µg) and moderate to high doses of THC (7.5, 15 mg) and MA (10, 20 mg) increase neural complexity, a neural correlate of consciousness. Neural complexity was assessed alongside spectral power and self-reported drug effects and mood states, including altered states of consciousness. Using resting state EEG, we detected dose-dependent increases in neural complexity after low doses of LSD, but not THC or MA. Self-reported drug effects after LSD were minimal, including some increases in anxiety and elation after the 26 µg dose relative to placebo, and no differences between the 13 µg dose and placebo on any subjective measure. THC increased ratings for altered states of consciousness and anxiety, and MA increased elation. In spectral power analyses, low doses of LSD reduced delta and theta power, while THC and MA bidirectional affected alpha power, with THC decreasing, and MA increasing alpha power. LSD reductions in low frequency power related to elation. No associations between neural complexity and either spectral power, self-reported drug effects, or mood states were found across the LSD, THC, and MA studies.

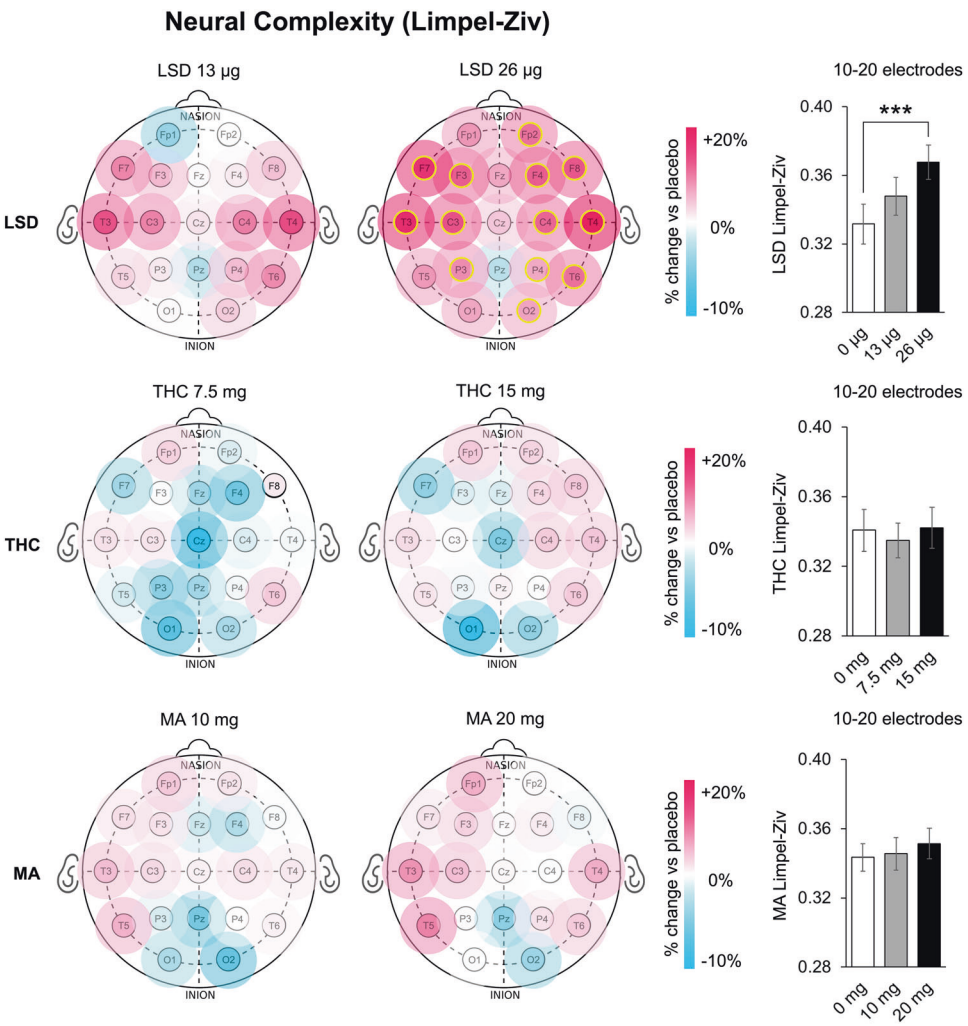

Fig. 2 Limpel-Ziv complexity across LSD, THC, and MA studies under 10–20 electrode placements of over prefrontal (Fp), frontal (F), temporal (T), parietal (P), occipital (O), and central (C) regions. Each dose condition shows % change relative to placebo. Red indicates increases and blue indicates decreases. Yellow rings indicate FDR-corrected significance in scalp electrodes relative to placebo conditions; seven significant electrodes in the 13 µg LSD condition did not pass FDR correction. Bar graphs show ANOVA results comparing the three doses for each study averaging all 10–20 scalp electrodes together are shown at right. ***$p < 0.001$.

Our main finding was that low doses of LSD, which were too low to affect altered states responses on the 5D-ASC, were nonetheless sufficient to increase Limpel-Ziv complexity. Greater Limpel-Ziv complexity has been reported after high doses of LSD (75 µg, intravenous [IV]) [75], psilocybin (225 mg/kg oral and 2 mg, IV) [75, 76], dimethyltryptamine (DMT, 20 mg, IV) [77], and ketamine (0.1–0.5 mg/kg, intravenous) [75, 78]. These doses also increase altered states responses, influencing prior interpretations that Limpel-Ziv complexity is a biomarker for altered states of consciousness [76] or "psychedelic state" [75]. A recent microdosing study reinforced this interpretation, finding no changes in Limpel-Ziv complexity after 0.5 g of dried psilocybin mushrooms [79]. Our work provides two key pieces of evidence that neural complexity is neither necessary nor sufficient for altered states of consciousness. First, greater Limpel-Ziv complexity was not necessary for altered states responses on the 5D-ASC after THC (7.5, 15 mg). Second, greater Limpel-Ziv complexity was not sufficient to induce altered states responses on the 5D-ASC after low doses of LSD (13, 26 µg).

What is the role of neural complexity after low doses of LSD? Historically dismissed as noise [80], signal complexity assists in the detection of weak signals, allowing subthreshold neurons to fire [81, 82]. The 5-HT2A receptor modulates sensitivity of neurons [36, 83], which may contribute, alongside the facilitation of excitatory synaptic transmission [33, 34], to a role for 5-HT2A activity in generating sources of complexity. The functional relevance of increased complexity after low doses of LSD is informed by prior work demonstrating that neural complexity is associated with better task performance [84], and is a better predictor of clinical outcomes to psychiatric treatment when compared to other brain and self-report measures [85]. Neural complexity is also generally reduced in individuals with mental disorders relative to healthy populations and increases with healthy brain development [80]. While some reports detected relationships between psychosis and neural complexity [86], others found that developmental increases in complexity were blunted in individuals with schizophrenia [87]. Here, we speculate that the somewhat lateralized pattern of complexity after LSD reflects changes in network activity, including default mode network disintegration [38, 39], given slight reductions in complexity under the midline Pz electrode over the posterior cingulate cortex [83]. Furthermore, in these same participants, we reported that the low doses of LSD increased neural responses to reward [29] and improved accuracy in detecting neutral faces relative to happy or angry faces [20]. Together, our findings that low doses of LSD increase neural complexity raise important

Fig. 3 Spectral power analysis across LSD, THC, and MA studies. Each dose condition shows % change relative to placebo. Red indicates increases and blue indicates decreases. Yellow rings map FDA-corrected significance in electrodes relative to placebo conditions. ANOVA results comparing the three doses for each study averaging all 10–20 scalp electrodes together are shown in Table S1.

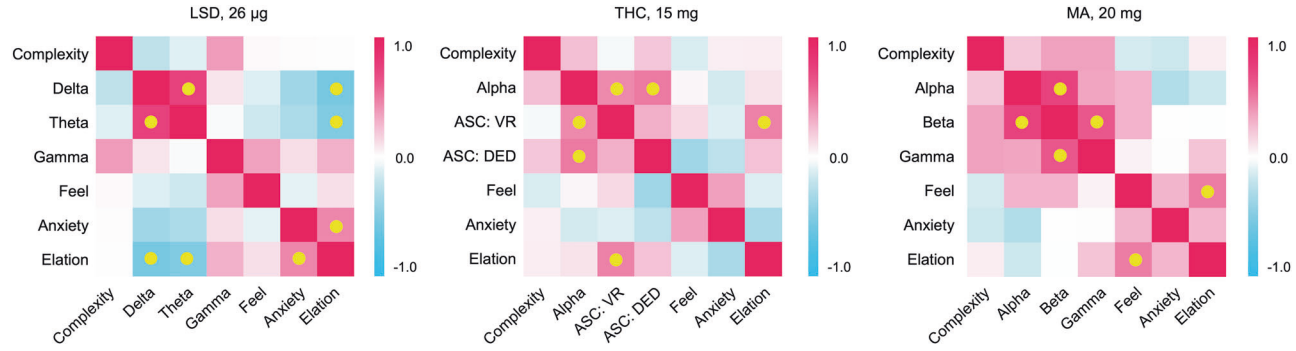

Fig. 4 Pearson correlations in the high-dose condition across LSD, THC, and MA studies. ASC: VR and ASC: DED refer to 5D-ASC Vigilance Reduction and Dread of Ego Dissolution, respectively. Yellow dots indicate significant correlation. 5D-ASC measures in the LSD study were not associated with EEG measures.

questions about its role in conscious processes, including how these roles may be operationalized and related to cognitive, behavioral, and therapeutic outcomes.

Complementing our analysis of neural complexity, we assessed spectral power across frequency bands. Whereas neural complexity reflects irregular fluctuations in neuronal activity, the power of neural oscillations reflects synchronized neuronal firing. We found no associations between changes in neural complexity and spectral power, supporting findings that neural complexity is not inherently linked to changes in oscillatory power [80]. Low doses of LSD reduced low frequency power in the delta and theta bands and increased high frequency power in the gamma band. Reduced theta has been reported after low, 0.5 g doses of dried psilocybin mushrooms [79]. Here, LSD had no effect on alpha power under 10–20 electrodes, whereas THC and MA bidirectionally affected alpha, with THC reducing and MA increased alpha power, particularly over frontal brain regions. THC reductions in alpha [57, 88] and psychostimulant increases in frontal alpha [89, 90] have been documented in prior reports.

Alpha oscillations are often associated with rest and inversely related to neural activity [91]. When eyes close, unperturbed neurons in the occipital lobe begin to synchronize in a resting rhythm, the alpha oscillation. When eyes open, diverse firing patterns return and desynchronize or reduce alpha power. Thus, MA-induced increases in frontal alpha may suggest a state with less mental contents, whereas THC-induced reductions in alpha may suggest altered states with active contents and disrupted cognition. Indeed, we previously reported that THC induces diverse phenomenological reports during rest [53] and impairs task performance [60]. Reductions in alpha power have been reported across psychedelics, including high doses of LSD (75 µg,IV) [92], psilocybin (2 mg, IV) [93], and DMT (20 mg, IV) [77] as a prominent signature of the psychedelic state, alongside increases in neural complexity [37]. Our findings here suggest that alpha desynchronization, rather than neural complexity, is a sensitive marker of altered states of consciousness. Together, alpha power and neural complexity may reflect discrete neural signatures representing the multifaceted nature of conscious states after psychedelics [52].

The current analysis includes both strengths and weaknesses. A key limitation is that three separate studies were pooled for the current analysis. However, each study included two doses and placebo following identical EEG procedures. In addition, the participants in all studies were not regular users (reported 0 use in last 30 days) of the experimental drug administered. As a result, the THC group reported less total lifetime uses of cannabis than the LSD and MA groups, however the groups were well matched on other demographic metrics. We note that our analysis did not include a measure to assess "richness of experience" which has previously been associated with Limpel-Ziv complexity [77]. Future studies should examine whether increased richness of experience can occur alongside Limpel-Ziv complexity independently from or prior to the induction of altered states of consciousness.

In conclusion, we report that low doses of LSD increase neural complexity (Limpel-Ziv) in the absence of altered states of consciousness (5D-ASC). At low doses, we speculate that 5-HT2A activation increases neural complexity via heightened neuronal sensitivity, and at high doses, greater 5-HT2A activation disrupts endogenous firing patterns that desynchronizes alpha rhythms and induces altered states. Increases in complexity after low doses of LSD, in the absence of psychedelic-like drug effects, raise important questions about potential roles for the diversity of neural signaling after low doses of LSD in conscious processes, which may have behavioral and therapeutic relevance.

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AUTHOR CONTRIBUTIONS

CHM for acquisition, analysis of data, and drafting of the manuscript. CH and IT for data acquisition. JF for the interpretation of data; critical revision of manuscript for intellectual content. RL for the interpretation of data; critical revision of manuscript for intellectual content. HdW for conception and design of the work; interpretation of data; critical revision of manuscript for intellectual content. All authors approved final manuscript for submission.

FUNDING

This research was supported by the National Institutes of Health [DA02812]. CHM was supported by the National Institutes of Health [T32DA043469]. Additional support was received as a Pilot Grant from the Department of Psychiatry and Behavioral Neuroscience, University of Chicago.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41386-024-01809-2.

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