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Psychedelics and Facial Expressions: the impact of an LSD microdose on the process of encoding emotional facial expressions

By

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Abstract

While LSD may have had a harsh reputation in decades previous, current research has been investigating its potential as a therapeutic modality. It has been shown that full doses of LSD are capable of providing therapeutic effects however, the concept of "microdosing", or the repeated use of very low doses has become increasingly popular. Yet, the literature does not provide consistent results to explain LSD's effects. The objective of the current study was to examine the effects of LSD (13 µg and 26 µg) versus placebo by use of electroencephalogram, event-related potential (ERP), event-related spectral perturbation (ERSP), and intertrial coherence (ITC) responses in healthy adults. Twenty healthy men and women, ages 18 to 35, participated in three EEG sessions in which they received placebo or LSD (13 µg and 26 µg) under double-blind conditions. During peak drug effect, EEG recordings were obtained by use of electrodes placed on scalp to identify the P300 and N170 components evoked during the visual oddball task. During the oddball task, LSD reduced ERP amplitudes of the P300 and N170 components. ERSPs exhibited decreases in power for the alpha frequency band and some theta frequencies. ITCs displayed relatively uniform distribution between trials. The reductions in P300 and N170 amplitudes were similar to those seen in full doses of LSD. Therefore, it is feasible to predict that microdoses of LSD may result in subtle behavioral and cognitive changes without requiring the full psychedelic effects of the drug.

The Impact of an LSD Microdose on the Process of Encoding Emotional Facial Expressions

Lysergic acid diethylamide (LSD) was originally synthesized in 1938 after Albert Hofmann, a chemist based in Basel, Switzerland, began to explore potential semisynthetic products derived from lysergic acid (Passie et al., 2008). The powerful psychological effects of the drug were discovered in 1943 after Dr. Hofmann took a dose of LSD to examine the drug's effects firsthand (Lee et al., 1992). After realizing LSD had altered his state of consciousness significantly, Dr. Hofmann began extensively documenting his subjective experience. The drug reportedly introduced a variety of both pleasant and unpleasant images, swirls of colors, and physiological changes such as dizziness (Hofmann, 1979). In the 1950s, the drug was harnessed and used to help individuals who experienced anxiety, depression, and even psychotic-like states (Gasser et al., 2015). However, the drug was quickly abused recreationally and even by medical professionals to the point of having to classify LSD as a schedule one drug and has maintained that classification in present day (US Drug Enforcement Administration, n.d.).

LSD is classified as a hallucinogenic drug as it elicits abrupt and intense changes in emotional state, feelings of euphoria, feelings of detachment to the real world, paranoia, hallucinations, and alterations in the perception of time (Katz et al., 1968; Passie et al., 2008). A typical full dose of LSD ranges from 75-150 µg. At this dose, an individual will feel the full effects of the drug's hallucinogenic properties and should expect the duration of the drug to last approximately 6 to 10 hours (Passie et al., 2008). An alternative is to take a microdose of LSD which typically ranges between 5 and 25 µg (Polito & Stevenson, 2019; Rootman et al., 2021). Additionally, microdoses are taken in repeated intervals approximately 2 to 4 times per week. The repeated usage helps to maintain sufficient amounts of the drug in the body and may be used for weeks, months, or even years though the latter is less common (Kuypers, 2020).

Existing Literature on the Psychological Effects of LSD

The classification of LSD as a schedule one drug promptly resulted in the temporary cessation of all testing on the drug (Malleson, 1971; Passie et al., 2008). However, the new classification as a schedule one drug did not stop the general population from using LSD recreationally. In fact, the continued usage of the drug only exacerbated the negative reputation that had enveloped LSD. During the 60's and 70's LSD became closely associated with the hippie movement and the idea that LSD had the power to change your chromosomes and compel people to complete outlandish acts (Tjio et al., 1969). After some time, Switzerland finally overcame the daunting illegal classification and began conducting LSD studies again. Some studies targeted individuals with terminal illnesses and anxiety related to end of life (Gasser et al., 2015) and others required healthy individuals that had used a psychedelic before. The latter is to ensure compliance with the Institutional Review Board (IRB) and ethical guidelines (Liechti, 2017).

Researchers began to document the responses of healthy individuals who had been administered a full dose of LSD and found there were a myriad of potential therapeutic benefits (Carhart-Harris et al., 2016; Pahnke et al., 1970; Polito & Stevenson, 2019; Sessa, 2012). In a study that utilized a dose size of 200 µg, results showed a significant effect in reducing anxiety symptoms (Gasser et al., 2014). An additional study that compared various LSD doses also concurred that there was a significant increase in positive mood and happiness as relayed by subjective reports (Hutten et al., 2020). The disadvantage of LSD is the strong psychedelic side effects that accompany a full dose of LSD hence, the concept of a microdose was developed (Fadiman, 2011; Polito & Stevenson, 2019). The idea is to maintain the therapeutic benefits of the drug while not having to endure the full hallucinogenic properties. Dr. James Fadiman was

one of the first to compile information on the concept of microdosing. Dr. Fadiman's book, *The Psychedelics Explorer's Guide: Safe, Therapeutic, and Sacred Journeys*, discusses the potential benefits of a microdose, the subjective experiences shared by those who actively utilize microdoses, and additional information to adequately inform readers about LSD before making the decision to use the drug in any capacity (Fadiman, 2011). Current studies are seeking information regarding the effects of a microdose on connectivity patterns in the brain and how it contributes to an individual's subjective experience (Bershad et al., 2020). Results across studies are mixed but favor the data that suggest a microdose does improve positive mood (Bershad et al., 2020; Carhart-Harris et al., 2016; Murray et al., 2021). Thus, it is important that future studies continue to modify and improve testing methods to provide accurate and beneficial data.

Time Frequency

Electroencephalograms (EEG) consist of amplitudes and latencies with positive and negative deflections and are collectively referred to as waveforms (Herrmann et al., 2014). Additionally, EEGs provide the opportunity to examine the resting-state oscillations of the brain. These oscillations provide a glimpse of the body's natural reaction to a drug without the involvement of stimuli or participation in cognitive tasks (Luck, 2014). When graphed, EEGs are in a time domain signal where the y-axis is labelled voltage, and the x-axis is labelled time. These waveforms and their resulting changes in averaged EEG signal voltage are created by averaging together each EEG thereby generating an event-related potential (ERP) (Başar et al., 1999). Therefore, an ERP is represented in a two-dimensional plot within a time domain signal (Herrmann et al., 2014).

On the other hand, researchers often utilize event-related oscillations (ERO) as they are depicted in a time frequency domain (Balconi & Pozzoli, 2007). An ERO is comprised of neural

oscillations from each of the five frequency bands and is generated spontaneously and in response to stimuli by neural tissue in the central nervous system (Başar, 2013). Visually, an ERO appears similar to an ERP but differs in that an ERO is associated with the oscillatory power within a specific frequency band (alpha [8-12 Hz], beta [13-20 Hz], delta [1-3 Hz], gamma [30-100 Hz], and theta [4-8 Hz]) rather than the voltage amplitude depicted in an ERP (Başar, 2013). EROs are particularly advantageous in this regard as it offers insight into which frequency bands are perturbed following the introduction of a stimulus. EEGs can be interpreted as a time, frequency, or time frequency domain and is selected based on the independent variables of a given study (Herrmann et al., 2014). A combination of time and frequency into a comprehensive domain allows researchers to examine the progression of a stimulus or effects of a drug over a specified time period in addition to examining the effects of the drug on the frequency bands (Herrmann et al., 2014).

Inter trial coherence (ITC) is a measure of phase synchronized time frequency activity that is computed from a single trial EEG (Nash-Kille & Sharma, 2014). ITC is depicted on a scale from 0 to 1 where 0 means the trials are uniformly distributed and where 1 means the latency window for each trial is constant. In order to obtain ITC, the stimulus must be phase-locked so that the individual trials are able to synchronize. ITC is important to consider as the synchronization of phases has been associated with the processing of information (Chikara et al., 2020).

Event-Related Spectral Perturbations

Event related spectral perturbations (ERSPs) address the ERP limitations by viewing these data in a time frequency domain. The approach does not use phase-locked events after the introduction of a stimulus. Instead, an ERSP depicts the averaged event-related changes in

spectral power for each epoch and frequency (Zhao & Zhang, 2007). Focus on the epoch length and frequency bands allows researchers to examine changes in EEG amplitudes and latencies for the duration of a participant's involvement with a task. ERSPs are of particular interest when designing studies with multiple trials and conditions as the responses can be averaged and generalized more accurately.

EEG Studies on Emotional Facial Expression Processing

There are inconsistencies within research regarding the best way to study the process of encoding emotional facial expressions. Within EEG research, one of the most effective ways to study this concept is by examining areas of activation across the scalp after the introduction of a stimulus. Researchers study these activations by analyzing individual event-related oscillations and combinations of these oscillations (Balconi & Lucchiari, 2008; Begleiter & Porjesz, 2006; Başar, 2012). It is thought to be particularly effective as the introduction of a stimulus modulates the power of oscillations within different frequency bands resulting in a clear depiction of the stimulus' effect on brain functions (Rangaswamy & Porjesz, 2008). EROs are presented in a time frequency domain and despite the averaging of these bands to engender valuable results, there are still inconsistencies regarding the importance of each frequency band in emotional facial processing (Balconi & Lucchiari, 2006).

Resting state activity refers to the electrical activity at the scalp when an individual is at rest and not completing any tasks. The default mode network (DMN) provides insight into brain activity associated with processing within the body (resting state) rather than the processing of external stimuli. This network is more activated when a participant is refraining from activity and less activated when performing a task (Balconi and Lucchiari, 2006). The changes in activation associated with switching from resting-state to attending to a task across the scalp are

reflected within the five frequency bands (alpha, beta, delta, gamma, and theta) which reports whether the stimulus resulted in a positive or negative deflection in an ERP (Murray et al., 2021). These deflections are then presented in terms of power and can be used to determine the level of desynchronization that occurs within a given frequency band. The amount of desynchronization within a band indicates the degree to which an individual tended to a task, for example, a lower alpha power, or the desynchronization of alpha is the result of an individual responding to a task.

A study conducted by Güntekin and Basar (2007) found that the alpha band not only plays a role in resting state brain modulation (Gu et al., 2019; Hermann & Knight, 2001) but is also implicated in the process of encoding emotional facial expressions. The authors found that after participants had been presented with an angry face, alpha amplitudes increased. The alpha frequency variability in response to emotional stimuli has led researchers to propose that the alpha band could be a mediator in determining how much attention should be allocated to a stimulus (Gu et al., 2019; Meng et al., 2016; Mazaheri et al., 2014). Furthermore, the beta band has been shown to exhibit increased amplitudes after viewing angry facial expressions (Güntekin & Basar, 2007). The theta frequency band has also been implicated in studies designed to process emotional facial expressions as it is thought to be related to processing emotional information and arousal (Balconi & Lucchiari, 2006). Additionally, the theta band has been shown to display increased power following the introduction of emotional content or discerning face significance (Aftanas et al., 2001; Balconi & Lucchiari, 2006). Research also suggests a possible link to the gamma frequency band (Balconi & Lucchiari, 2008; Li et al., 2015). It has been suggested that the gamma frequency band plays an essential role in the conscious

processing of emotional faces and fluctuates depending on the valence of the facial expression (Balconi & Lucchiari, 2008).

Examining areas of scalp activation during an emotional face oddball task results in broad patterns of electrical activity that can be associated with the processing of different stimuli. Of particular interest, researchers often view the P300 and N170 components as they are thought to be linked to the processing of facial expressions (Gu et al., 2019). The N170 generally has the highest amplitudes in the occipitotemporal sections of the scalp. The 'N' refers to the negative deflection from baseline activity and the 170 refers to the spike in voltage that occurs approximately 170ms after the introduction of a stimulus. Increased amplitudes on the scalp for the N170 reflect increased activation in the visual processing components used for facial recognition (Gao et al., 2019). The P300 generally sees the most pronounced activity in the frontal regions of the scalp. The 'P' refers to the positive deflections from baseline activity that occurs anytime between 300 and 800 ms after stimulus introduction. Increased amplitudes of the P300 represents an increase in allocation of attentional resources also utilized for facial recognition. A study was conducted by Almeida et al., (2016) to analyze the level of phase coherence after participants were introduced to emotional facial expressions. The study found that when compared to angry and neutral expressions, fear emotions had higher coherence across all five frequency bands. Higher coherence among phases suggests a more consistent response across trials. For the fearful faces, higher coherence may imply that the processing of fearful stimuli may require a more pronounced response than some of the other emotions.

Present Study

The relationship between encoding facial expressions and the influence of a drug on these processes has limited findings. This is especially true for psychedelics such as LSD due to

clinical trial protocols and ethical guidelines on state and federal levels. As a result, there is little research that explains how LSD impacts the process of encoding emotional facial expressions. Therefore, this study is examining the effects of LSD microdose administration on the processing of neutral faces using an oddball task. In a previous analysis of the current study data conducted by Murray et al., (2021) ERP data suggested that a microdose of LSD decreased the amplitudes of the N170 and P300 in response to angry and neutral faces. Research discerning which frequency bands are most closely related to the encoding of facial emotions is inconsistent with some frequency bands being consistently recognized and others hardly at all. However, the N170 and P300 play an invariable role in the encoding and recognition of emotional facial expressions (Murray et al., 2021).

The study predicts that there will be decreased amplitudes for the N170 and P300 after the introduction of a visual oddball task. Additionally, it is hypothesized that the alpha (Hermann & Knight, 2001; Hermann et al., 2014) and theta (Basar et al., 2001) frequency bands will be most impacted by changes in dose size with higher dose size resulting in lower power and desynchronization. Existing literature suggests there should be minimal if any differences for the delta, beta, and gamma frequency bands. Finally, the study predicts that there will be low phase trial coherence as the images in the study are neutral.

Methods

Participants

Healthy subjects (N = 20, 10 males) ages 19 to 35 participated. These 20 participants were taken as a subset from the original 22 participants in the Murray et al., (2021) paper. They were screened 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 32 kg/m^2, and at least one prior use of a classical psychedelic (e.g., LSD, psilocybin, N, N-dimethyl-tryptamine [DMT]) or 3.4-methylenedioxymethamphetamine (MDMA). Exclusion criteria were 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. All subjects were provided written informed consent. All study procedures were approved by the Institutional Review Board (IRB) of the Biological Sciences Division at The University of Chicago. Full participant demographics are described in Table 1.

Table 1. Participant Demographics

Category	n or mean ± SD (range)
Subjects	20
Male	10
Female	8
Other	1
Prefer not to say	1
Age, years	25 ± 3.9
Race	
Caucasian	16
American Indian/ Alaska Native	1
Asian	1
More than one race	1
Unknown	1

Study Design

The study utilized a within-subject, double-blind design to examine the effects of a low dose of LSD on subjective experiences and EEG outcomes. Healthy adults participated in three five-hour

sessions in which participants were randomly assigned to either a placebo, 13µg, or 26µg of LSD. Prior to and in 60-minute intervals following drug administration, subjective mood states and cardiovascular measures were recorded. At the time of drug peak effect, 120 to 180 minutes after drug administration, EEG recordings were obtained to assess oscillatory activity during resting state and event-related potential responses to infrequent stimuli. Full details of the study design and procedure have been reported by Murray et al. (2021).

EEG Measures

EEG Acquisition: EEG recordings were collected using a 128 sintered Ag/AgCl active electrodes (ActiveTwoTM system, BioSemi B.V., Amsterdam) placed according to equilateral layout on the head cap. Additional electrodes were placed at reference locations of the mastoids (located behind the ears), around the eye to detect eye blinks, and on the chest to detect EKG artifacts (8 peripheral electrodes in total). The analog-to-digital box receiving the electrode leads was battery powered to electrically isolate participants. EEG data was acquired continuously, amplified, and digitized using BioSemi ActiveView software. Digitization of electrode placement reflecting actual head shape was conducted using a PatriotTM Digitizer stylus (Polhemus Co., Colchester VT) and locator software (Source Signal Imaging, Inc., San Diego CA). The stylus touches each electrode site until registered by software (5-10 minutes total). EEG recordings occurred in a sound attenuated room, with the subject sitting comfortably. EEG recordings were high pass filtered (1 Hz), and low pass filtered (60 Hz, -12 dB/octave) to remove extraneous high and low frequency noise. EEG and electrooculogram (EOG) signals were processed by voltage-controlled amplifiers and digitized (16 bit/ 500 Hz sampling rate for storage and analysis. Data was processed offline based on data stored on computer workstation hard drives.

Emotional Faces Oddball Task: The objective of the oddball task is to assess event-related potentials, event-related spectral perturbations, and inter trial coherence. The oddball task presented images of angry, neutral, and happy facial expressions with happy faces being more frequent. The frequent happy faces and infrequent angry and neutral facial expressions were presented in a 3:1 ratio (Eckman and Friesen, 1976). Each facial expression was portrayed by the same two models. Each facial expression group was presented individually (i.e., all angry or all neutral) with order counterbalanced across participants. Participants were asked to select between two buttons choosing the right button for happy expressions and the left button for angry and neutral expressions. Any incorrect EEG trial data were discarded. Facial expressions were presented on a screen for 1500 ms, followed by a blank screen for 1000 ms, followed by a fixation cross for 1000 ms. A total of 320 face stimuli were presented in three blocks (160 for each facial expression group). The entirety of the task lasted for 15 minutes. For the purpose of this study, the time and frequency analyses for the neutral faces were the primary outcomes of interest. The Pz electrode was selected a priori to measure the P300 component, the PO 9 and 10 electrodes were selected a priori to measure the N170 component (Fig. S1). Event-related spectral perturbation and inter trial coherence were also collected during the oddball trials. Data were epoched from -500 to 1000 ms around stimulus triggers and P300 amplitudes were measured within a 450 to 800 ms time window. The N170 component was measured within a 150-220 ms time window. ERSPs were assessed for changes in event-related oscillatory power during oddball epochs. ITCs were assessed to measure the amount of phase synchronization between trials.

Data Analysis

EEG Preprocessing: Data were preprocessed using the EEGLAB extension v2022.0 (Delorme & Makeig, 2004) for MATLAB (Mathworks, Inc.). Data containing gross movement artifacts were manually inspected and eliminated and then re-referenced to the average reference. Gross movements were defined by interruptions of signal that occurred across all electrodes in continuous data. Other artifactual noise, including eye blink, eye movement, muscle, or EKG related artifacts, were removed after independent component analysis (ICA) based on topography and morphology of ICA components. After ICA, peripheral electrodes were removed from analysis. Analysts were blind to drug condition during preprocessing steps to prevent bias during manual inspection.

ERP Analysis: Following ICA, data were epoched from -500 to 1000 ms around stimulus triggers. Data files were analyzed using EEGLAB Study function with multiple designs. ERP analyses were performed on the Pz, PO 9, and PO 10 electrodes, selected a priori for analysis of the P300 component (parietal (Pz/ A19)), and N170 visual processing component (left parieto-occipital PO 9/D32; right parieto-occipital PO 10/ B10), respectively.

ERSP and ITC Analysis: ERSPs and ITCs were analyzed with statistical p-value maps for each electrode. Electrodes of interest were selected a priori and include the A19 (reflects the P300), B10 and D32 (reflects the N170).

Statistical Analysis

EEG Measures: Repeated measures ANOVAs were performed on the P300 and N170 latency of each participant with dose as the within-subjects measure. ERSPs and ITCs were analyzed by use of statistical *p*-value maps. Scalp topographies were generated by selecting all electrodes from all participants and averaging the trials.

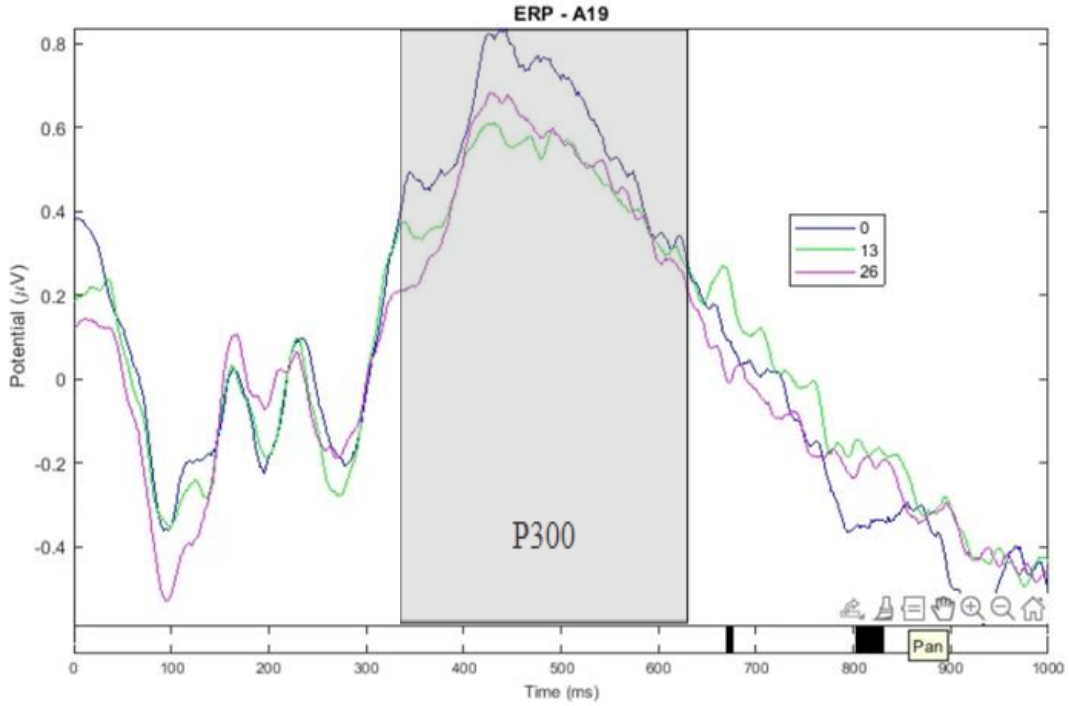
Results

ERP Analysis

A one-way repeated measures ANOVA were performed with dose as the within-subject factor. The Pz (A19) electrode showed a clear P300 ERP response approximately 450 ms after the introduction of the stimulus (Fig. 1). All three conditions exhibited a positive deflection with the placebo group displaying the highest potential. The microdose groups were slightly less elevated but not significantly different from the placebo.

Figure 1

Electrode Pz P300 Response

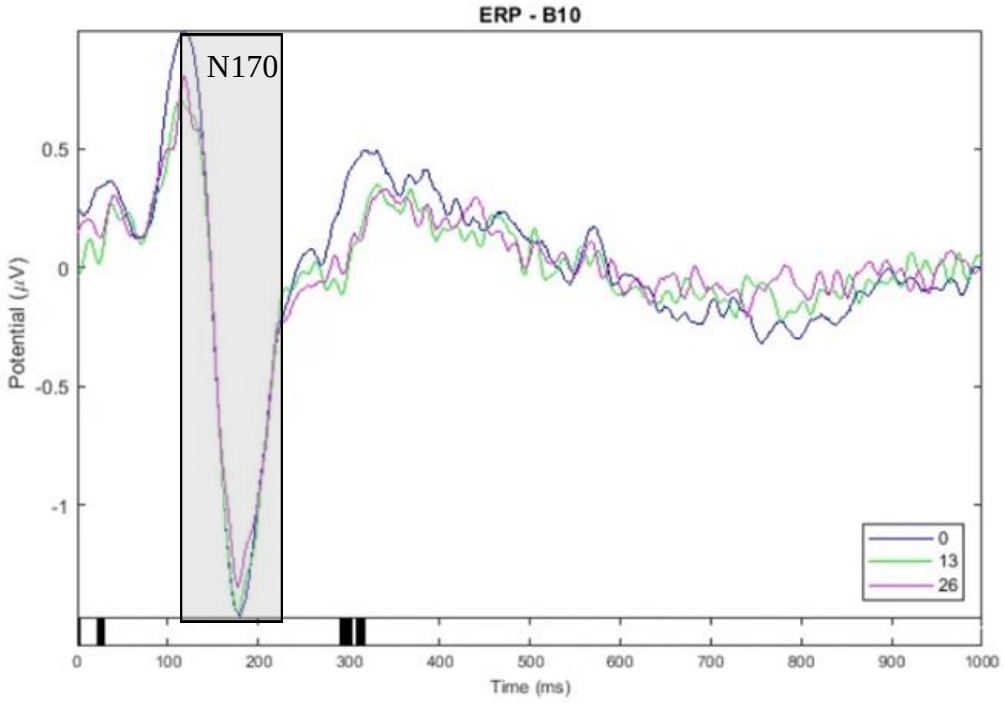


Note. P300 event-related potentials (ERPs) for the Pz (A19) electrode in response to rare neutral facial expressions in the oddball task. Stimuli were presented at time zero. A one-way repeated measures ANOVA did not depict a significant difference between the three conditions. Significant statistical differences are marked by solid black blocks at the base on the graph.

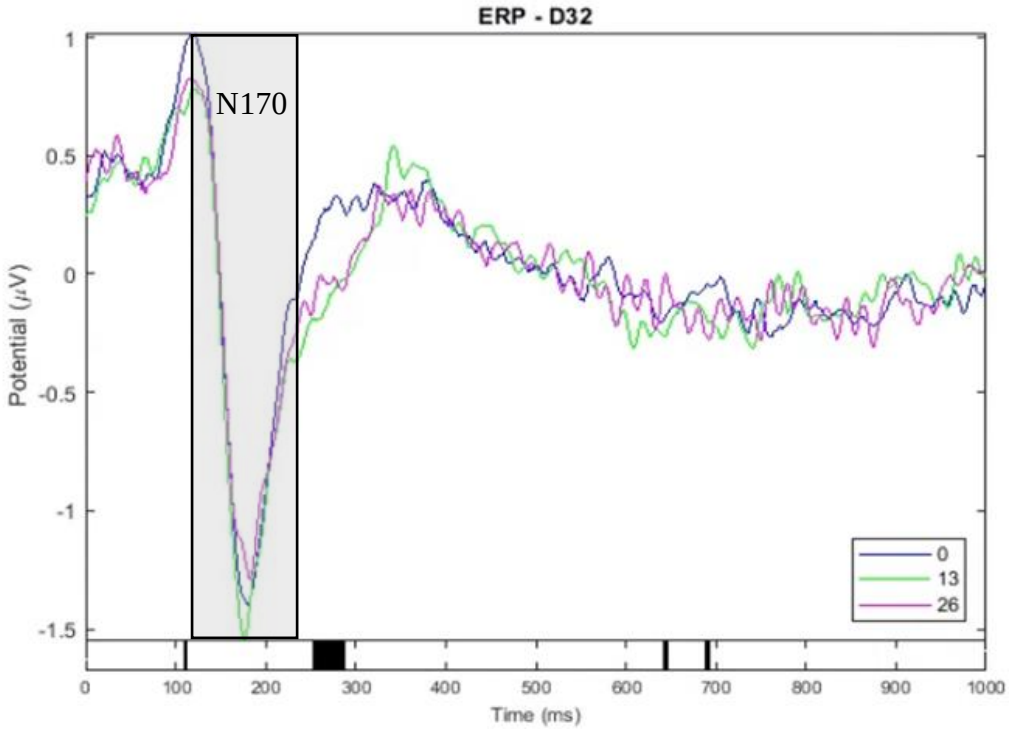
The PO 9 and PO 10 electrodes were selected a priori to represent N170 activity. In general, these electrodes exhibited a negative deflection approximately 170 ms after introducing the stimulus (Fig. 2). These electrodes also displayed negative deflections closer to 200 or 250 ms after stimulus introduction. The averaged ERPs from all participants are topographically displayed in Figure 3 for the P300 and N170 component time ranges. The red electrodes displayed in the far right panel indicate electrodes with statistically significant differences between the three conditions. The P300 shows electrodes of significance within the left frontal lobe. The N170 shows electrodes of significance primarily within the left parietal and left frontal lobes. Figure 4 topographically depicts the ERPs during the 200 – 250 ms time range and shows which electrodes have statistically significant differences between the three conditions.

Figure 2

PO 9 Electrode N170 Response



PO 10 Electrode N170 Response

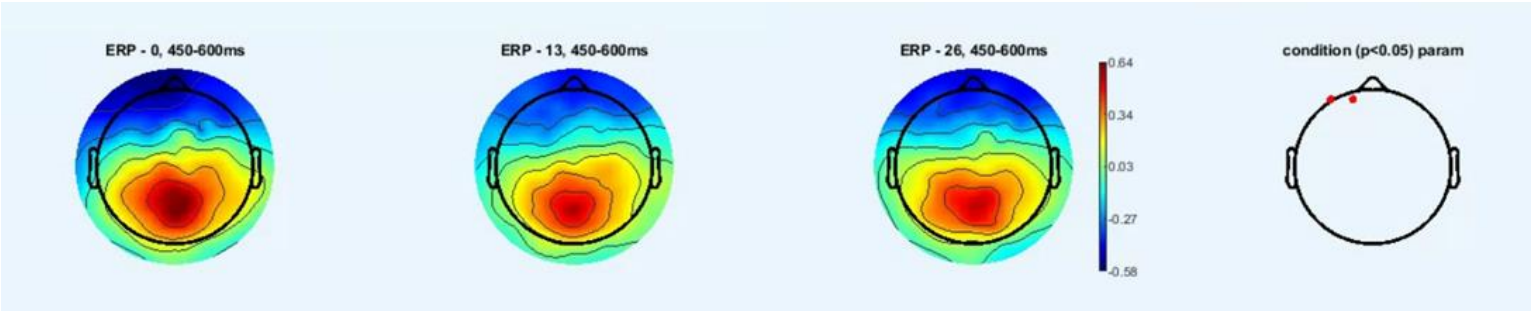


Note. N170 event-related potentials (ERPs) for the PO 9 and PO 10 electrodes in response to rare neutral facial expressions in the oddball task. Doses are in micrograms. Stimuli were presented at time zero. A repeated-measures ANOVA resulted in prominent N170 responses however, there were no significant statistical differences between the placebo condition, the 13 µg of LSD condition, and the 26 µg of LSD condition in the N170 time range (150-220 ms). Significant statistical differences are marked by solid black blocks at the base on the graph.

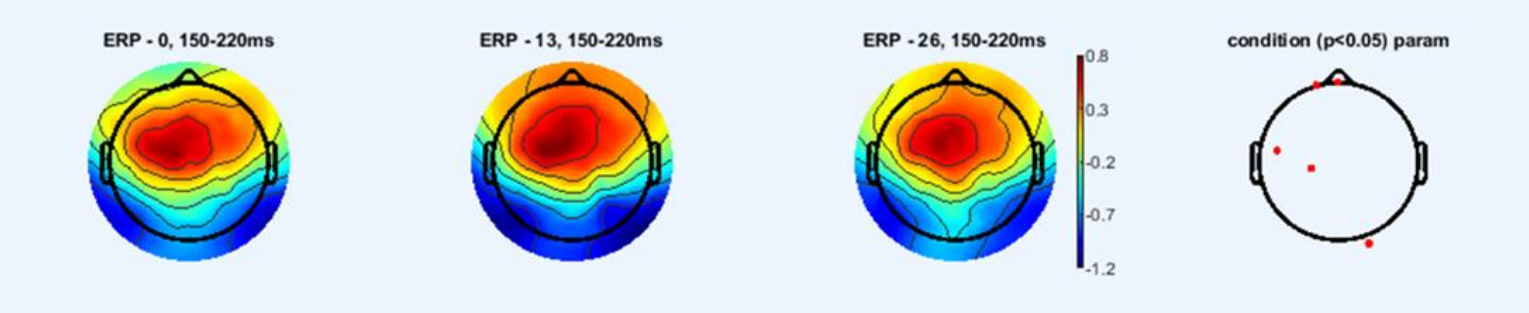
Figure 3

Averaged Scalp Topographies for the P300 and N170

(A)



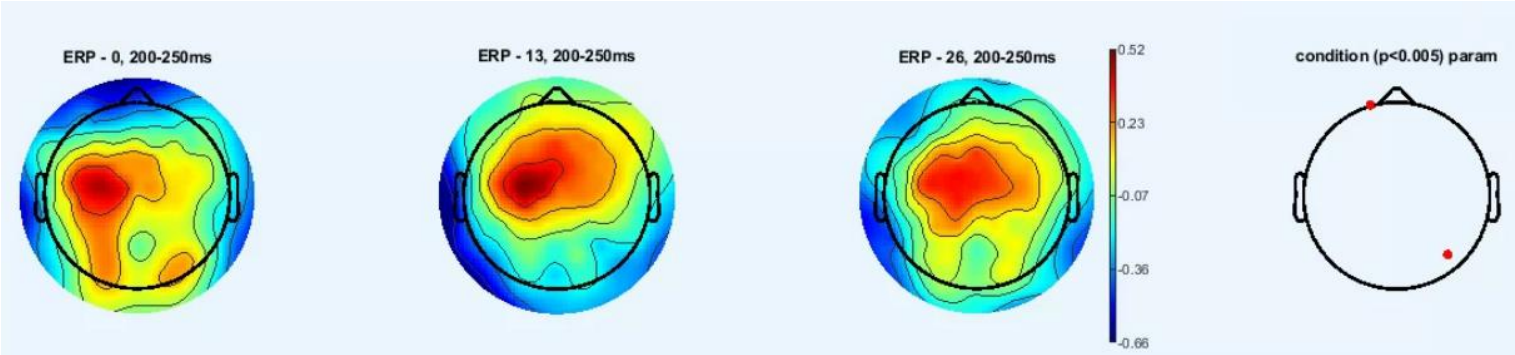
(B)



Note. To depict the P300 (A) and N170 (B), scalp topographies were averaged for each subject. Right: red dots indicate electrodes were significant differences across the placebo condition, 13 µg of LSD, and 26 µg of LSD condition ($p < 0.05$).

Figure 4

Averaged Scalp Topography for 200-250 ms



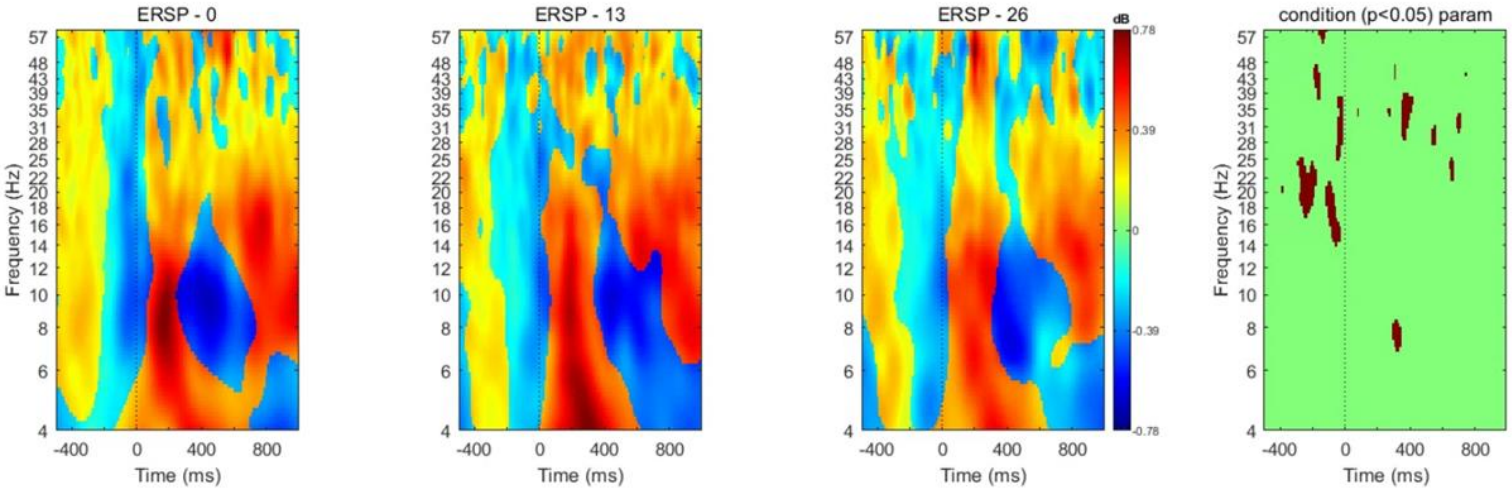
Note. The scalp topographies were averaged for each subject within the 200-250 ms time range. Right: red dots indicate electrodes with significant differences across the 13 µg, 26 µg, and placebo condition ($p < 0.005$).

Time Frequency Analyses

ERSP Analysis: The ERSPs depicted an overall decrease in alpha and theta frequencies though differences were not statistically significant for the PO 9 and PO 10 electrodes. The Pz electrode produced an ERSP with statistically significant differences between conditions and displayed a P300 response (Fig. 5). The PO 9 and PO 10 electrodes in general, did not produce statistically significant differences between the three conditions (Fig. 6).

Figure 5

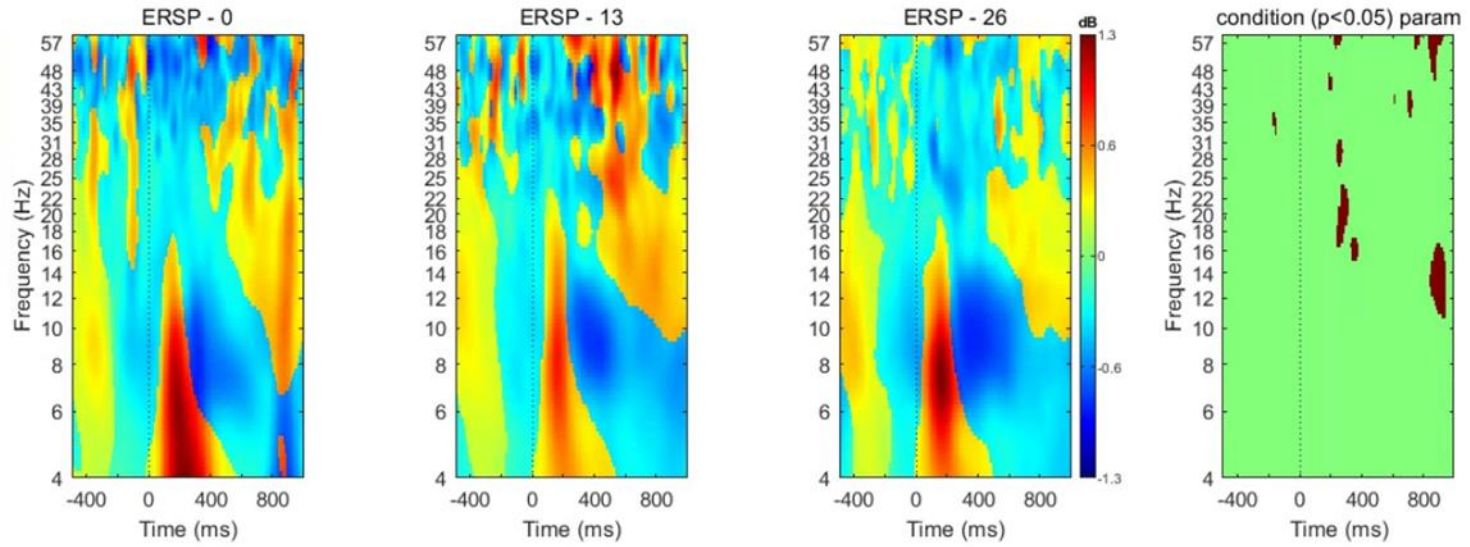
Electrode Pz ERSP Response



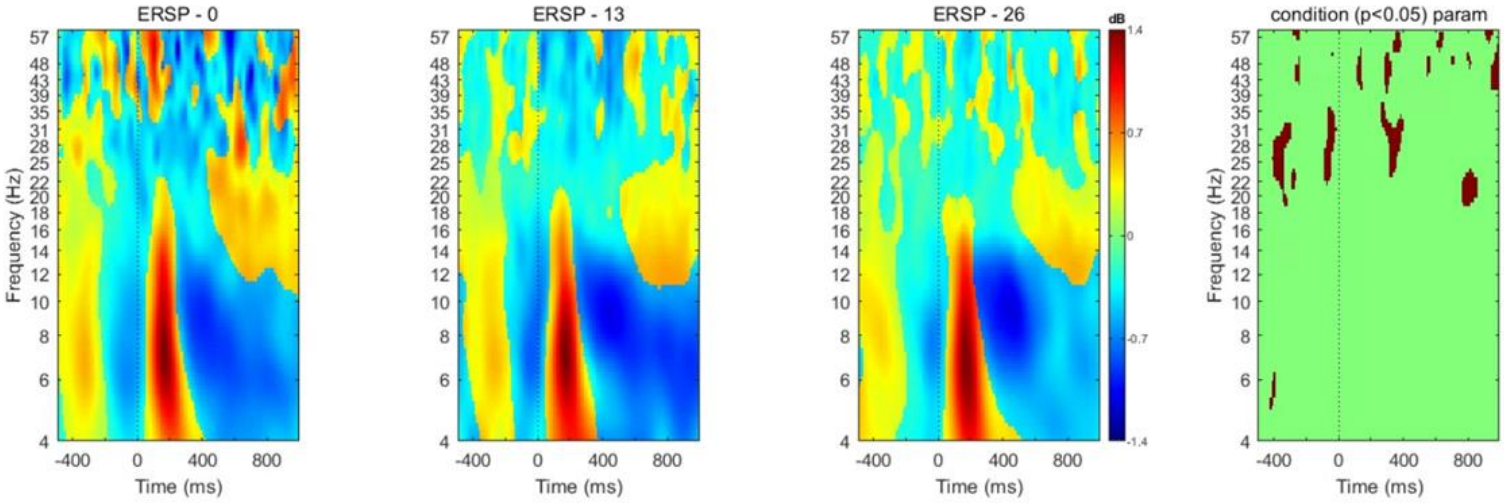
Note. ERSP time frequency analysis from the Pz/A19 electrode as a result of stimulus introduction during the oddball task. Stimulus introduction occurred at time zero. Heat map depicts deviations from baseline in spectral power in decibels where blue indicates reductions in event-related power. Power reductions were confined to the theta (4-8 Hz) and alpha (8-13 Hz) frequencies. The green panel displays the differences between the 13µg, 26 µg, and placebo groups. The dark red spots indicate significant areas of difference in theta reduction (desynchronization) ($p < 0.05$).

Figure 6

PO 9 ERSP Response



PO 10 ERSP Response



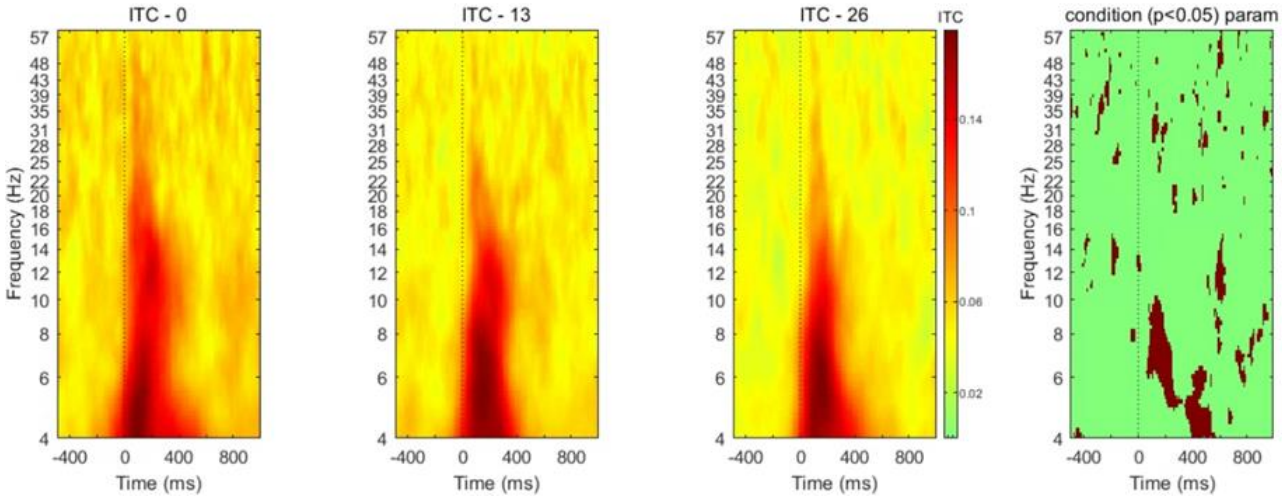
Note. ERSP time frequency analysis from the PO 9/B10 and PO 10/D32 electrodes as a result of stimulus introduction during the oddball task. Stimulus introduction occurred at time zero. Heat map depicts deviations from baseline in spectral power in decibels where blue indicates reductions in event-related power. Power reductions were primarily confined to the theta (4-8 Hz), alpha (8-13 Hz) frequencies however, reductions were not statistically significant. The

green panels display the differences between the 13 µg, 26 µg, and placebo group. The dark red spots indicate significant areas of desynchronization within frequency bands ($p < 0.05$).

ITC Analysis: The ITCs generated from the Pz electrode displayed significant statistical differences between all of the conditions (Fig. 7). The differences occurred within the theta (4-8 Hz) and alpha (8-13 Hz) frequency bands. For the PO 9 and 10 electrodes, some displayed statistical differences between the three conditions (Fig. 8). Areas that did display statistical significance were within the theta and alpha frequencies. Trials resulted in low ITC values meaning the trials are close to uniform distribution.

Figure 7

Pz Electrode ITC Response

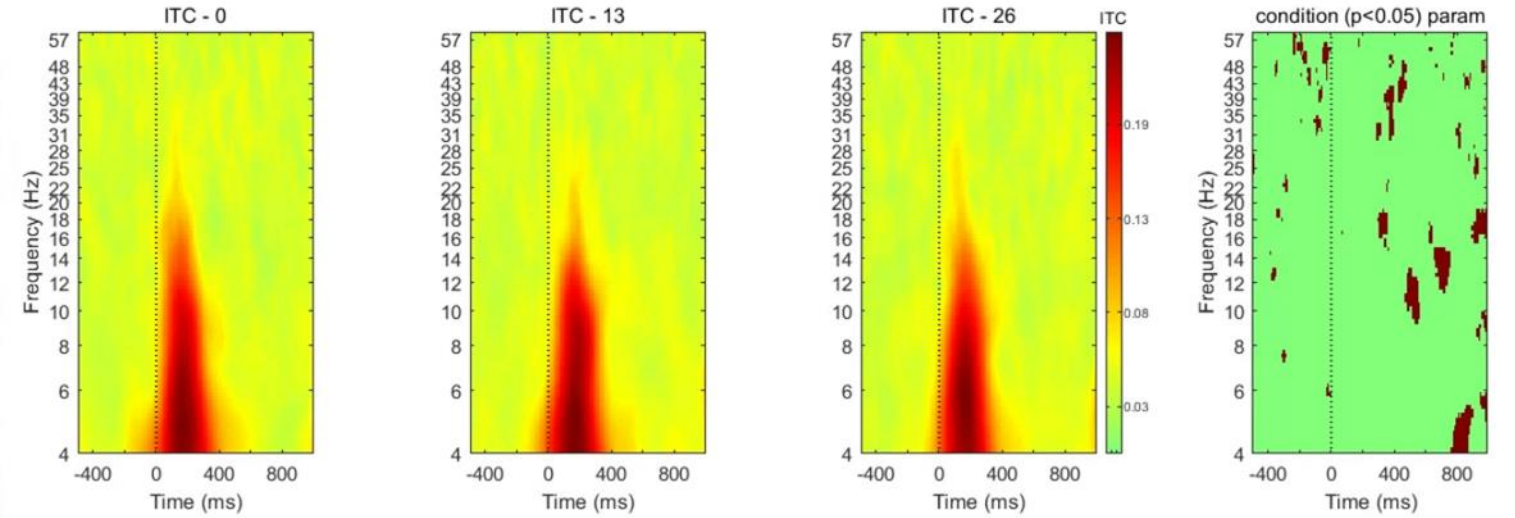


Note. ITC time frequency analysis from the Pz electrode as a result of stimulus introduction. Stimulus introduction occurred at time zero. The dark red indicates the latency window for each frequency band are close to constant for each trial where green indicates the trials are uniformly distributed. The green panel displays areas of difference between the 13 µg, 26 µg, and the

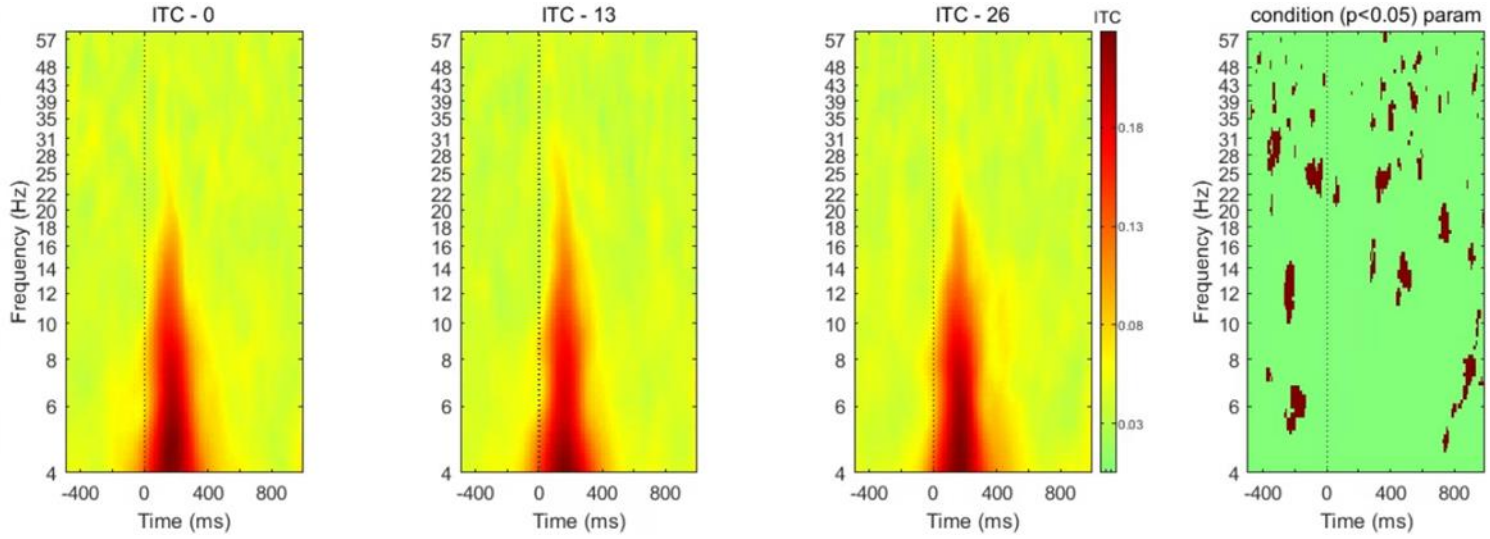
placebo condition. The dark red spots indicate areas of difference for the theta (1-4 Hz) and alpha (4-13 Hz) frequencies ($p < 0.05$).

Figure 8

PO 9 Electrode ITC Responses



PO 10 Electrode ITC Response



Note. ITC time frequency analysis from the PO 9 and PO 10 electrodes as a result of stimulus introduction. Stimulus introduction occurred at time zero. The dark red indicates the latency window for each frequency band are close to constant for each trial and green indicates the trials are uniformly distributed. The green panel displays the differences between all three conditions. The dark red spots indicate areas of desynchronization within frequency bands ($p < 0.05$).

Discussion

The goal of the study was to determine the impact of an LSD microdose on the process of encoding neutral facial expressions in healthy participants by use of electrophysiological measures. To assess modulation of ERPs, ERSPs, and ITCs participants were asked to participate in visual oddball tasks. The overall finding of the study is that LSD microdoses generally do not have statistically significant effects when viewing neutral facial expressions. ERP amplitudes are present for the P300 and N170 but are not statistically significant, ERSPs showed power reductions for the alpha and theta frequencies but were not significant, and ITCs showed that the trials were close to uniform in distribution and there was statistical significance for differences between conditions within the alpha and theta frequencies. Electrodes topographically identified showed statistically significant differences between the conditions and were identified in areas confirmed by literature (Başar-Eroglu et al., 1992). The introduction of unexpected stimuli in the oddball task in addition to LSD microdoses resulted in reduced neural responses. Changes in the P300 and N170 as a result of LSD microdose introduction are crucial to examine as it may enlighten the process of encoding emotional facial expressions and how they are perceived. In the current study, it is important to acknowledge that despite clear P300 and N170 responses, the differences between conditions were not statistically significant. An important difference between the current study and the parent paper by Murray et al., (2021) is that their study was

able to identify statistically significant differences for the P300 and N170. Some potential explanations for the difference could be the exclusion of two participants present in the original study or the fact that only neutral facial expressions were examined as compared to neutral and angry.

The P300 was captured by analyzing the ERP of the Pz electrode. The ERP shows a clear P300 response beginning around 350 ms and concludes just after 600 ms. At approximately 650 ms, the Pz ERP displays a statistically significant difference between conditions. Existing literature has shown that neutral images produce the largest amplitudes and latencies as compared to pleasant or angry expressions (Morita et al., 2001). To build upon this study, it would be useful to include pleasant and angry expressions to conduct a direct comparison of amplitudes and latencies. When analyzing the ERPs topographically during a 450-600 ms time range, there are two electrodes in the left frontal region that had statistically significant differences between conditions. This difference suggests the LSD microdose conditions do have an impact on the way neutral facial expressions are processed. A paper by Murray et al., (2021) showed that as the microdose of LSD increases, the ability to correctly identify and respond to negative facial expressions decreases. A future study should also include negative and positive facial expressions to compare ERP responses.

The N170 is a crucial component to consider when attempting to understand the process of encoding emotional facial expressions. The N170 is thought to be enhanced when responding to faces, particularly when recognizing facial structure (Black et al., 2017; Eimer et al., 2011). The current study was correct in hypothesizing there would be a negative deflection approximately 170 ms after stimulus introduction. However, the PO 9 and PO 10 ERPs did not display significant statistical differences between microdose conditions for the N170 but instead,

significant differences were found closer to 200 or 250 ms after stimulus introduction. The N200 has primarily thought to be responsible for recognizing the complexity of stimuli.

The N200, while important for interpreting stimuli related to facial feature identification, does not have a clear function. Some researchers propose that the N200 is related to recognizing stimuli complexity while others suggest it deals more with encoding emotional facial expressions (Balconi & Canavesio, 2016). This study only utilized neutral facial expressions which creates difficultly when discerning which function is more accurate.

The N250 is nicknamed the "affect modulation" component and is thought to display higher amplitudes when viewing negative facial expressions (Caharel et al., 2005; Turetsky et al., 2007). The lack of negative facial expressions explains why the N250 was only seen in some of the figures above but may suggest that the N250 has some minor role in analyzing neutral expressions as well. For example, the N250 component is thought to be present within the frontal regions of the brain and figure 3B depicts red electrodes with statistically significant differences between conditions.

Existing literature has confirmed the importance of the alpha frequency band during resting-state, with alpha band power being the highest when the brain is at rest and refraining from tasks. The current study produced ERSPs which displayed decreases in alpha power for the P300 and N170, consistent with current literature (Hermann & Knight, 2001; Basar et al., 1997; Blau et al., 2007). The study also predicted there would be decreases in theta power as a result of introducing LSD microdoses.

This prediction was partially correct, the ERSPs displayed reductions in power for the theta frequency band for the P300 but did not show significant results for the N170. The remaining frequency bands, delta, beta, and gamma were relatively unchanged and did not

provide any statistically significant results. Existing literature is uncertain about the role these frequency bands play in emotion facial recognition and how LSD impacts their function.

The study did encounter several limitations. The first concern is the small sample size of participants. In small groups, the averaged data is more prone to false positives and can lead to incorrect assumptions about generalizability. Additionally, a small sample size does not take into consideration any potential differences between the sexes. An additional confound is the role of individual differences and sex. Data analyses were unable to attribute any differences in sex and therefore, should be examined in the future. An important consideration when analyzing these data is to acknowledge that all of the participants of the study underwent a thorough screening process to ensure they were healthy across several criterium. The selective process ensures the results of the study are the exclusive results of the drug's effect however, it significantly reduces the amount of generalizability to the rest of the population. To be included in the study, the participants had to have had at least one prior experience with a classical psychedelic drug. This criteria is important for ethical guidelines but suggests the participant may recognize the differences between dose groups. The expected response could skew data especially within a small sample size. Finally, choosing to select only the neutral facial expressions does result in some limitations of data application. The neutral expressions were chosen for analyses because they are thought to reflect the brain's most basic responses to identifying and encoding facial expressions. Subtracting the emotion from the face allows EEGs to show how an individual processes a face rather than the emotional complexities associated with it. To improve upon this study, future studies should include several facial expressions to compare the responses while also examining the impact of an LSD microdose.

Conclusions

The current study contributes to existing literature as it has provided more insight into how classical psychedelics alter the process of encoding neutral facial expressions. In generations previous, few studies had explored the impact of LSD as a result of the strict scheduling set in place by the DEA. In addition to uncertainty with LSD, the concept of a microdose still has quite limited data especially as it relates to human participants. The current study found that implementing microdoses of LSD reduced ERP amplitudes and led to ERSP power reductions. Some literature has suggested that LSD microdoses be implemented as a therapeutic modality because of its ability to alter the way negative facial expressions are encoded (Carhart-Harris & Friston, 2019; Murray et al., 2021). For example, individuals with borderline personality disorder (BPD) often incorrectly identify their emotions as more negative as result of inadequate interpersonal effectiveness skills and a poor subjective sense of their social environment (Linehan, 1993). Prescribing a patient with BPD a microdose of LSD has the potential to allow the individual to reduce their negative evaluations of others and their surroundings without the intentional work associated with therapy. Future studies will be necessary to extend upon the current findings and to work with populations diagnosed with mental health disorders. In addition to adding happy and angry facial expressions, it may also be beneficial to directly compare the effects of a full dose of LSD to a microdose. This will allow researchers to identify significant differences across several areas of evaluation. With future research, LSD microdoses have the potential to offer therapeutic benefits when used with the proper supervision and preparation.

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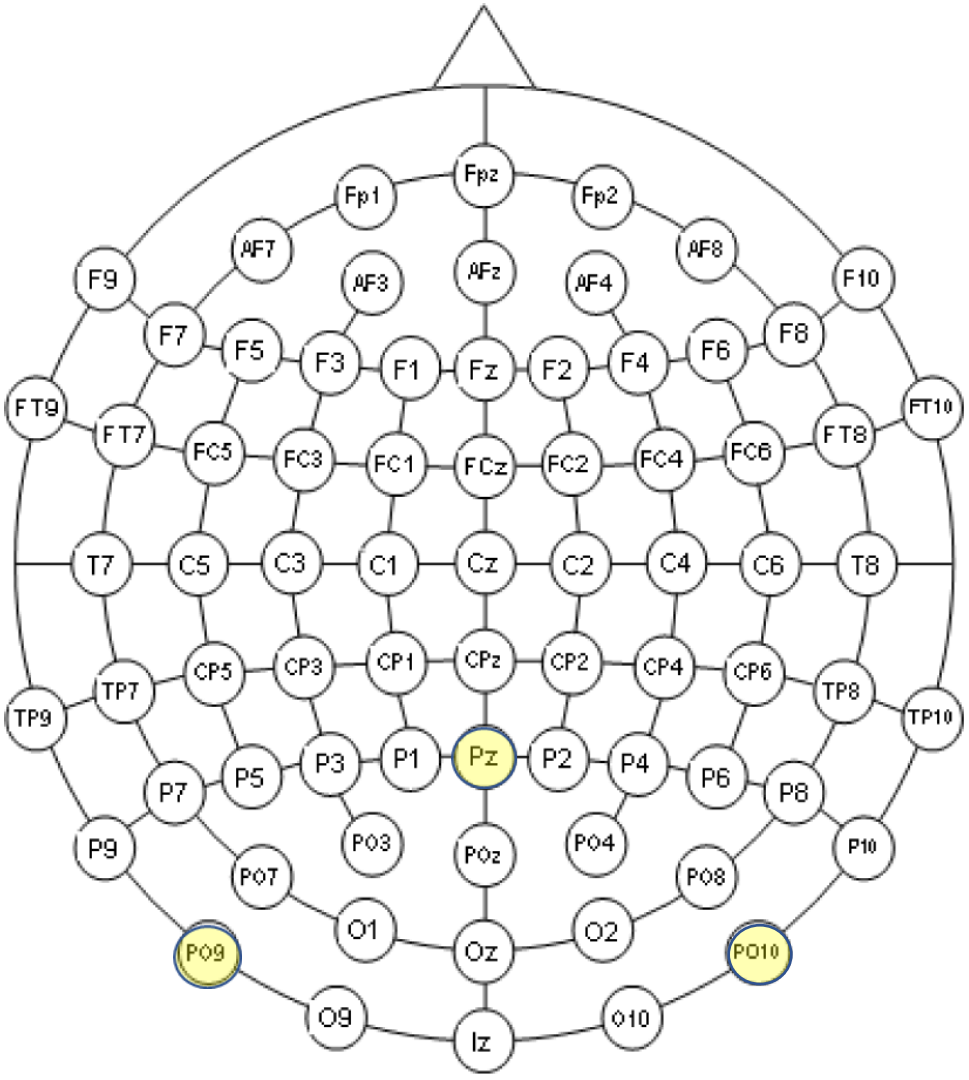
Supplemental Information

Fig. S1

128 Channel Head Cap Layout



*Note***.** Electrode placement on the BioSemi 128 channel-head-cap-layout. Electrodes selected for this study include Pz, PO 9, and PO 10.