Psychopharmacology (2022) 239:2829–2840
https://doi.org/10.1007/s00213-022-06164-y

ORIGINAL INVESTIGATION

Δ9-THC reduces reward-related brain activity in healthy adults

Conor H. Murray[1] · James E. Glazer[2] · Royce Lee[1] · Robin Nusslock[2] · Harriet de Wit[1]

Received: 17 January 2022 / Accepted: 12 May 2022 / Published online: 25 May 2022
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2022

Abstract

Rationale Greater availability of cannabis in the USA has raised concerns about adverse effects of the drug, including possible amotivational states. Lack of motivation may be assessed by examining acute effects of cannabinoids on reward processing.

Objectives This study examined single doses of delta-9-tetrahydrocannabinol (Δ9-THC; 7.5, 15 mg oral) in healthy adults using a version of the monetary incentive delay (MID) task adapted for electroencephalography (EEG; e-MID) in a within-subjects, double blind design.

Methods Two phases of reward processing were examined: anticipation, which occurs with presentation of cues that indicate upcoming reward, punishment, or neutral conditions, and outcome, which occurs with feedback indicating hits or misses. During anticipation, we measured two event-related potential (ERP) components: the P300, which measures attention and motivation, and the LPP, which measures affective processing. During outcome processing, we measured P300 and LPP, as well as the RewP, which measures outcome evaluation.

Results We found that Δ9-THC modulated outcome processing, but not reward anticipation. Specifically, both doses of Δ9-THC (7.5 and 15 mg) reduced RewP amplitudes after outcome feedback (hits and misses) relative to placebo. Δ9-THC (15 mg) also reduced P300 and LPP amplitudes following hits compared to misses, relative to both placebo and 7.5 mg Δ9-THC.

Conclusions These findings suggest that Δ9-THC dampens responses to both reward and loss feedback, which may reflect an "amotivational" state. Future studies are needed to determine generalizability of this effect, such as its pharmacological specificity and its specificity to monetary vs other types of reward.

Keywords EEG · Reward · Δ9-THC · Cannabis

Introduction

Fueled by the easing of legal restrictions, cannabis use in the USA is rising. For instance, from 2002 to 2019, the percentage of adults who reported using cannabis in the past year increased from 7.0 to 15.2% (U.S. Department of Health and Human Services 2019). The increase in use raises concerns about possible adverse effects of cannabis use, including the development of amotivational states (Lac and Luk 2018; Petrucci et al. 2020). Amotivation is a psychological condition defined as "a reduction in the motivation to initiate or persist in goal-directed behavior" (Barch and Dowd 2010). This state can be operationalized by assessing behavioral or neural responses to either anticipation or receipt of reward and loss (Lawn et al. 2016; Skumlien et al. 2021). There is some evidence that even single doses of Δ9-tetrahydrocannabinol (Δ9-THC), the principal psychoactive constituent of cannabis, modulate brain responses to receipt of monetary reward (Jansma et al. 2013; van Hell et al. 2012).

In the brain, Δ9-THC is a partial agonist at cannabinoid receptors (CB_1Rs), which regulate synaptic transmission at several sites including dopamine terminals (Piomelli 2003, 2014). CB_1Rs are densely expressed in the mesocorticolimbic dopamine circuit, which is involved in motivation and reward (Bloomfield et al. 2019). Δ9-THC is known to affect activity within this circuit, both through indirectly

✉ Harriet de Wit
hdew@uchicago.edu

[1] Department of Psychiatry and Behavioral Neuroscience, University of Chicago, 5841 S Maryland Ave, MC3077, Chicago, IL 60637, USA

[2] Department of Psychology, Northwestern University, 2029 Sheridan Road, Evanston, IL 60208, USA

facilitating the release of dopamine (Araque et al. 2017; Augustin and Lovinger 2018; Cheer et al. 2007; Wang and Lupica 2014), and through disrupting cortical processes (Cortes-Briones et al. 2015; Kovacs et al. 2012; Radhakrishnan et al. 2015), either of which may dampen the motivational value of rewards (Grabenhorst and Rolls 2011; Grabenhorst et al. 2008; Harvey et al. 2007; Keedwell et al. 2005).

Neural responses to reward are typically assessed using the monetary incentive delay (MID) task (Knutson et al. 2000; Skumlien et al. 2021). The MID can be used to examine brain responses during two temporally distinct stages of reward processing: anticipation of reward and consumption of reward outcomes. One longitudinal study used the MID task with fMRI in chronic cannabis users and found that cannabis users showed blunted responses to anticipation of reward in the nucleus accumbens, as well as other brain regions involved in processing rewards (Martz et al. 2016). Other fMRI studies examined the acute effects of Δ9-THC (8 mg, vaporized) on reward processing (Jansma et al. 2013; van Hell et al. 2012), with mixed results. Specifically, one study found that Δ9-THC attenuated brain responses to feedback (van Hell et al. 2012), while another found no effect of Δ9-THC on feedback responses (Jansma et al. 2013). In contrast to the finding with chronic cannabis users, neither of these studies found an effect of Δ9-THC on brain activity during reward anticipation.

Although fMRI provides critical clues regarding the neural effects of drugs, its relatively low temporal resolution makes it difficult to measure the time course of neural activity, including the brief components of the anticipation and outcome phases of reward processing. In the present study, we leveraged the strong temporal resolution of event-related potential (ERP) methods to assess the acute effects of Δ9-THC in healthy adults on both anticipation of rewards and receipt of rewards, using a version of the MID adapted for EEG (e-MID; Broyd et al. 2012).

The e-MID is a sensitive measure of reward processing assessing the two phases of reward processing: anticipation and outcome (Broyd et al. 2012; Donamayor et al. 2012; Nusslock and Alloy 2017). Cues presented during the anticipation phase evoke the P300 and late-positive potential (LPP) components. The P300 is a robust measure of attention and allocation of attention resources (Gevins and Cutillo 1993; Novak and Foti 2015; Polich 2007), and it has been associated with both the valence and magnitude of upcoming reward (Wu and Zhou 2009). It occurs approximately 300–450 ms post-cue presentation at central-parietal electrode sites (Nieuwenhuis et al. 2011). The LPP component is a positive potential that provides a measure of sustained affective processing (Groen et al. 2008; von Borries et al. 2013). During the outcome processing phase, stimuli that provide feedback about reward outcomes evoke the reward-positive potential (RewP) component, followed by P300 and LPP components (Broyd et al. 2012; Glazer et al. 2018). The RewP peaks approximately 250–350 ms at frontocentral electrode sites after favorable feedback and is reduced or absent after unfavorable feedback, therefore providing a measure of outcome evaluation. The RewP is linked to reward-related activity in the mesocorticolimbic circuit (Becker et al. 2014; Carlson et al. 2011; Foti et al. 2014). It has been studied in monetary gambling tasks (Nieuwenhuis et al. 2011; San Martín 2012) and has been associated with amotivation and anhedonia in psychiatric conditions including depression, schizophrenia, and substance use disorders (Lee et al. 2015; Parvaz et al. 2016; Pegg and Kujawa 2020; Proudfit 2015). During outcome feedback, the RewP is followed by the P300, thought to be associated with motivational salience, and the LPP, associated with the affective processing of outcomes (Glazer et al. 2018). During feedback, hits produce a greater increase in the RewP, P300, and LPP than misses, and both hits and misses on reward and punishment conditions produce greater responses than neutral conditions.

Although several studies have examined effects of cannabinoids on ERPs, to our knowledge these have not specifically examined reward-related processes. Acute intravenous, smoked, and oral doses of cannabis or Δ9-THC are known to reduce P300 responses during attention tasks (Bocker et al. 2010; D'Souza et al. 2012; Hart et al. 2010; Roser et al. 2008), which suggest that the drug may also reduce P300 or other components of reward processing.

We used the e-MID to assess RewP, P300, and LPP components during both the anticipation and outcome phases of reward processing after oral doses of Δ9-THC (7.5 and 15 mg) and placebo in healthy male and female infrequent cannabis users. We examined infrequent users, who reported using cannabis less than 20 times in their lives and not during the last month, to minimize variability in responses related to tolerance and desensitization. We chose the oral route administration of Δ9-THC because its effects last for several hours (Wachtel et al. 2002). We hypothesized that Δ9-THC would reduce reward-related neural activity, as measured by EEG, at either phase. We examined two doses of Δ9-THC and assessed RewP, P300, and LPP to examine the effects of the drug on the two phases of reward processing.

Methods

Study design

This study used a within subject design in which healthy adults received capsules containing Δ9-THC (7.5 or 15 mg) or placebo (Murray et al. 2022). They participated in three

5-h sessions, in which the drug was administered under double-blind and randomized conditions. EEG recordings were obtained 180 min to 240 min after drug administration, near the expected time of peak subjective and behavioral effects of Δ9-THC.

Subjects

Participants were healthy male and female adults (12 male, 12 female; aged 18–40) who had used cannabis 1–20 times in their lifetime but had not used the drug in the last 30 days. Individuals reporting recent use were excluded to minimize confounding factors related to repeated Δ9-THC exposure or CB_1R desensitization (Burston et al. 2010; Wiley et al. 2007). A negative urine test for Δ9-THC was required at each session. Subjects 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, and body mass index of 19 to 26 kg/m^2. Exclusion criteria 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 regular medication aside from birth control.

Orientation session

Prior to experimental sessions, subjects reviewed the protocol, provided informed consent, received presession instructions, and practiced study tasks and questionnaires. They were instructed to abstain from alcohol for 24 h and other recreational drugs for at least 2 days before each session. They were permitted to consume their normal amounts of caffeine and nicotine up to 3 h before sessions. During the orientation session, subjects were instructed also to have a normal night's sleep and fast for 12 h before the sessions. To minimize drug-specific expectancies, subjects were told they might receive a placebo, stimulant, sedative, or cannabinoid drug. Subjects provided informed consent during the orientation prior to beginning the study procedures, which were approved by the University of Chicago Institutional Review Board.

Experimental sessions

Subjects attended three 5-h sessions from 9 am to 2 pm, separated by at least 7 days. A granola bar was provided at arrival as a standardized breakfast. Compliance to drug abstention was verified by urinalysis (CLIAwaived Instant Drug Test Cup, San Diego, CA) and breath alcohol testing (Alcosensor III, Intoximeters, St. Louis, MO). Female subjects provided urine samples for pregnancy tests and were tested at any phase of the menstrual cycle. After compliance tests, Δ9-THC (7.5 or 15 mg) or placebo was administered orally under double-blind conditions. Subjects completed ratings of subjective drug effects (e.g., do you feel a drug effect, do you like the drug effect) at regular intervals during the sessions. EEG recordings were obtained from 180 to 240 min after Δ9-THC effects plateau and remain elevated (Wachtel et al. 2002). After EEG recordings, subjects were provided with rideshare service and were discharged.

Drug

Δ9-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 two doses enable assessment of dose–response effects. The 15 mg and 7.5 mg doses reflect the amount of Δ9-THC in one-half and one-quarter of a cannabis cigarette containing 0.2 g of 15% Δ9-THC, respectively. These oral doses of Δ9-THC produce both subjective and behavioral effects (Broyd et al. 2016; Hartman and Huestis 2013; Pabon and de Wit 2019).

e-MID task

Stimuli were presented using E-Prime software (Psychology Software Tools, Pittsburgh, PA). The task consisted of 150 trials. On each trial (Fig. 1), a fixation cross was displayed for 2000 ms followed by a reward, punishment, or neutral cue for 1000 ms indicating whether participants could win $1.50, avoid losing $0.75, or whether no money could be won or lost. Participants were instructed to maximize positive outcomes in all conditions. After each cue, a fixation cross was displayed for a randomly jittered time interval between 2000 and 2500 ms. Then, a white square was presented and participants were required to rapidly make a button press before the square disappeared in order to win, or avoid losing, money. After each response, another fixation cross was displayed for 2000 ms, followed by feedback stimuli indicating outcomes, presented for 1500 ms. All outcomes were delivered as feedback with the words "Win" or "Lose" indicating whether the button press to the white square was sufficiently rapid or not (i.e., a hit or a miss). Hits during reward conditions resulted in a monetary reward of $1.50 per trial, while misses during punishment conditions resulted in a monetary loss of $0.75 per trial. All other outcomes resulted in no monetary rewards or losses (i.e., $0.00). Each block contained 30 trials with 10 instances of each cue stimulus presented randomly without replacement. There were 5 blocks for a total of 150 trials. Unknown to participants, the duration that the white square appeared on the screen dynamically updated throughout the e-MID task

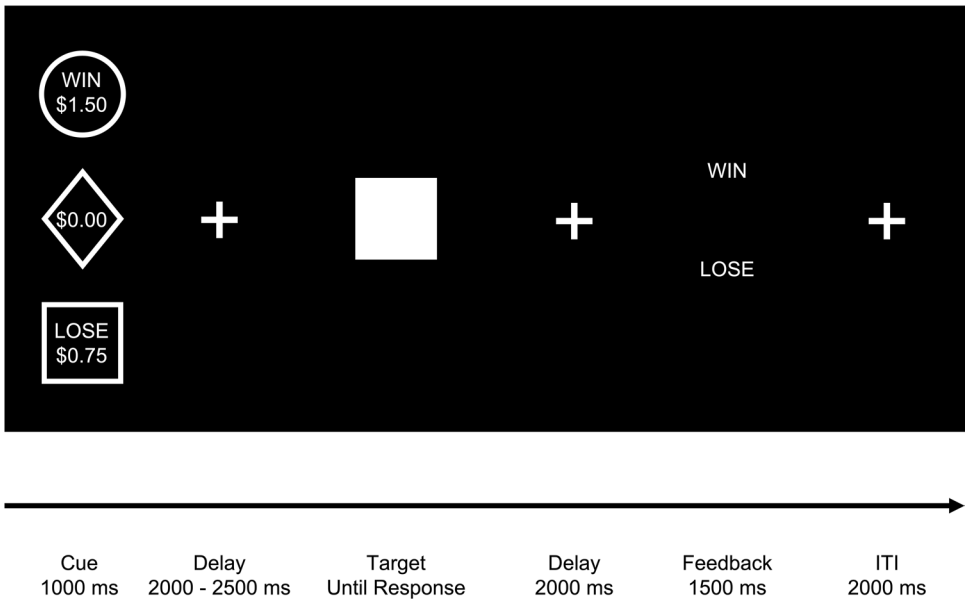

Fig. 1 Trial progression of the e-MID task. Reward, punishment, or neutral cues were presented in the form of circles encasing "Win $1.50," squares encasing "Lose $0.75," or diamonds encasing "$0.00." Responses to filled circles were made as quickly as possible after a fixation cross was displayed for a randomly jittered time interval between 2000 and 2500 ms. Following another 2000 ms delay, feedback was provided to indicate hits "WIN" or misses "LOSE." ITI, intertrial interval

to maintain a task difficulty such that participants successfully hit the target on approximately 50% of the trials, calculated separately for each trial type (Novak and Foti 2015). Supplementary Table 1 shows that the adaptive algorithm indeed resulted in 50% accuracy across the task conditions. Consistent with similar studies, the duration of the white square decreased by 20 ms after hits and increased by 20 ms after misses (Knutson et al. 2000).

Data acquisition

EEG recordings were collected using a 128 sintered Ag/AgCl active electrodes (ActiveTwo™ system, BioSemi B.V., Amsterdam) placed according to equiradial layout on the head cap. Additional electrodes were placed at reference locations of the mastoids, 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 were acquired continuously, amplified, and digitized using Biosemi ActiveView software. Digitization of electrode placement reflecting actual head shape was conducted using a Patriot™ 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 the software (5–10 min total). EEG recordings occurred in a sound attenuated room, with the subject sitting comfortably. EEG and 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.

EEG preprocessing

All offline processing was performed using EEGLAB (Delorme and Makeig 2004) and ERPLAB (Lopez-Calderon and Luck 2014) in MatLab (The Math Works, Inc.). Raw EEG data were resampled at 250 Hz, re-referenced to the average of the left and right mastoid, and 64 channels were retained consistent with the 10–20 system (Jasper 1958). Next, line noise was subtracted using a sliding window to adaptively estimate sine wave amplitude (Mullen et al. 2012). Two files were then created using a high pass filter for each participant: one with a 0.01 Hz cutoff and another with a 1.0 Hz cutoff used only for independent component analysis (ICA). Next, noisy channels were identified and removed from both files using visual inspection and large scalp artifacts were removed from the 1.0 Hz ICA file using automated artifact rejection that removed continuous data segments if any scalp electrode exceeded a voltage threshold of 500 µV. Artifacts were detected in a 500 ms time window that slides across the full continuous data every 250 ms. Next, ICA was performed on the 1.0 Hz filtered file and the resulting ICA weights were applied to the 0.01 Hz filtered file. ICA components corresponding to ocular and muscular artifacts were then removed from the 0.01 Hz filtered file via visual inspection. This file was then low-pass filtered with a 30 Hz cutoff and segmented into epochs from -200 to 1000 ms time-locked to each cue and feedback stimulus onset. Epochs were then baseline corrected using the 200 ms pre-stimulus interval and automated artifact rejection was performed to identify and remove epochs with large data artifacts. Specifically, epochs were removed if any channel exceeded a 100 µV threshold in a 200 ms time window that slides across the

entire epoch in steps of 100 ms. An average of 27.69 trials per feedback-condition (SD: 3.24) were retained for analysis after artifact rejection. Finally, single-trial epochs were averaged together separately for each condition resulting in three averaged cue epochs (i.e., reward, punishment, and neutral) and six averaged feedback epochs (i.e., win and lose following each cue).

Following prior research recommending at least 20 averaged trials to accurately measure the RewP (Marco-Pallares et al. 2011), all participants had an average of greater than 20 trials per-feedback condition after artifact rejection and were all therefore retained for analyses. The RewP component was assessed between 250 and 350 ms after outcome feedback and is not associated with reward anticipation after cue presentation. Specifically, the RewP was calculated by the average amplitude in a ± 50 ms time window where the difference between positive and negative feedback conditions is maximal (Novak and Foti 2015). This difference was largest around ~ 300 ms in our data. The RewP was assessed under the Cz electrode, which was selected for analysis based on where the RewP is maximally positive (Glazer et al. 2018). The P300 component was assessed between 350 and 450 ms after outcome feedback or cue presentation under the POz electrode. The LPP component was assessed between 450 and 800 ms after outcome feedback or cue presentation under the POz electrode. The P300 and LPP components were calculated by the average amplitudes in these time windows. The POz electrode was selected based on where these components are maximally positive (Glazer et al. 2018).

Statistical analysis

For our analysis of reward anticipation after cue presentation, separate 3 (dose: placebo, 7.5 mg Δ9-THC, and 15 mg Δ9-THC) × 3 (condition: reward, punishment, and neutral cues) way repeated measures ANOVAs were conducted for P300 and LPP components. For our analysis of outcome processing after feedback, separate 3 (dose: placebo, 7.5 mg Δ9-THC, and 15 mg Δ9-THC) × 3 (condition: reward, punishment, and neutral cues) × 2 (outcome: hits or misses) way repeated measures ANOVAs were conducted for RewP, P300, and LPP components. Difference waves (hits minus misses across the reward, punishment, and neutral conditions) were calculated for each dose only during follow-up *t*-tests to explore significant dose × outcome interactions. We corrected for multiple comparisons using Fisher's protected *t*-tests, which requires a significant omnibus ANOVA *F* test to proceed to pairwise follow-up comparisons (Cohen et al. 2002).

Results

Demographic characteristics

The mean age of participants was 25 (Table 1). Participants reported an average of 5 months since their last cannabis use and 12 total lifetime uses. Participants reported drinking alcohol about once a week, and most reported no lifetime use of stimulants, opiates, classical psychedelics, or MDMA.

Timing of EEG

Inspection of subjective ratings of drug effects showed that the EEG measures were collected near to the peak and during the plateau of drug effects (Fig. 2).

P300 and LPP in response to cues during reward anticipation

The anticipatory cues produced their expected effects on P300 and LPP, but the drug did not affect either of these. Cue-P300 analyses (Supplementary Fig. 1A) revealed a significant main effect of cue condition ($F_{2,46} = 25.397$, $p < 0.001$, $\eta_p^2 = 0.525$) while no effects of dose emerged. Follow-up *t*-tests revealed increased Cue-P300 amplitudes for reward and punishment cues compared to neutral cues

Table 1 Demographics and drug use characteristics

Category	*n* or mean ± SD (range)
Subjects (male/female)	24 (12/12)
Age, years	25 ± 6.7 (18–34)
Body mass index, kg/m^2	23.0 ± 2.5 (19.5–26.6)
Weight, lbs	151.8 ± 23.2 (101–185)
Race	
Caucasian	13
African American	1
Asian	1
Other/ > 1 race	9
Current drug use	
Cannabis, months since last use	5.3 ± 7.5 (1–24)
Alcohol, drinks/week (*n* = 16)	3.1 ± 3.3 (0–12)
Alcohol, drinking days/week	1.4 ± 1.6 (0–6)
Tobacco, times/week (*n* = 3)	0.3 ± 1.0 (0–5)
Caffeine, servings/day (*n* = 22)	1.0 ± 0.9 (0–2)
Total lifetime drug use, nonmedical	
Cannabis (*n* = 24)	12.2 ± 6.7 (1–20)
Classical psychedelic (*n* = 8)	0.8 ± 1.6 (0–6)
MDMA (*n* = 1)	0.2 ± 0.6 (0–2)
Stimulant (*n* = 4)	0.4 ± 1.1 (0–5)
Opiate (*n* = 0)	0

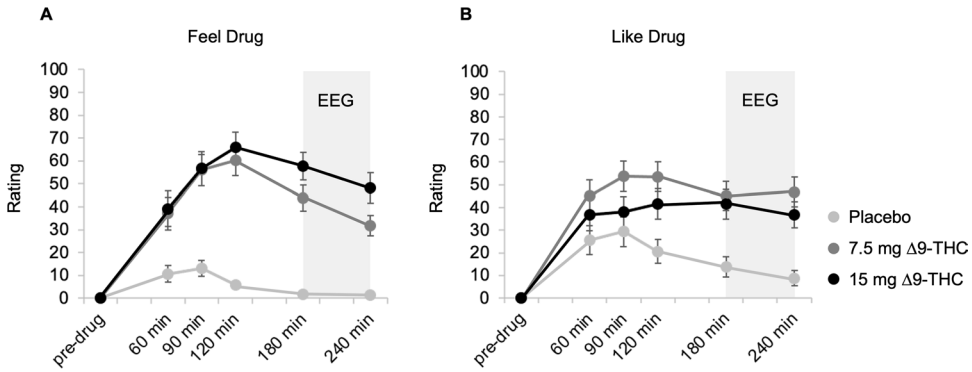

Fig. 2 Time course of subjective drug effects. Ratings indicate magnitude of feeling a drug effect (**A**) and liking a drug effect (**B**); gray shaded region indicates period of EEG assessments

($t_{23} = 5.905$, $p < 0.001$ and $t_{23} = 7.059$, $p < 0.001$). Cue-P300 amplitudes for reward and punishment cues did not significantly differ ($p = 0.355$). Cue-LPP analyses (Supplementary Fig. 1B) revealed a significant main effect of condition ($F_{2,46} = 9.552$, $p < 0.001$, $\eta_p^2 = 0.293$) while no effects of dose emerged. Follow-up *t*-tests revealed increased Cue-LPP amplitudes for reward cues compared to punishment ($t_{23} = 2.606$, $p = 0.016$) and neutral cues ($t_{23} = 3.994$, $p = 0.001$). Cue-LPP amplitudes for punishment and neutral cues did not significantly differ ($p = 0.069$). Individual conditions for each of the nine responses during reward anticipation are also shown (Supplementary Fig. 1C).

RewP in response to feedback on monetary outcomes

During outcomes, feedback stimuli produced their expected effects on the RewP and both doses of Δ9-THC reduced RewP amplitudes, whether hits or misses. RewP analyses (Fig. 3) revealed a significant main effect of dose ($F_{2,46} = 6.463$, $p = 0.003$, $\eta_p^2 = 0.219$), main effect of outcome ($F_{1,23} = 15.855$, $p = 0.001$, $\eta_p^2 = 0.408$), and main effect of cue condition also emerged ($F_{1,23} = 16.830$, $p < 0.001$, $\eta_p^2 = 0.423$). None of the interactions reached statistical significance. Follow-up *t*-tests on the main effect of dose showed that RewP amplitudes were reduced for both 7.5 ($t_{23} = -2.988$, $p = 0.007$) and 15 mg Δ9-THC ($t_{23} = -3.211$, $p = 0.004$) relative to placebo, while the two Δ9-THC doses did not significantly differ ($p = 0.879$). Follow-up *t*-tests on the main effect of outcome showed increased RewP amplitudes for hits compared to misses ($t_{23} = 3.982$, $p = 0.001$), while follow-up tests on the main effect of cue condition showed increased RewP amplitudes for reward and punishment feedback over neutral feedback ($t_{23} = 4.692$, $p < 0.001$ and $t_{23} = 4.170$, $p < 0.001$) while reward and punishment feedback did not significantly differ ($p = 0.120$). No other significant effects were observed. Thus, both doses of Δ9-THC reduced the evaluation of monetary outcomes, whether hits or misses. Traces for RewP responses separated across doses, cue conditions, and outcomes are provided in supplemental (Supplementary Fig. 2).

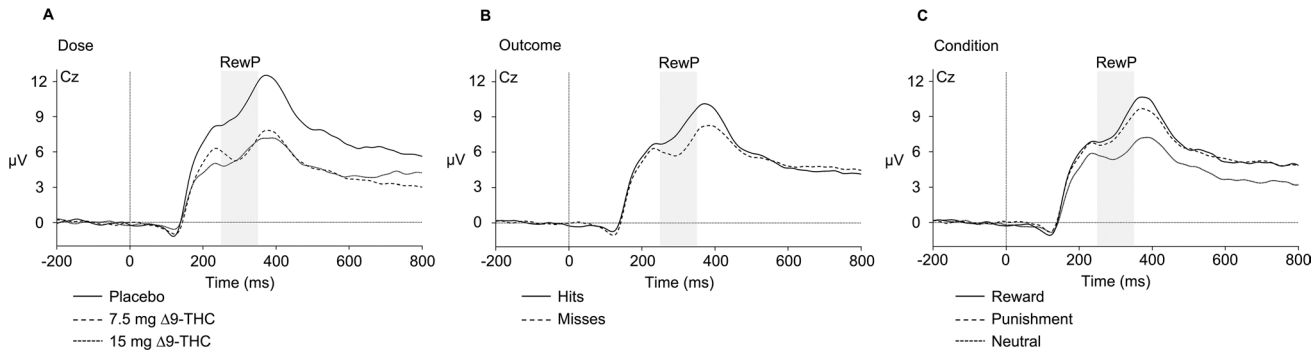

Fig. 3 RewP components in response to feedback (outcomes) in the e-MID task. **A** RewP amplitudes as a function of dose (placebo, 7.5, 15 mg Δ9-THC; oral) (repeated-measures ANOVA, $p < 0.01$, $n = 24$). **B** RewP amplitudes as a function of positive (hits) or negative (misses) feedback (repeated-measures ANOVA, $p < 0.01$, $n = 24$). **C** RewP amplitudes as a function of cue condition presented at the start of each trial (reward, punishment, neutral) (repeated-measures ANOVA, $p < 0.001$, $n = 24$). Shaded region indicates window of analysis (250–350 ms post-stimulus)

P300 in response to feedback on monetary outcomes

During outcomes, feedback stimuli produced their expected effects on the P300, and 15 mg Δ9-THC reduced P300 amplitudes of hits compared to misses, relative to the 7.5 mg and placebo doses. P300 analyses (Fig. 4) revealed a significant dose × outcome interaction on the P300 ($F_{2,46} = 6.459$, $p = 0.004$, $\eta_p^2 = 0.219$). To examine this interaction, hits minus misses difference waves were calculated separately for placebo, 7.5, and 15 mg Δ9-THC. Follow-up *t*-tests revealed that 15 mg Δ9-THC significantly reduced the P300 difference wave relative to both placebo and 7.5 mg Δ9-THC ($t_{23} = 3.291$, $p = 0.003$ and $t_{23} = 2.172$, $p = 0.040$), while placebo and 7.5 mg Δ9-THC did not significantly differ ($p = 0.133$). P300 analyses did not reveal a main effect of dose; however, main effects of outcome ($F_{1,23} = 26.934$, $p < 0.001$, $\eta_p^2 = 0.539$) and cue condition were found ($F_{1,23} = 10.156$, $p = 0.001$, $\eta_p^2 = 0.306$). Follow-up *t*-tests on outcome revealed increased P300 amplitudes for hits compared to misses ($t_{23} = 5.190$, $p = 0.001$). On cue condition, follow-up tests showed increased P300 amplitudes for reward and punishment feedback compared to neutral feedback ($t_{23} = 4.041$, $p = 0.001$ and $t_{23} = 3.010$, $p = 0.006$). Reward and punishment feedback did not significantly differ ($p = 0.295$). Here, 15 mg Δ9-THC reduced the motivational salience of hits compared to misses, relative to the 7.5 mg and placebo doses. Traces for P300 responses separated across doses, cue conditions, and outcomes are provided in supplemental (Supplementary Fig. 3).

LPP in response to feedback on monetary outcomes

During outcomes, feedback stimuli produced their expected effects on the LPP and 15 mg Δ9-THC reduced LPP amplitudes of hits compared to misses, relative to the 7.5 mg and placebo doses. LPP analyses (Fig. 4) revealed that a significant dose × outcome interaction ($F_{2,46} = 6.559$, $p = 0.008$, $\eta_p^2 = 0.222$) also emerged. Once again, to examine the interaction, hits minus misses difference waves were calculated separately for placebo, 7.5, and 15 mg Δ9-THC. Follow-up *t*-tests revealed 15 mg Δ9-THC significantly reduced the

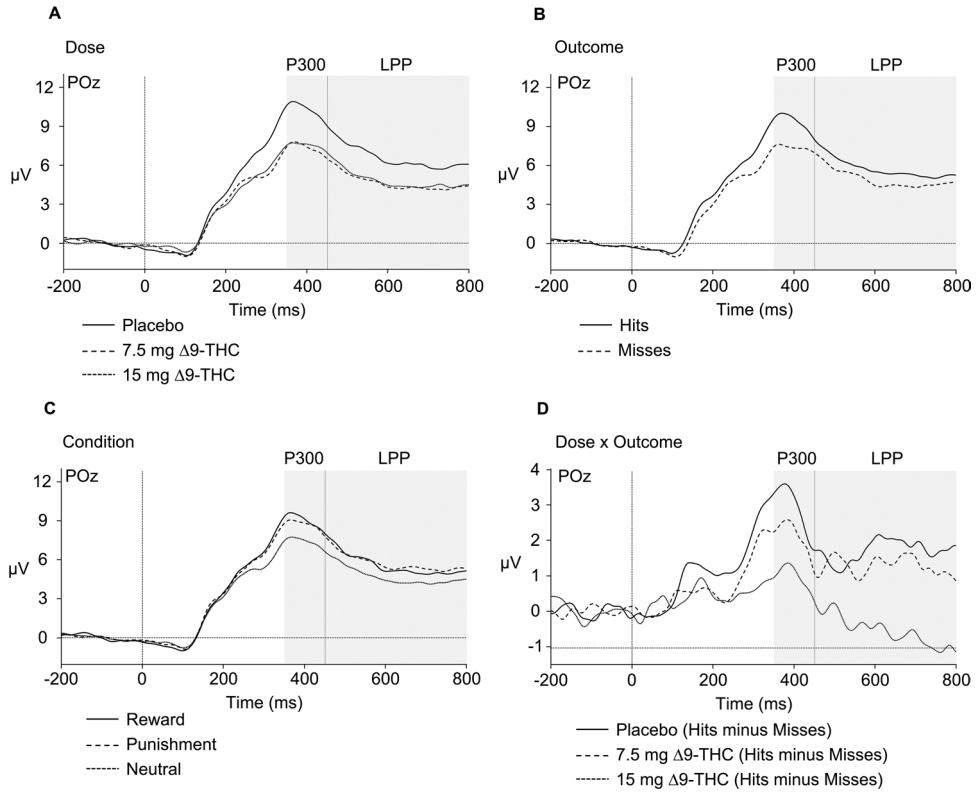

Fig. 4 P300 and LPP components in response to feedback (outcomes) in the e-MID task. **A** P300 and LPP amplitudes as a function of dose (placebo, 7.5, 15 mg Δ9-THC; oral) (n.s., $n = 24$). **B** P300 and LPP amplitudes as a function of positive (hits) or negative (misses) feedback (repeated-measures ANOVA, P300, $p < 0.001$; LPP n.s., $n = 24$). **C** P300 and LPP amplitudes as a function of cue condition presented at the start of each trial (reward, punishment, neutral) (repeated-measures ANOVA; P300, $p < 0.01$; LPP, $p < 0.05$, $n = 24$). **D** Hits minus misses difference waves for each dose (placebo, 7.5, 15 mg Δ9-THC; oral) (*t*-tests, P300, 15 mg $p < 0.01$ vs placebo, 7.5 mg $p < 0.05$ vs placebo; LPP, 15 mg $p < 0.01$ vs placebo, 7.5 mg $p < 0.05$ vs placebo, $n = 24$). Shaded regions indicate windows of analyses (350–450 ms post-stimulus, P300; 450–800 ms post-stimulus, LPP)

LPP difference wave relative to both placebo and 7.5 mg Δ9-THC ($t_{23}=3.892$, $p=0.001$ and $t_{23}=2.194$, $p=0.039$), while placebo and 7.5 mg Δ9-THC did not significantly differ ($p=0.430$). LPP analyses did not reveal a main effect of dose and resulted in a marginal main effect of outcome ($p=0.053$). However, we found a main effect of cue condition ($F_{1,23}=15.855$, $p=0.001$, $\eta_p^2=0.408$). Follow-up *t*-tests on the main effect of cue condition revealed increased LPP amplitude for reward and punishment feedback compared to neutral feedback ($t_{23}=2.179$, $p=0.040$ and $t_{23}=2.585$, $p=0.017$), while reward and punishment feedback did not significantly differ ($p=0.712$). Here, 15 mg Δ9-THC reduced the affective impact of hits compared to misses, relative to the 7.5 mg and placebo doses. Traces for LPP responses separated across doses, cue conditions, and outcomes are provided in supplemental (Supplementary Fig. 3).

Task performance

We assessed both reaction time and accuracy of hits and misses (Supplementary Fig. 4). Δ9-THC, cue condition, and outcomes produced their anticipated effects on reaction times, with a significant dose × condition × outcome interaction ($F_{1,23}=8.539$, $p=0.008$, $\eta_p^2=0.271$), and significant main effects of dose ($F_{1,23}=10.200$, $p=0.004$, $\eta_p^2=0.307$), condition ($F_{1,23}=17.925$, $p<0.001$, $\eta_p^2=0.438$), and outcome ($F_{1,23}=117.352$, $p<0.001$, $\eta_p^2=0.836$). Δ9-THC dose-dependently slowed reaction times. Reaction times were also slower after punishment and neutral cue conditions relative to reward, and after misses relative to hits. Thus, fastest reaction times were found during hits with rewarding conditions after placebo. We confirmed that subjects responded on the e-MID with ~ 50% accuracy, which is consistent with the algorithm used by the e-MID task (Supplementary Table 1).

Discussion

Our goal was to examine whether moderate (7.5 mg) or higher (15 mg) doses of oral Δ9-THC affect the neurophysiological processing of monetary rewards and losses using the e-MID, during either anticipation of rewards or receipt of rewards. We examined three ERP components of reward processing: the RewP, P300, and LPP in response to stimuli that signaled either anticipation or receipt of reward. The drug did not significantly affect P300 and LPP amplitudes during anticipation of monetary outcomes. However, P300 and LPP amplitudes were reduced during feedback on hits compared to misses after the 15 mg dose relative to placebo, and both doses of Δ9-THC reduced RewP amplitudes to feedback on hits and misses relative to placebo. This pattern of findings suggests that Δ9-THC reduced reward-related brain activity, characterized by a decrease in the evaluation of monetary outcomes and a reduction in the motivational salience and the affective impact of rewarding hits compared to misses.

Our main finding was that Δ9-THC reduced components of reward processing during outcomes of reward and loss. Specifically, Δ9-THC reduced the evaluation (RewP) of outcomes, whether hits or misses, while blunting the motivational salience (P300) and affective impact (LPP) of hits compared to misses. Our findings corroborate and extend prior work investigating the role of Δ9-THC on reward processing. The findings are consistent with one study using fMRI-MID, in which Δ9-THC (8 mg, vaporized) reduced neural responses during the receipt of monetary rewards but did not affect reward anticipation (van Hell et al. 2012). These authors found that Δ9-THC blunted activation of the right superior frontal gyrus in response to reward outcomes (van Hell et al. 2012). The right superior frontal gyrus is rich in CB_1R expression (Choi et al. 2012; Long et al. 2012) and has been associated with reward evaluation and allocation of attentional resources (Wallis and Kennerley 2010). Our findings are also consistent with two reports that Δ9-THC reduced the likelihood of high-effort choices in the Effort Expenditure for Rewards task (Lawn et al. 2016). One study used 8 mg vaporized Δ9-THC and the other used 7.5 and 15 mg oral Δ9-THC. Using other indices of "reward," one study showed that Δ9-THC (8 mg vaporized) dampened responses to music, as indicated by reduced fMRI signals in brain regions sensitive to emotion and reward (Freeman et al. 2018). The present findings may also be compared to reports of reduced dopamine function in the striatum in cannabis users, relative to non-users (Bloomfield et al. 2014). In the Bloomfield study, the reductions in dopamine function were correlated with subjective apathy, perhaps an after-effect of repeated exposure to cannabis.

The advantage of ERP studies is the high temporal resolution that can decompose the precise time course of reward processing. Our results revealed that Δ9-THC reduced ERP amplitudes across three temporally distinct components of reward consumption that reflect separate psychological processes and covary with unique neuroanatomical correlates (Glazer et al. 2018): the drug reduced the evaluation (RewP), motivational salience (P300), and affective impact (LPP) of outcome feedback. First, Δ9-THC decreased RewP amplitudes for both reward and loss outcomes during feedback evaluation. Reduced RewP amplitudes during feedback evaluation have been linked to attenuated reinforcement learning signals in the basal ganglia and anterior cingulate cortex (Foti et al. 2011; Ruchsow et al. 2002), such as prediction error encoding (Glazer and Nusslock 2021), suggesting that Δ9-THC may disrupt these learning signals from both rewards and losses. Second, Δ9-THC also blunted P300 and LPP amplitudes for reward compared to loss feedback

during the motivational salience and affective impact stages. Reduced P300 amplitudes have been linked to decreased motivated attention and working memory updating in the hippocampus (Paller and Kutas 1992), and reduced LPP amplitudes have been linked to decreased emotional processing in the amygdala (Bradley et al. 2003). P300 elicited by feedback in our task may reflect additional processes, including valence (Glazer et al. 2018). Future work will need to manipulate feedback information to further tease apart these processes. Our results suggest that Δ9-THC may reduce the encoding of rewards compared to losses in working memory and subsequently blunt the associated emotional impact. These results are consistent with the idea that Δ9-THC may induce "amotivational" states through its effects on neural systems during reward feedback processing.

What cellular and synaptic mechanisms may be involved in Δ9-THC's blunted response to monetary rewards? CB_1Rs are abundant and widespread in the brain to regulate and inhibit the release of several neurotransmitters (Piomelli 2003, 2014). The endocannabinoid system is involved in both the anticipatory "wanting" and consummatory "liking" phases of reward processing (Solinas et al. 2008), which are thought to be mediated primarily by dopamine and opioid signaling, respectively (Treadway and Zald 2011). Although CB_1Rs are not expressed on dopaminergic axon terminals, they are densely expressed in midbrain nuclei that house dopaminergic cell bodies (Bloomfield et al. 2019). Within these nuclei, CB_1Rs are predominately expressed on GABAergic inhibitory interneurons surrounding dopamine cells (Tsou et al. 1998). When activated by endogenous ligands or Δ9-THC, these CB_1Rs reduce GABA release, which disinhibits dopamine cell activity and facilitates dopaminergic signaling throughout the mesostriatal and mesocorticolimbic pathways of the brain to enhance "wanting" behaviors (Araque et al. 2017; Augustin and Lovinger 2018; Cheer et al. 2007; Wang and Lupica 2014). Endocannabinoids have also been shown to drive endogenous opioid-dependent "liking" in the striatum. These dual roles of cannabinoid signaling in both "wanting" and "liking" might suggest that Δ9-THC would increase EEG responses to both reward anticipation, or outcome, just as amphetamine does (Cavanagh et al. 2022). However, both the current EEG study and a prior fMRI study (van Hell et al. 2012) found that Δ9-THC blunted responses specifically in the consummatory, outcome phase. It is possible that Δ9-THC interferes with the cognitive demands of outcome processing, including evaluation and the recruitment of working memory, which are not required by anticipatory processing (Grabenhorst and Rolls 2011; Grabenhorst et al. 2008). This is consistent with widely reported cognitive impairments induced Δ9-THC, which are mediated by the disruption of coordinated firing patterns of cortical neurons, and are associated with reduced ERP amplitudes during cognitive tasks (Cortes-Briones et al. 2015; Kovacs et al. 2012; Radhakrishnan et al. 2015). Future research is needed to test this prediction.

Our study includes both strengths and limitations. Strengths included the sample size of 24, inclusion of both men and women, and the within-subject, double blind design with two doses of Δ9-THC and a placebo. The study used a validated reward task and a sensitive measure of neural response, which yielded the expected patterns of response (Broyd et al. 2012). Limitations of the study include the use of Δ9-THC rather than cannabis plant, limiting conclusions that can be drawn about real-world use of cannabis. However, Δ9-THC is widely recognized to be the primary active component of cannabis, and the doses can be readily controlled. Further, it is not known whether the effects of Δ9-THC reported here are generalizable to more heterogeneous subject samples, such as those with some psychiatric symptomatology, or older or younger than those tested here, or to higher doses of the drug.

Together, our findings indicate that Δ9-THC reduces the evaluation of outcomes and blunts the motivational salience and affective impact of reward, without affecting the anticipatory response. These data inform the effects of acute Δ9-THC on reward processing and amotivational states. Many questions remain. For example, what is the pharmacological specificity of the Δ9-THC effects, and would similar effects be observed with drugs that produce similar, sedative-like effects? To what extent are the effects of Δ9-THC similar to the effects of whole-plant cannabis, perhaps due to "entourage" effects? Are the effects reported here similar in more heterogeneous samples, including those with psychiatric symptoms? Future pharmaco-EEG studies will reveal how repeated cannabis use affects measures of reward processing obtained with the MID and other reward tasks, in a wide spectrum of individuals.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00213-022-06164-y.

Funding This research was supported by the National Institutes of Health (DA02812). CHM was supported by the National Institutes of Health (T32DA043469). The authors declare no biomedical financial interests or potential conflicts of interest related to this project. HdW is or has been scientific advisor to PharmAla Biotech, Awakn Life Sciences, Gilgamesh Pharmaceuticals, and Schedule I Therapeutics for projects unrelated to this study, and has received research support from the Beckley Foundation for an unrelated project.

References

Araque A, Castillo PE, Manzoni OJ, Tonini R (2017) Synaptic functions of endocannabinoid signaling in health and disease. Neuropharmacology 124:13–24. https://doi.org/10.1016/j.neuropharm.2017.06.017

Augustin SM, Lovinger DM (2018) Functional relevance of endocannabinoid-dependent synaptic plasticity in the central nervous system. ACS Chem Neurosci 9(9):2146–2161. https://doi.org/10.1021/acschemneuro.7b00508

Barch DM, Dowd EC (2010) Goal representations and motivational drive in schizophrenia: the role of prefrontal-striatal interactions. Schizophr Bull 36(5):919–934. https://doi.org/10.1093/schbul/sbq068

Becker MP, Nitsch AM, Miltner WH, Straube T (2014) A single-trial estimation of the feedback-related negativity and its relation to BOLD responses in a time-estimation task. J Neurosci 34(8):3005–3012

Bloomfield MA, Morgan CJ, Kapur S, Curran HV, Howes OD (2014) The link between dopamine function and apathy in cannabis users: an [18F]-DOPA PET imaging study. Psychopharmacology 231(11):2251–2259. https://doi.org/10.1007/s00213-014-3523-4

Bloomfield MAP, Hindocha C, Green SF, Wall MB, Lees R, Petrilli K, Costello H, Ogunbiyi MO, Bossong MG, Freeman TP (2019) The neuropsychopharmacology of cannabis: a review of human imaging studies. Pharmacol Ther 195:132–161. https://doi.org/10.1016/j.pharmthera.2018.10.006

Bocker KBE, Gerritsen J, Hunault CC, Kruidenier M, Mensinga TT, Kenemans JL (2010) Cannabis with high delta(9)-THC contents affects perception and visual selective attention acutely: an event-related potential study. Pharmacol Biochem Behav 96(1):67–74. https://doi.org/10.1016/j.pbb.2010.04.008

Bradley MM, Sabatinelli D, Lang PJ, Fitzsimmons JR, King W, Desai P (2003) Activation of the visual cortex in motivated attention. Behav Neurosci 117(2):369–380. https://doi.org/10.1037/0735-7044.117.2.369

Broyd SJ, Richards HJ, Helps SK, Chronaki G, Bamford S, Sonuga-Barke EJ (2012) An electrophysiological monetary incentive delay (e-MID) task: a way to decompose the different components of neural response to positive and negative monetary reinforcement. J Neurosci Methods 209(1):40–49. https://doi.org/10.1016/j.jneumeth.2012.05.015

Broyd SJ, van Hell HH, Beale C, Yucel M, Solowij N (2016) Acute and chronic effects of cannabinoids on human cognition-a systematic review. Biol Psychiatry 79(7):557–567. https://doi.org/10.1016/j.biopsych.2015.12.002

Burston JJ, Wiley JL, Craig AA, Selley DE, Sim-Selley LJ (2010) Regional enhancement of cannabinoid CB_1 receptor desensitization in female adolescent rats following repeated delta-tetrahydrocannabinol exposure. Br J Pharmacol 161(1):103–112. https://doi.org/10.1111/j.1476-5381.2010.00870.x

Carlson JM, Foti D, Mujica-Parodi LR, Harmon-Jones E, Hajcak G (2011) Ventral striatal and medial prefrontal BOLD activation is correlated with reward-related electrocortical activity: a combined ERP and fMRI study. Neuroimage 57(4):1608–1616

Cavanagh JF, Olguin SL, Talledo JA, Kotz JE, Roberts BZ, Nungaray JA, Sprock J, Gregg D, Bhakta SG, Light GA, Swerdlow NR, Young JW, Brigman JL (2022) Amphetamine alters an EEG marker of reward processing in humans and mice. Psychopharmacology 239(3):923–933. https://doi.org/10.1007/s00213-022-06082-z

Cheer JF, Wassum KM, Sombers LA, Heien ML, Ariansen JL, Aragona BJ, Phillips PE, Wightman RM (2007) Phasic dopamine release evoked by abused substances requires cannabinoid receptor activation. J Neurosci 27(4):791–795. https://doi.org/10.1523/JNEUROSCI.4152-06.2007

Choi K, Le T, McGuire J, Xing G, Zhang L, Li H, Parker CC, Johnson LR, Ursano RJ (2012) Expression pattern of the cannabinoid receptor genes in the frontal cortex of mood disorder patients and mice selectively bred for high and low fear. J Psychiatr Res 46(7):882–889. https://doi.org/10.1016/j.jpsychires.2012.03.021

Cohen J, Cohen P, West SG, Aiken LS (2002) Applied multiple regression/correlation analysis for the behavioral sciences, 3rd edn. Routledge. https://doi.org/10.4324/9780203774441

Cortes-Briones J, Skosnik PD, Mathalon D, Cahill J, Pittman B, Williams A, Sewell RA, Ranganathan M, Roach B, Ford J, D'Souza DC (2015) Delta(9)-THC disrupts gamma (gamma)-band neural oscillations in humans. Neuropsychopharmacology 40(9):2124–2134. https://doi.org/10.1038/npp.2015.53

D'Souza DC, Fridberg DJ, Skosnik PD, Williams A, Roach B, Singh N, Carbuto M, Elander J, Schnakenberg A, Pittman B, Sewell RA, Ranganathan M, Mathalon D (2012) Dose-related modulation of event-related potentials to novel and target stimuli by intravenous delta(9)-THC in humans. Neuropsychopharmacology 37(7):1632–1646. https://doi.org/10.1038/npp.2012.8

Delorme A, Makeig S (2004) EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 134(1):9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009

Donamayor N, Schoenfeld MA, Munte TF (2012) Magneto- and electroencephalographic manifestations of reward anticipation and delivery. Neuroimage 62(1):17–29. https://doi.org/10.1016/j.neuroimage.2012.04.038

Foti D, Carlson JM, Sauder CL, Proudfit GH (2014) Reward dysfunction in major depression: multimodal neuroimaging evidence for refining the melancholic phenotype. Neuroimage 101:50–58

Foti D, Weinberg A, Dien J, Hajcak G (2011) Event-related potential activity in the basal ganglia differentiates rewards from nonrewards: response to commentary. Hum Brain Mapp 32(12):2267–2269. https://doi.org/10.1002/hbm.21357

Freeman TP, Pope RA, Wall MB, Bisby JA, Luijten M, Hindocha C, Mokrysz C, Lawn W, Moss A, Bloomfield MAP, Morgan CJA, Nutt DJ, Curran HV (2018) Cannabis dampens the effects of music in brain regions sensitive to reward and emotion. Int J Neuropsychopharmacol 21(1):21–32. https://doi.org/10.1093/ijnp/pyx082

Gevins A, Cutillo B (1993) Spatiotemporal dynamics of component processes in human working-memory. Electroencephalogr Clin Neurophysiol 87(3):128–143. https://doi.org/10.1016/0013-4694(93)90119-G

Glazer J, Nusslock R (2021) Outcome valence and stimulus frequency affect neural responses to rewards and punishments. Psychophysiology e13981. https://doi.org/10.1111/psyp.13981

Glazer JE, Kelley NJ, Pornpattananangkul N, Mittal VA, Nusslock R (2018) Beyond the FRN: broadening the time-course of EEG and ERP components implicated in reward processing. Int J Psychophysiol 132(Pt B):184–202. https://doi.org/10.1016/j.ijpsycho.2018.02.002

Grabenhorst F, Rolls ET (2011) Value, pleasure and choice in the ventral prefrontal cortex. Trends Cogn Sci 15(2):56–67. https://doi.org/10.1016/j.tics.2010.12.004

Grabenhorst F, Rolls ET, Bilderbeck A (2008) How cognition modulates affective responses to taste and flavor: top-down influences on the orbitofrontal and pregenual cingulate cortices. Cereb Cortex 18(7):1549–1559. https://doi.org/10.1093/cercor/bhm185

Groen Y, Wijers AA, Mulder LJ, Waggeveld B, Minderaa RB, Althaus M (2008) Error and feedback processing in children with ADHD and children with autistic spectrum disorder: an EEG event-related potential study. Clin Neurophysiol 119(11):2476–2493. https://doi.org/10.1016/j.clinph.2008.08.004

Hart CL, Ilan AB, Gevins A, Gunderson EW, Role K, Colley J, Foltin RW (2010) Neurophysiological and cognitive effects of smoked marijuana in frequent users. Pharmacol Biochem Behav 96(3):333–341. https://doi.org/10.1016/j.pbb.2010.06.003

Hartman RL, Huestis MA (2013) Cannabis effects on driving skills. Clin Chem 59(3):478–492. https://doi.org/10.1373/clinchem.2012.194381

Harvey PO, Pruessner J, Czechowska Y, Lepage M (2007) Individual differences in trait anhedonia: a structural and functional magnetic resonance imaging study in non-clinical subjects. Mol Psychiatry 12(8):767–775. https://doi.org/10.1038/sj.mp.4002021

Jansma JM, van Hell HH, Vanderschuren LJ, Bossong MG, Jager G, Kahn RS, Ramsey NF (2013) THC reduces the anticipatory nucleus accumbens response to reward in subjects with a nicotine addiction. Transl Psychiatry 3:e234. https://doi.org/10.1038/tp.2013.6

Jasper H (1958) Report of the committee on methods of clinical examination in electroencephalography. Electroencephalogr Clin Neurophysiol 10:370–375

Keedwell PA, Andrew C, Williams SC, Brammer MJ, Phillips ML (2005) The neural correlates of anhedonia in major depressive disorder. Biol Psychiatry 58(11):843–853. https://doi.org/10.1016/j.biopsych.2005.05.019

Knutson B, Westdorp A, Kaiser E, Hommer D (2000) FMRI visualization of brain activity during a monetary incentive delay task. Neuroimage 12(1):20–27. https://doi.org/10.1006/nimg.2000.0593

Kovacs FE, Knop T, Urbanski MJ, Freiman I, Freiman TM, Feuerstein TJ, Zentner J, Szabo B (2012) Exogenous and endogenous cannabinoids suppress inhibitory neurotransmission in the human neocortex. Neuropsychopharmacology 37(5):1104–1114. https://doi.org/10.1038/npp.2011.262

Lac A, Luk JW (2018) Testing the amotivational syndrome: marijuana use longitudinally predicts lower self-efficacy even after controlling for demographics, personality, and alcohol and cigarette use. Prev Sci 19(2):117–126. https://doi.org/10.1007/s11121-017-0811-3

Lawn W, Freeman TP, Pope RA, Joye A, Harvey L, Hindocha C, Mokrysz C, Moss A, Wall MB, Bloomfield MA, Das RK, Morgan CJ, Nutt DJ, Curran HV (2016) Acute and chronic effects of cannabinoids on effort-related decision-making and reward learning: an evaluation of the cannabis 'amotivational' hypotheses. Psychopharmacology 233(19–20):3537–3552. https://doi.org/10.1007/s00213-016-4383-x

Lee JS, Jung S, Park IH, Kim JJ (2015) Neural basis of anhedonia and amotivation in patients with schizophrenia: the role of reward system. Curr Neuropharmacol 13(6):750–759. https://doi.org/10.2174/1570159x13666150612230333

Long LE, Lind J, Webster M, Weickert CS (2012) Developmental trajectory of the endocannabinoid system in human dorsolateral prefrontal cortex. BMC Neurosci 13:87. https://doi.org/10.1186/1471-2202-13-87

Lopez-Calderon J, Luck SJ (2014) ERPLAB: an open-source toolbox for the analysis of event-related potentials. Front Hum Neurosci 8:213. https://doi.org/10.3389/fnhum.2014.00213

Marco-Pallares J, Cucurell D, Münte TF, Strien N, Rodriguez-Fornells A (2011) On the number of trials needed for a stable feedback-related negativity. Psychophysiology 48(6):852–860

Martz ME, Trucco EM, Cope LM, Hardee JE, Jester JM, Zucker RA, Heitzeg MM (2016) Association of marijuana use with blunted nucleus accumbens response to reward anticipation. JAMA Psychiat 73(8):838–844. https://doi.org/10.1001/jamapsychiatry.2016.1161

Mullen T, Worrell G, Makeig S (2012) Multivariate principal oscillation pattern analysis of ICA sources during seizure. Annu Int Conf IEEE Eng Med Biol Soc 2012:2921–2924. https://doi.org/10.1109/embc.2012.6346575

Murray CH, Huang Z, Lee R, de Wit H (2022) Adolescents are more sensitive than adults to acute behavioral and cognitive effects of THC. Neuropsychopharmacology. https://doi.org/10.1038/s41386-022-01281-w

Nieuwenhuis S, De Geus EJ, Aston-Jones G (2011) The anatomical and functional relationship between the P3 and autonomic components of the orienting response. Psychophysiology 48(2):162–175. https://doi.org/10.1111/j.1469-8986.2010.01057.x

Novak KD, Foti D (2015) Teasing apart the anticipatory and consummatory processing of monetary incentives: an event-related potential study of reward dynamics. Psychophysiology 52(11):1470–1482. https://doi.org/10.1111/psyp.12504

Nusslock R, Alloy LB (2017) Reward processing and mood-related symptoms: an RDoC and translational neuroscience perspective. J Affect Disord 216:3–16. https://doi.org/10.1016/j.jad.2017.02.001

Pabon E, de Wit H (2019) Developing a phone-based measure of impairment after acute oral (9)-tetrahydrocannabinol. J Psychopharmacol 33(9):1160–1169. https://doi.org/10.1177/0269881119862533

Paller KA, Kutas M (1992) Brain potentials during memory retrieval provide neurophysiological support for the distinction between conscious recollection and priming. J Cogn Neurosci 4(4):375–392. https://doi.org/10.1162/jocn.1992.4.4.375

Parvaz MA, Gabbay V, Malaker P, Goldstein RZ (2016) Objective and specific tracking of anhedonia via event-related potentials in individuals with cocaine use disorders. Drug Alcohol Depend 164:158–165

Pegg S, Kujawa A (2020) The effects of a brief motivation manipulation on reward responsiveness: a multi-method study with implications for depression. Int J Psychophysiol 150:100–107

Petrucci AS, LaFrance EM, Cuttler C (2020) A comprehensive examination of the links between cannabis use and motivation. Subst Use Misuse 55(7):1155–1164. https://doi.org/10.1080/10826084.2020.1729203

Piomelli D (2003) The molecular logic of endocannabinoid signalling. Nat Rev Neurosci 4(11):873–884. https://doi.org/10.1038/nrn1247

Piomelli D (2014) More surprises lying ahead. The endocannabinoids keep us guessing. Neuropharmacology 76 Pt B:228–234. https://doi.org/10.1016/j.neuropharm.2013.07.026

Polich J (2007) Updating P300: an integrative theory of P3a and P3b. Clin Neurophysiol 118(10):2128–2148. https://doi.org/10.1016/j.clinph.2007.04.019

Proudfit GH (2015) The reward positivity: from basic research on reward to a biomarker for depression. Psychophysiology 52(4):449–459

Radhakrishnan R, Skosnik PD, Cortes-Briones J, Sewell RA, Carbuto M, Schnakenberg A, Cahill J, Bois F, Gunduz-Bruce H, Pittman B, Ranganathan M, D'Souza DC (2015) GABA deficits enhance the psychotomimetic effects of delta9-THC. Neuropsychopharmacology 40(8):2047–2056. https://doi.org/10.1038/npp.2015.58

Roser P, Juckel G, Rentzsch J, Nadulski T, Gallinat J, Stadelmann AM (2008) Effects of acute oral delta9-tetrahydrocannabinol and standardized cannabis extract on the auditory P300 event-related potential in healthy volunteers. Eur Neuropsychopharmacol 18(8):569–577. https://doi.org/10.1016/j.euroneuro.2008.04.008

Ruchsow M, Grothe J, Spitzer M, Kiefer M (2002) Human anterior cingulate cortex is activated by negative feedback: evidence from event-related potentials in a guessing task. Neurosci Lett 325(3):203–206. https://doi.org/10.1016/s0304-3940(02)00288-4

San Martín R (2012) Event-related potential studies of outcome processing and feedback-guided learning [review]. Front Human Neurosci 6(304). https://doi.org/10.3389/fnhum.2012.00304

Skumlien M, Langley C, Lawn W, Voon V, Curran HV, Roiser JP, Sahakian BJ (2021) The acute and non-acute effects of cannabis on reward processing: a systematic review. Neurosci Biobehav Rev 130:512–528. https://doi.org/10.1016/j.neubiorev.2021.09.008

Solinas M, Goldberg SR, Piomelli D (2008) The endocannabinoid system in brain reward processes. Br J Pharmacol 154(2):369–383. https://doi.org/10.1038/bjp.2008.130

Treadway MT, Zald DH (2011) Reconsidering anhedonia in depression: lessons from translational neuroscience. Neurosci Biobehav Rev 35(3):537–555. https://doi.org/10.1016/j.neubiorev.2010.06.006

Tsou K, Brown S, Sanudo-Pena M, Mackie K, Walker J (1998) Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system. Neuroscience 83(2):393–411

U.S. Department of Health and Human Services (2019) S. A. a. M. H. S. A., Center for Behavioral Health Statistics and Quality. National survey on drug use and health 2019. https://datafiles.samhsa.gov/

van Hell HH, Jager G, Bossong MG, Brouwer A, Jansma JM, Zuurman L, van Gerven J, Kahn RS, Ramsey NF (2012) Involvement of the endocannabinoid system in reward processing in the human brain. Psychopharmacology 219(4):981–990. https://doi.org/10.1007/s00213-011-2428-8

von Borries AKL, Verkes RJ, Bulten BH, Cools R, de Bruijn ERA (2013) Feedback-related negativity codes outcome valence, but not outcome expectancy, during reversal learning. Cogn Affect Behav Neurosci 13(4):737–746. https://doi.org/10.3758/s13415-013-0150-1

Wachtel SR, ElSohly MA, Ross SA, Ambre J, de Wit H (2002) Comparison of the subjective effects of delta(9)-tetrahydrocannabinol and marijuana in humans. Psychopharmacology 161(4):331–339. https://doi.org/10.1007/s00213-002-1033-2

Wallis JD, Kennerley SW (2010) Heterogeneous reward signals in prefrontal cortex. Curr Opin Neurobiol 20(2):191–198. https://doi.org/10.1016/j.conb.2010.02.009

Wang H, Lupica CR (2014) Release of endogenous cannabinoids from ventral tegmental area dopamine neurons and the modulation of synaptic processes. Prog Neuropsychopharmacol Biol Psychiatry 52:24–27. https://doi.org/10.1016/j.pnpbp.2014.01.019

Wiley JL, O'Connell MM, Tokarz ME, Wright MJ Jr (2007) Pharmacological effects of acute and repeated administration of delta(9)-tetrahydrocannabinol in adolescent and adult rats. J Pharmacol Exp Ther 320(3):1097–1105. https://doi.org/10.1124/jpet.106.108126

Wu Y, Zhou X (2009) The P300 and reward valence, magnitude, and expectancy in outcome evaluation. Brain Res 1286:114–122. https://doi.org/10.1016/j.brainres.2009.06.032

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.