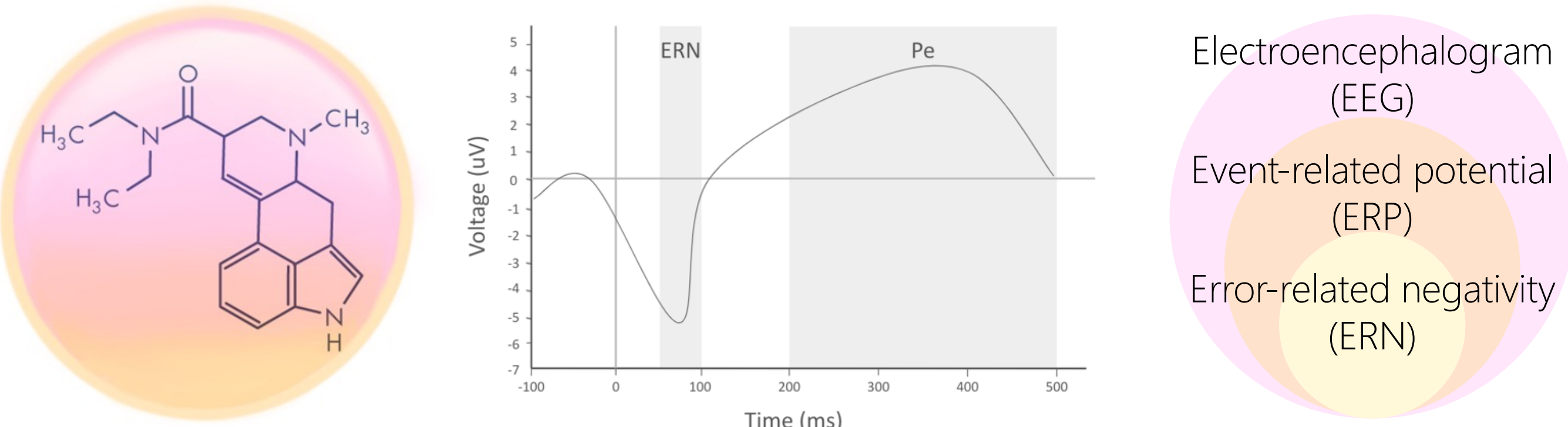


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Introduction

- Lysergic acid diethylamide (LSD)** is a classic psychedelic that has shown therapeutic potential for psychiatric conditions
 - “Microdosing”: about 1/10 of a high dose, reportedly producing both subjective and neural effects¹
- Error-related negativity (ERN)** is an event-related potential (ERP) that corresponds to automatic processing of mistakes — something has gone worse than expected²
- Error-related positivity (Pe)** is an ERP that closely follows the ERN and is associated with conscious error awareness³
 - Enhanced ERN and Pe are associated with OCD, anxiety, PTSD
- Electrophysiological monetary incentive delay (eMID)** task
 - A timed response task involving three Cues with different motivational valence, and two possible Outcomes (win/hit or lose/miss)



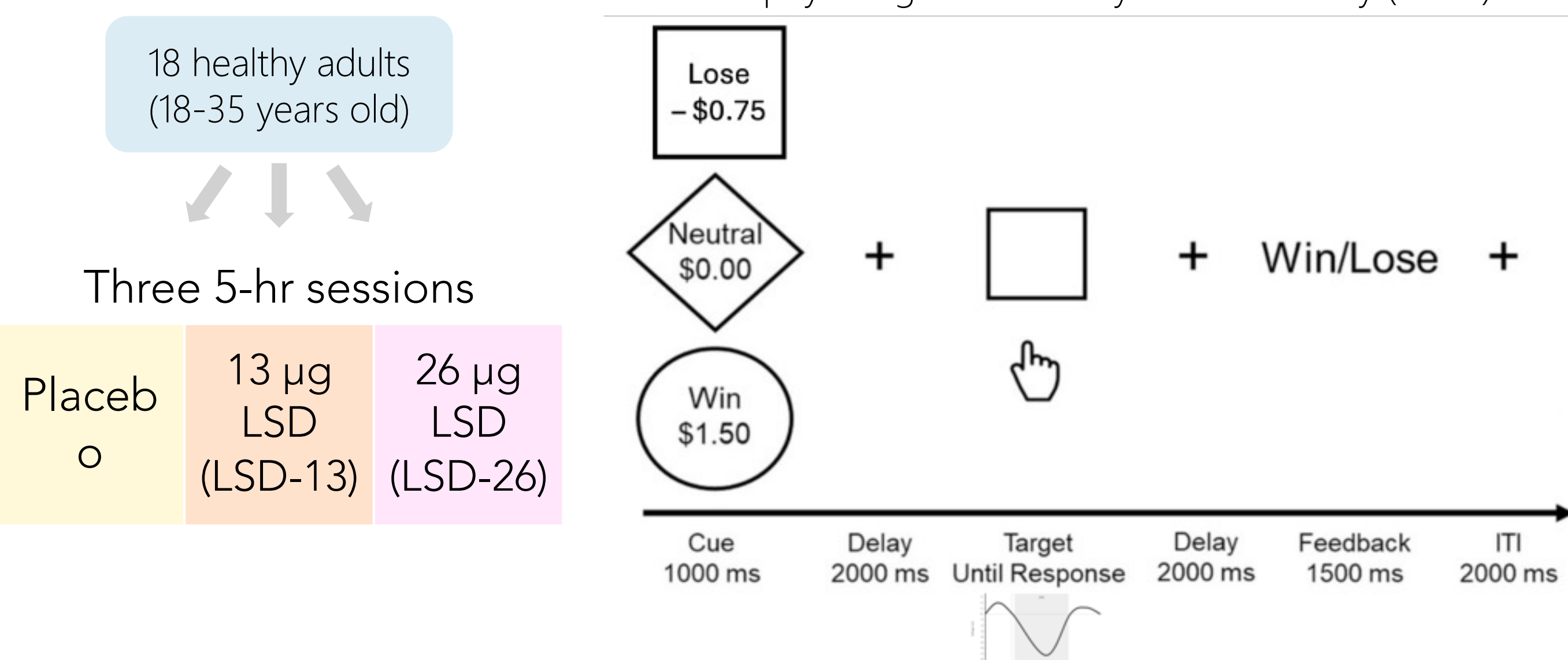
Hypotheses

- Administration of low-dose LSD **decreases** error processing in the brain by attenuating **ERN and Pe amplitude** in a dose-dependent manner
- The greatest LSD-induced reduction in ERN and Pe amplitude will be observed for **punishment and reward cues** and **miss outcomes**

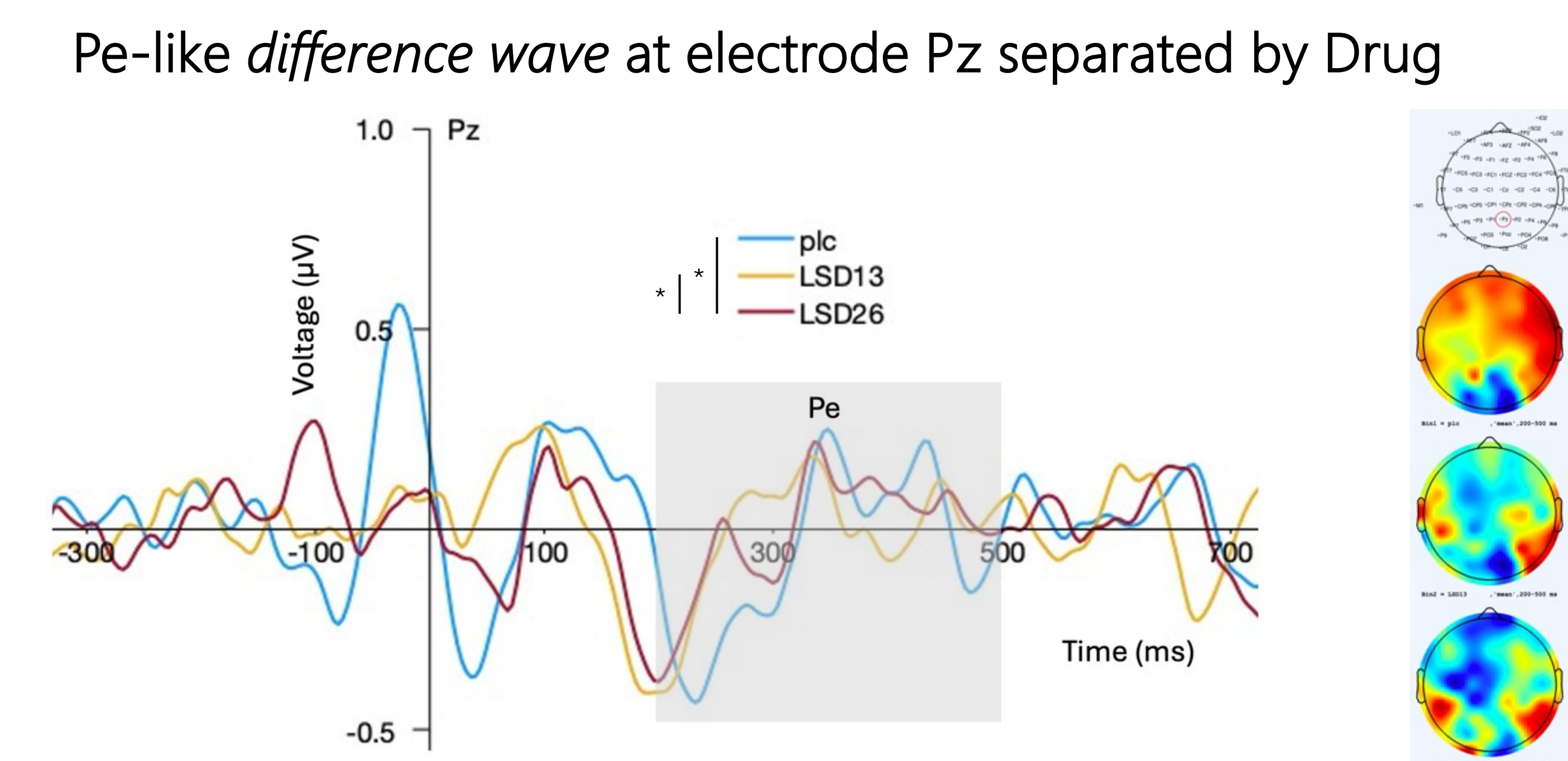
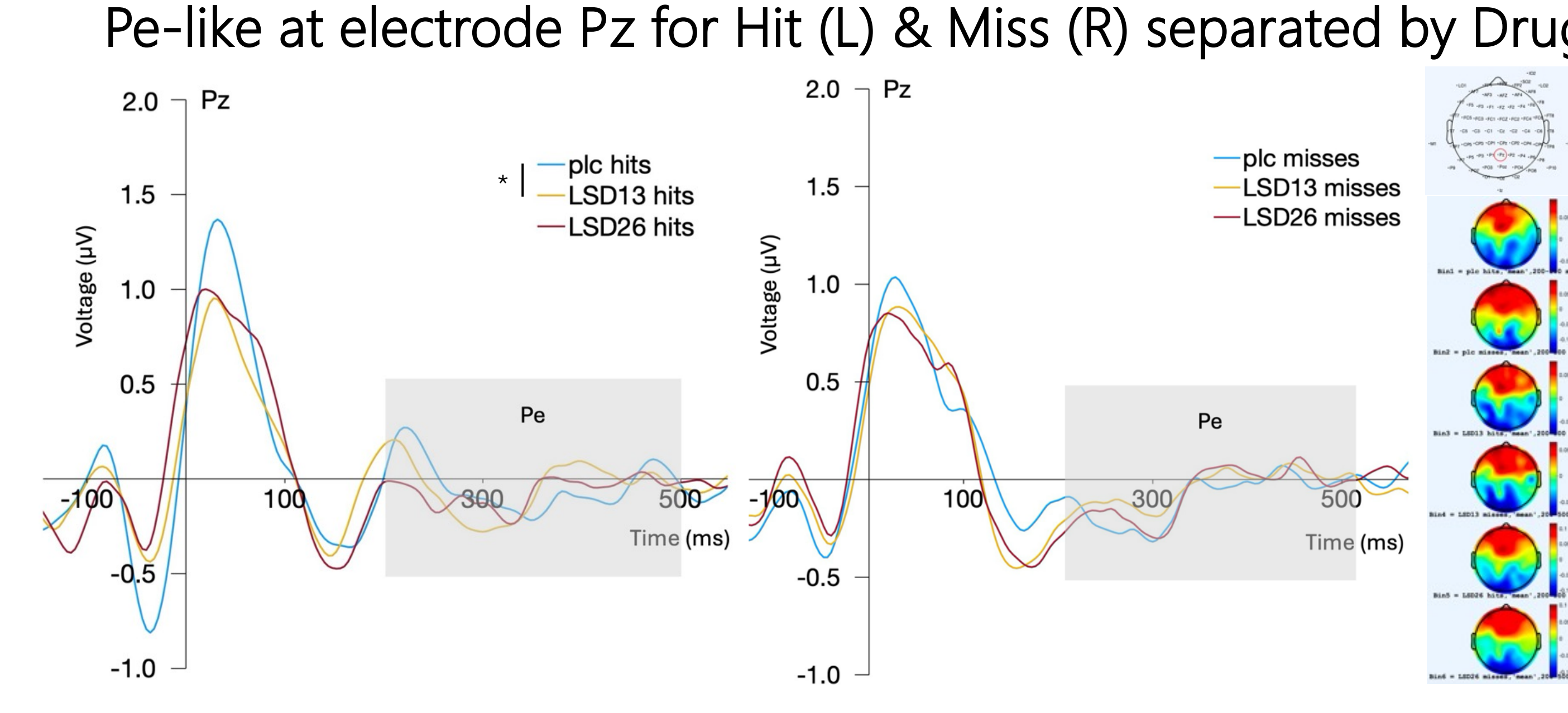
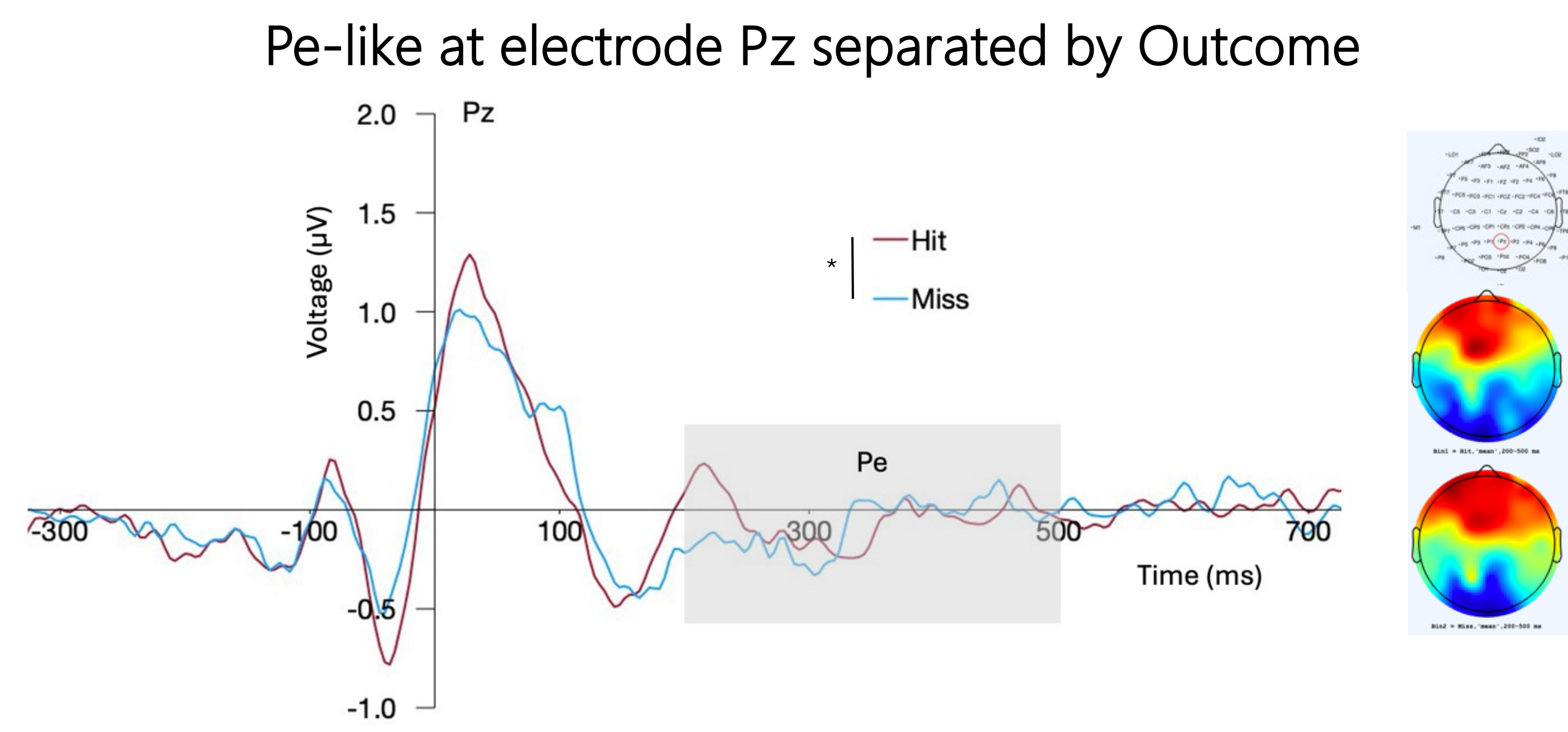
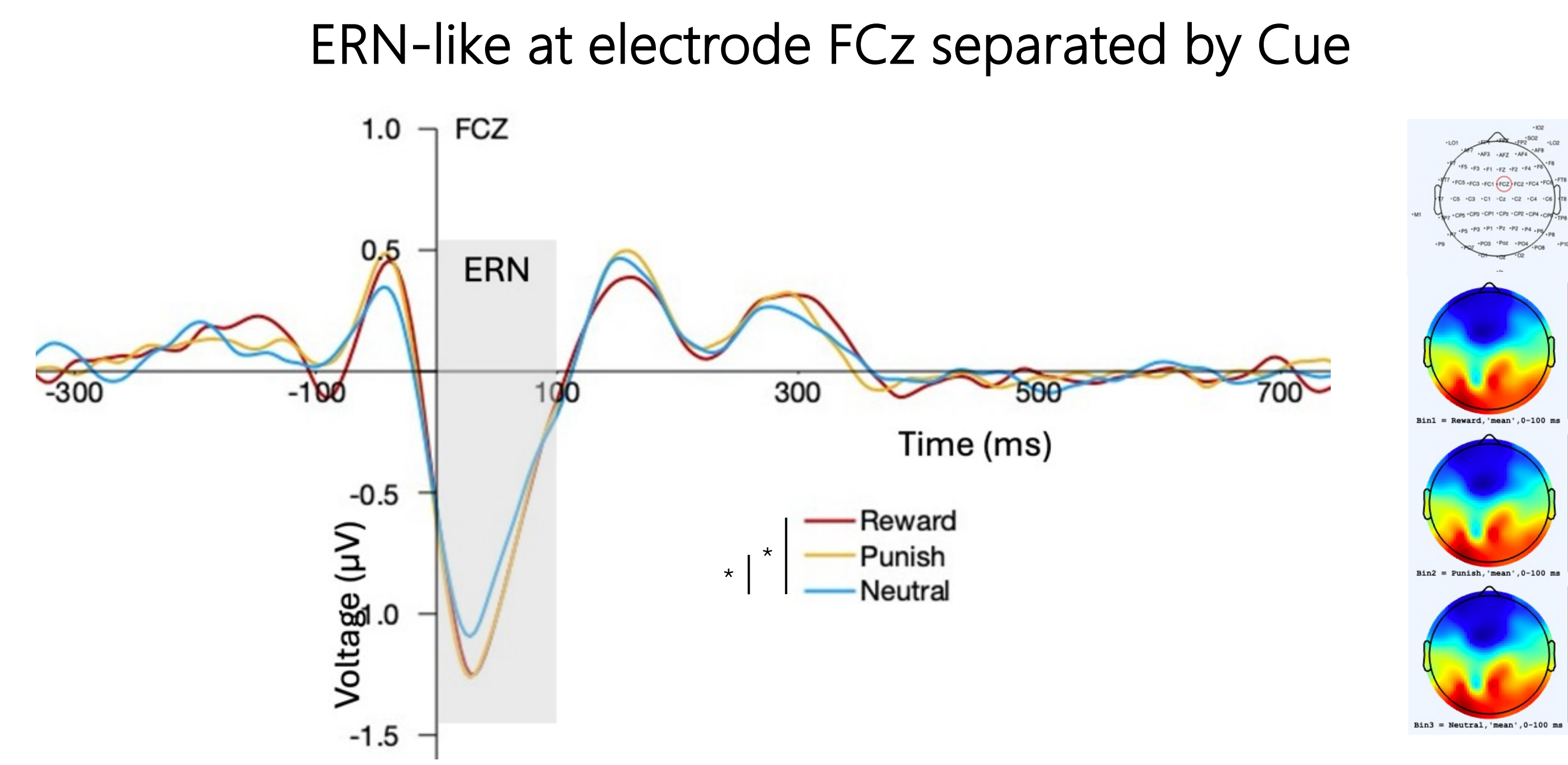
Methods

- Following IRB approval, 18 adult subjects were enrolled in the study
- Each participant took part in three 3-hr **Drug** sessions: randomly received placebo, 13 µg LSD, 26 µg LSD tartrate
- During each session, participants completed a timed response task: the electrophysiological monetary incentive delay (eMID) task
 - Three possible **Cues**: Reward, Punishment, Neutral
 - Two possible **Outcomes**: Hit (Win), Miss (Lose)
 - 180 trials total: 30 for each combination of Cue and Outcome
- EEG recordings obtained during the eMID task
 - Recorded from 120-180 min after drug administration, 128 electrodes
- Three-way repeated measures ANOVA and follow-up t-tests were performed using SPSS to determine the effects of Drug, Cue, and Outcome on ERN amplitude and latency

Electrophysiological monetary incentive delay (eMID) task



Results



Demographics

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/m ²	22.4 ± 2.9 (18-28.2)
Race	
Caucasian	15
African American	1
Asian	2
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

Conclusions

- Drug**
 - First study of a psychedelic drug and error-monitoring ERPs
 - Low doses of LSD have no significant effect on ERN-like ERP
 - Low doses of LSD attenuate Pe-like difference wave amplitude
 - LSD (and thus serotonin agonism) may reduce ability to distinguish between “correct” and “incorrect”
- Cue**
 - ERN-like amplitude for Neutral Cues was significantly smaller than for both Reward and Punishment Cues
 - Supports previous evidence that ERN is increased by more salient stimuli. Suggests ERN-like ERP may serve as correlate for motivational salience
- Outcome**
 - ERN-like amplitudes were similar across Hit and Miss Outcomes
 - eMID lacks a discriminatory aspect and emphasis on reaction time
 - Pe-like amplitudes were greater for Hit (vs. Miss) Outcomes
 - Opposite from expected effect; possibly due to the carefulness required to suppress early responses. Pe is associated with post-error slowing⁴
 - Outcome x Drug interaction: For Hit Outcome, Pe-like amplitudes greater for Placebo than LSD-13 and LSD-26
 - LSD reduces Pe-like for Hit only (vs. Miss); Hit is more like a traditional “error”

Limitations

- eMID task: lacks a discriminatory component
- Small sample size (17 participants)
- Cannot conclude that higher doses of LSD would not modulate the ERN and Pe

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