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Cannabis users demonstrate enhanced neural reactivity to reward: An event-related potential and time-frequency EEG study

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ABSTRACT

Introduction: Disruptions in neural measures of reward responsiveness are implicated in risk for and the development of Substance Use Disorders (SUDs) in general, but it is not clear if this is also true for Cannabis Use Disorder (CUD). To date, no studies have examined neural reward responsiveness in cannabis users using EEG.
Methods: Cannabis users (CU; n = 67) and non-users (n = 60) were drawn from larger studies of individuals with and without internalizing and externalizing psychopathology. Groups were matched on current and lifetime psychopathology. Participants completed a validated monetary reward task during electroencephalogram (EEG). One-way between subject analysis of covariance (ANCOVA) models examined group differences in four EEG indicators of reward responsiveness - the reward positivity (RewP) and feedback negativity (FN) event-related potentials and two time–frequency measures (reward-related delta and loss-related theta).
Results: CU demonstrated an enhanced RewP to the attainment of monetary reward compared to non-users (p = .004), even after controlling for relevant covariates. Secondary analyses found that occasional CU, but not current CUD or remitted CUD, showed enhanced RewP compared to non-users. There were no significant differences in FN, reward-related delta, or loss-related theta time–frequency measures between groups.
Conclusions: To our knowledge, this is the first study to show preliminary evidence that CU have an enhanced RewP to reward and the extent of disruption may be related to CUD status. Our findings suggest that greater neural reward responsiveness may only be seen among occasional CU, not necessarily among CU with current or remitted CUD.

1. Introduction

The increasing availability of cannabis in the U.S. is a serious concern due to the negative health and mental health outcomes associated with cannabis use (Brook, Lee, Brown, & Finch, 2012; Crane, Schuster, Fusar-Poli, & Gonzalez, 2013; Degenhardt, Hall, & Lynskey, 2003; Fergusson & Boden, 2008; Meier et al., 2012). Disruptions in neural measures of reward responsiveness are implicated in risk for and the development of Substance Use Disorders (SUDs) in general, but it is not clear if this is also true for Cannabis Use Disorder (CUD). It is crucial that we better understand how neural measures of reward responsiveness may be disrupted among cannabis users (CU) to inform prevention and intervention efforts.

SUDs, including CUD, are considered to be diseases of the brain's reward system (Volkow et al., 2010). Many individuals use substances like cannabis to experience the positive, rewarding effects of the drug. Similar to other drugs, cannabis modulates brain reward circuitry and related neurotransmitter systems (Bloomfield, Ashok, Volkow, & Howes, 2016; Weinstein, Livny, & Weizman, 2017), increasing feelings of reward or euphoria. Individuals with disrupted reward responsiveness (i.e., hyper- or hypo-active neural responses to reward) may be more likely to use substances like cannabis, as these individuals may be more sensitive to reward from the substance and/or may minimize punishment or losses associated with the substance. Several studies have shown that adolescents at risk for SUD show hyperactive brain reward circuitry to rewards (Bjork, Chen, Smith, & Hommer, 2010; Ivanov et al.,

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2012; Stice & Yokum, 2014; Stice, Yokum, & Burger, 2013), suggesting that hyperactivation of brain reward circuitry to drug and non-drug rewards pre-date substance use and may be a risk factor for SUDs. Indeed, despite some evidence that individuals at risk for SUD demonstrate hypoactive brain reward circuitry to reward (Blum et al., 2000), a growing number of longitudinal studies indicate that hyperactivation to rewards is a risk factor for Alcohol Use Disorder (AUD) and SUD in general (see Heitzeg, Cope, Martz, & Hardee, 2015). As substance use progresses and SUD develops, neuroadaptations occur in brain reward circuitry, "hijacking" brain reward circuitry (Volkow, Koob, & McLellan, 2016). During the transition to SUD, brain reward circuitry becomes hypoactive, or less sensitive, to rewards (Volkow et al., 2016). Although some evidence suggests that structural abnormalities in reward circuitry in SUD seem to normalize after prolonged abstinence (Gould, Duke, & Nader, 2014; Volkow et al., 2015), it is not known if hypoactive reward responsiveness in SUD remains in remitted SUD, after prolonged abstinence. Taken together, individuals at risk for SUD appear to exhibit hyperactive reward responsiveness, but this transitions to hypoactive reward responsiveness as substance use progresses and SUD develops. It is important to note that most of this literature has studied individuals at risk for or who meet criteria for AUD and SUDs other than CUD. Therefore, it is unclear whether these findings are also seen among CU at risk for CUD and those with CUD.

Several fMRI studies suggest that reward responsiveness is also disrupted in CU. Previous fMRI findings have been mixed, with some studies showing hyperactive neural reward activation to reward among chronic CU (Filbey et al., 2016; Nestor, Hester, & Garavan, 2010) and adolescent regular CU (Acheson et al., 2015) compared to non-users, while others demonstrated hypoactive or no difference in neural reward activation to reward among chronic CU compared to non-users (Enzi, Lissek, Edel, Tegenthoff, Nicolas, Scherbaum, & Roser, 2015; van Hell et al., 2010). The mixed findings may be due to different reward tasks (i.e., drug reward via cue-reactivity tasks versus non-drug reward tasks), different stages of reward processing (i.e., reward anticipation versus reward outcome), and/or small sample sizes. However, a recent *meta*-analysis of fMRI studies of reward processing with heterogeneous CU found increased BOLD activation of key brain reward regions, including the striatum, during reward-related tasks among CU compared to non-users (Yanes et al., 2018). To our knowledge, no studies have examined EEG measures of reward responsiveness in CU. EEG measures have better temporal resolution than fMRI (Klumpp & Shankman, 2018) and thus can elucidate information regarding earlier stages of reward processing among CU.

Reward-related processing has been examined using several different tasks and stages of reward-related processing. Some tasks capture reward anticipation, which is often thought to reflect motivational processes, while other tasks capture reward receipt, which is often thought to reflect learning processes and/or reward responsiveness (see Luijten, Schellekens, Kuhn, Machielse, & Sescousse, 2017). Although these stages are thought to be distinct, both engage the ventral striatum, a key node in brain reward circuitry (Oldham et al., 2018). Many fMRI studies studying SUD use the Monetary Incentive Delay (MID) task to capture both reward anticipation and reward receipt (Luijten et al., 2017). On the other hand, many EEG studies use the Doors task to capture reward receipt. The Doors task is a well validated, effective probe of neural reward responsiveness that has been shown to reliably elicit monetary loss- and gain-related brain activity during EEG (Carlson, Foti, Mujica-Parodi, Harmon-Jones, & Hajcak, 2011). Given the excellent psychometric properties of the Doors task during EEG and evidence that neural reward responsiveness captured during the Doors task likely originates from the striatum (Foti, Weinberg, Dien, & Hajcak, 2011), we chose to use the Doors task in the current study.

One way that studies have operationalized reward responsiveness during EEG is with the reward positivity (RewP), an event-related potential (ERP) that is maximal at frontocentral electrode sites and occurs approximately 250–350 ms following the receipt of a reward. This ERP component was previously termed the feedback negativity (FN), and has traditionally been analyzed as the difference in average reactivity to rewards versus losses (see Proudfit, 2015). Specifically, the RewP traditionally was computed as a difference score of rewards minus losses, while the FN traditionally was computed as a difference score of losses minus rewards. However, recent psychometric studies suggest that reactivity to rewards and losses can be better analyzed using a regression-based approach (Meyer, Lerner, De Los Reyes, Laird, & Hajcak, 2017). This approach computes two sets of residuals reflecting (a) neural reactivity to reward independent of reactivity to loss (the RewP), and (b) neural reactivity to loss independent of reactivity to reward (the FN). This approach is better suited than difference scores for isolating neural activity related to a specific process of interest because the RewP and FN obtained from this regression-based approach are orthogonal. The RewP and FN residual scores also have superior psychometric properties compared to traditional difference scores (Bress, Meyer, & Proudfit, 2015; Ethridge & Weinberg, 2018).

As additional indicators of reward processing, these ERPs can be decomposed into frequency bands - activity in the delta frequency band (<3 Hz) to monetary gain and activity in the theta frequency band (4–7 Hz) to monetary loss (Bernat, Nelson, & Baskin-Sommers, 2015; Foti, Weinberg, Bernat, & Proudfit, 2015; B. D. Nelson et al., 2018; L. D. Nelson, Patrick, Collins, Lang, & Bernat, 2011). Importantly, reward-related delta and loss-related theta time–frequency measures are independent components that contribute to the time-domain ERP measures RewP and FN, but they also provide unique information about reward responsiveness, explaining additional variance that the ERPs are not able to capture (Foti et al., 2015; B. D. Nelson et al., 2018; Webb et al., 2017). Therefore, reward-related delta and loss-related theta time–frequency measures seem to be capturing different reward-related processes than the RewP or FN. Source localization studies indicate that the striatum is involved in reward-related delta and the anterior cingulate cortex is involved in loss-related theta (Foti et al., 2015). The exact functions of time–frequency measures are not yet clear, but some evidence indicates that reward-related delta may represent salience and motivational relevance (Knyazev, 2007), while loss-related theta may index error processing (Cohen, Elger, & Ranganath, 2007; Nelson et al., 2018).

In sum, the goal of this study is to compare CU and non-users on four neurophysiological measures related to reward and loss processing - the RewP, FN, and time–frequency measures of reward and loss – with the hypothesis that CU would demonstrate an enhanced RewP and reward-related delta to initial attainment of monetary rewards compared to non-users. Importantly, given the robust association between various psychopathologies and reward and loss processing (Shankman, Katz, DeLizza, Sarapas, Gorka, & Campbell, 2014), the present study controlled for co-occurring psychopathology. As secondary analyses, we examined if cannabis use history and CUD status differentially affects reward responsiveness among occasional CU (OC), current CUD (cCUD), and remitted/past CUD (rCUD) compared to non-users on ERP and time–frequency EEG measures.

2. Methods

2.1. Participants

Participants were primarily drawn from a larger study (see Shankman et al., 2018; Weinberg, Liu, Hajcak, & Shankman, 2015) funded through the National Institute of Mental Health's Research Domain Criteria initiative (Shankman & Gorka, 2015) and focused on identifying shared and distinct transdiagnostic affective and neurobiological abnormalities across psychopathologies. Therefore, the inclusion criteria aimed to recruit individuals with and without a broad range of internalizing and externalizing symptoms. Participants were recruited via advertisements posted in the community, local psychiatric clinics, nearby college campuses and in area newspapers/websites. All

participants in this study were free from major medical and neurological illness. Exclusion criteria for all participants were left-handedness, history of mania or psychosis, or current cognitive dysfunction (e.g., traumatic brain injury, pervasive developmental disorder). To increase statistical power, seven participants (three occasional CU and four non-users) were drawn from a second study with nearly identical recruitment strategies and inclusion/exclusion criteria (Burkhouse, Gorka, Afshar, & Phan, 2017). Full descriptions and the inclusion/exclusion criteria of the larger studies are in the Supplement.

CU with (a) occasional use (OC; endorsing cannabis use > 1x in the past month, but < 1x a week), (b) current CUD (cCUD), or (c) remitted (past) CUD (rCUD) were identified from the larger studies. Non-users were identified from the larger studies if they denied cannabis use in the past month. Non-users were then pseudo-randomly selected to match the CU group on demographic factors, as well as current and past psychopathology (other than SUD and AUD), blind to EEG data.

CU (n = 67) and non-users (n = 60) were matched on several demographic characteristics including age, years of education, gender, race/ethnicity, and prevalence of psychiatric conditions other than SUD or AUD (p-values > 0.05). Participant characteristic and demographic information for CU and non-user groups, as well as CU subgroups (OC, cCUD, rCUD) is shown in Table 1.

The University of Illinois at Chicago Institutional Review Board approved the studies, and informed consent was obtained from all participants. All participants were compensated for their time and all procedures complied with the Helsinki Declaration. Participants were asked to abstain from cannabis and other substance use for 24 h prior to EEG lab visit, which was assessed by asking participants if they had used any substances in the past 24 h at the lab visit.

2.2. Assessment of psychopathology

Lifetime diagnoses of Axis I disorders were assessed via the Structured Clinical Interview for DSM-5 Disorders (SCID-5; First, Williams, Karg, & Spitzer, 2015) by doctoral students and bachelor's level research assistants that were trained to criterion on the SCID and were supervised by a licensed clinician. Consistent with the RDoC initiative (Kozak & Cuthbert, 2016), comorbidity was permitted (see Table 1). Participants also completed the Inventory of Depression and Anxiety Symptoms (IDAS-II; Watson et al., 2012) – a 99-item self-report measure assessing symptoms of emotional disorders during the previous two weeks.

2.3. Assessment of cannabis and alcohol use

Participants were asked about the number of days they used cannabis and the number of alcoholic drinks they drank per week in the past month. Participants from study 1 (CU n = 64; non-users n = 57) were also asked about whether or not they had used cannabis in their lifetime, the number of days they used cannabis, and the number of alcoholic drinks they drank per week in the past six months. Not surprisingly, CU reported greater cannabis use during the past month and past six

Table 1
Participant Characteristics.

	Non-Users (NU) $N = 60$	Cannabis Users (CU) $N = 67$	Group Difference	Occasional CU (OC) $n = 21$	Current CUD (cCUD) $n = 22$	Remitted CUD (rCUD) $n = 24$	Subgroup Differences
Age	22.20 (3.13)	22.07 (3.86)	*ns*, $p = .78$	21.48 (5.29)	22.14 (2.71)	22.54 (3.52)	*ns*, $p = .78$
Gender (% Female)	62%	54%	*ns*, $p = .37$	67%	36%	58%	*ns*, $p = .16$
Race (% Caucasian)	43%	52%	*ns*, $p = .05$	62%	50%	46%	*ns*, $p = .25$
Substance Use							
Past month marijuana (times/month)*	0.00 (0.00)	11.12 (26.39)	$p = .002$	1.57 (1.16)	30.18 (40.10)	2.00 (3.41)	all < cCUD
Past 6 months marijuana (times/month)*^	0.00 (0.00)	73.54 (165.29)	$p = .001$	13.40 (31.11)	176.37 (244.32)	29.40 (81.33)	NU, OC, rCUD < cCUD
Past month alcohol (drinks/week)*	1.41 (2.40)	5.75 (5.87)	$p < .001$	4.24 (3.62)	6.38 (5.79)	6.34 (7.17)	NU, OC < CUD
Past 6 months alcohol (drinks/week)*^	1.55 (2.43)	5.51 (5.62)	$p < .001$	4.29 (3.84)	6.64 (5.16)	5.43 (6.97)	NU < CUD
Lifetime Marijuana Use (% Used)*^	16%	100%	$p < .001$	100%	100%	100%	NU < all CU
Psychiatric Diagnoses and Medication							
Current CUD*	0%	33%	$p < .001$	0%	100%	0%	all < cCUD
Past CUD*	0%	69%	$p < .001$	0%	100%	100%	NU, OC < CUD
Current AUD*	0%	12%	$p = .006$	0%	36%	0%	all < cCUD
Past AUD*	0%	38%	$p < .001$	0%	68%	42%	NU, OC < CUD
Current Other SUD	0%	3%	*ns*, $p = .17$	0%	9%	0%	*ns*, $p = .16$
Past Other SUD*	5%	49%	$p < .001$	29%	59%	58%	NU < OC < CUD
Current MDD	3%	5%	*ns*, $p = .73$	5%	5%	4%	*ns*, $p = .99$
Past MDD	33%	44%	*ns*, $p = .27$	20%	45%	63%	NU, OC < rCUD
Current PTSD	2%	0%	*ns*, $p = .29$	0%	0%	0%	–
Past PTSD	7%	12%	*ns*, $p = .30$	0%	22%	16%	*ns*, $p = .11$
Current Panic Disorder	0%	0%	–	0%	0%	0%	–
Past Panic Disorder	5%	9%	*ns*, $p = .37$	5%	5%	17%	*ns*, $p = .26$
Current Social Anxiety Disorder	8%	17%	*ns*, $p = .16$	5%	18%	25%	*ns*, $p = .11$
Past Social Anxiety Disorder	17%	24%	*ns*, $p = .29$	10%	23%	38%	*ns*, $p = .10$
Current Specific Phobia	13%	20%	*ns*, $p = .34$	15%	36%	8%	*ns*, $p = .06$
Past Specific Phobia	15%	26%	*ns*, $p = .14$	25%	41%	13%	*ns*, $p = .07$
Current GAD	3%	5%	*ns*, $p = .73$	10%	5%	0%	*ns*, $p = .39$
Past GAD	8%	18%	*ns*, $p = .11$	20%	18%	17%	*ns*, $p = .44$
Taking Psychotropic Meds*	7%	20%	$p = .04$	17%	27%	17%	*ns*, $p = .10$
IDAS-II Anxiety Composite*	7.38 (1.93)	8.80 (2.96)	$p = .002$	8.30 (2.84)	9.81 (3.62)	8.31 (2.15)	NU < cCUD
IDAS-II Depression*	35.10 (10.33)	41.01 (14.91)	$p = .01$	41.10 (16.98)	42.82 (14.27)	39.29 (12.97)	*ns*, $p = .07$

Note. All values are means and standard deviations unless otherwise noted; AUD, Alcohol Use Disorder; CUD, Cannabis Use Disorder; GAD, Generalized Anxiety Disorder; IDAS-II, Inventory of Depression and Anxiety Symptoms (IDAS); MDD, Major Depressive Disorder; ns, non-significant; PTSD, Post-Traumatic Stress Disorder; ^study 1 participants (CU n = 64; NU n = 57); *, p < .05.

months, as well as more alcoholic drinks per week during the past month and past six months than non-users (see Table 1).

2.4. EEG reward task

Participants completed a validated reward-guessing game, the 'Doors' task (see Proudfit, 2015), during EEG that consisted of 60 trials (study 1) or 40 trials (study 2). On each trial, participants were asked to choose one of two doors shown side by side on a computer monitor; the graphic remained visible until a choice was made. A fixation mark then appeared for 1000 ms, followed by a feedback screen for 2000 ms. Feedback consisted of either a green "↑", indicating a win of $0.50, or a red "↓", indicating a loss of $0.25; these amounts were chosen to give gains and losses equivalent subjective values (Tversky & Kahneman, 1992). Participants were told they had a chance of winning between $0 and $15.00 at the end of the task depending on their performance. However, unbeknownst to the participant, the task was rigged, as their behavior during the task had no impact on actual outcomes and therefore was not analyzed or reported. All participants received $10 for the task. After receiving feedback, a fixation mark was presented for 1500 ms, followed by a screen reading "Click for the next round," which remained onscreen until participants responded. Participants received 30 trials and 20 trials in study 1 and study 2, respectively, for both win and loss feedback. Trials were presented in a random order.

2.5. EEG data acquisition and preprocessing

Continuous EEG was recorded during the task using an elastic cap and the ActiveTwo BioSemi system (BioSemi, Amsterdam, Netherlands). Study 1 used a 64-electrode montage and study 2 used a 30-electrode montage based on the 10/20 system. One electrode was placed on each mastoid. Electrooculogram (EOG) generated from eye movements and eyeblinks was recorded using four facial electrodes: two electrodes located approximately 1 cm outside the outer edge of the right and left eyes measured horizontal eye movements, and one electrode placed approximately 1 cm below the left eye and electrode FP1 were used to measure vertical eye movements and blinks. The data were digitized at a sampling rate of 1024 Hz, using a low-pass fifth order sinc filter with a −3 dB cutoff point at 208 Hz. Each active electrode was measured online with respect to a common mode sense (CMS) active electrode located

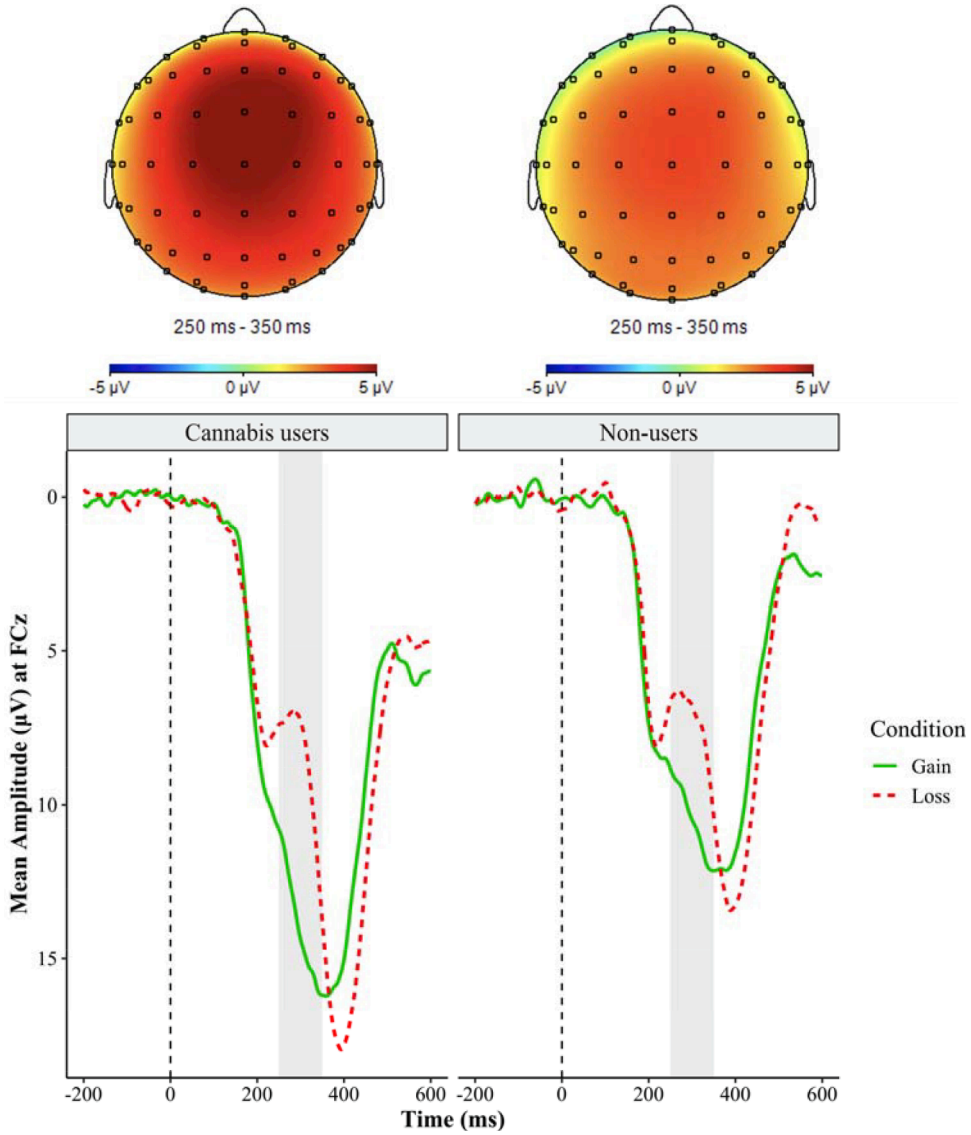

Fig. 1. Topographic scalp maps of neural activity depict the Win minus Loss difference 250–350 ms after the response for all cannabis users on the left and for non-users on the right. Response-locked ERP waveform for Win and Loss trials for all cannabis users on the left and for non-users on the right with greater values at the bottom of the y-axis and smaller values at the top of y-axis.

between PO3 and POz, producing a monopolar (non-differential) channel. CMS forms a feedback loop with a paired driven right leg (DRL) electrode located between POz and PO4, reducing the potential of the participants and increasing the common mode rejection rate (CMRR). Off-line analyses were performed using Brain Vision Analyzer 2 software (Brain Products, Gilching, Germany). Data were re-referenced to the average of the two mastoids and high-pass (0.1 Hz) and low-pass (30 Hz) filtered. Standard eyeblink and ocular corrections were performed (Gratton, Coles, & Donchin, 1983) and semiautomated artifact rejection procedures removed artifacts with the following criteria: voltage step of>50 μV between sample points, a voltage difference of 300 μV within a trial, and a maximum voltage difference of<0.5 μV within 100 ms intervals. Additional artifacts were removed using visual inspection. Data were baseline corrected using the 200 ms interval prior to feedback. ERPs were averaged across win and loss trials, and the RewP was scored as the mean amplitude 250–350 ms following feedback at frontal site FCz, where the win minus loss difference was maximal (Fig. 1). The mean number of artifact-free trials for FCz for each condition were 28.20 (SD = 3.89) for win trials and 27.97 (SD = 4.32) for loss trials for study 1 and 18.86 (SD = 2.61) for win trials and 18.71 (SD = 3.40) for loss trials for study 2. The RewP is usually quantified as the gain minus loss difference score (see Proudfit, 2015), with more positive values for the difference score indicating greater reactivity to reward. The FN is usually quantified as the loss minus gain difference score, with more positive values for the difference score indicating greater reactivity to loss. However, recent evidence suggests that residuals provide a more reliable ERP measure (see Meyer et al., 2017). Therefore, residualized RewP scores were calculated by regressing Loss trials on Win trials. Residualized FN scores were calculated by regressing Win trials on Loss trials. Win and Loss trials were significantly related in both models: $R^2 = 0.81$, $F(1,127) = 247.63$, $p < .001$. Split-half reliabilities for the Win and Loss condition for each group were calculated using the correlation between the averages of odd- and even-numbered trials corrected using the Spearman-Brown prophecy formula (Nunnally & Bernstein, 1994), and ranged between 0.83 and 0.95.

To extract time–frequency bands, we implemented a complex Morlet wavelet transformation using a Morlet parameter c of 3.5 applied to the data from 0.5 to 20 Hz in 30 frequency steps distributed on a logarithmic scale and with a baseline correction of 500 to 300 ms prestimulus (Cohen, 2014). The results of the wavelet transformations were averaged within each participant and condition (wins, losses), yielding a measure of total power. To test for group and condition differences, we extracted wavelet layers corresponding to delta (central frequency: 2.3 Hz; spectral bandwidth: 1.3 Hz) and theta (central frequency: 5.6 Hz; spectral bandwidth: 3.2 Hz) activity. Similar to previous studies (Bernat et al., 2015; Nelson et al., 2018; Webb et al., 2017), we found that theta power was maximal at FCz and was scored as the mean activity from 300 to 500 ms at electrode FCz (Fig. 2). Delta power was also maximal at FCz and was scored as the mean activity from 100 to 300 ms (Fig. 2). Residualized loss-related theta activity was calculated by regressing Win theta power on Loss theta power. Residualized reward-related delta activity was calculated by regressing Loss delta power on Win delta power.

2.6. Statistical analysis

Analyses were performed using SPSS 24.0 (IBM). Group differences in participant characteristics were examined using t-tests. One-way between subject analysis of covariance (ANCOVA) models were used with group (CU, non-user) as the independent variable and EEG measures (RewP, FN, reward-related delta, loss-related theta) as separate dependent variables. Past other SUD, current and past Alcohol Use Disorder (AUD), current psychotropic medication use, race/ethnicity, the IDAS-II depression subscale, and a composite of the IDAS-II anxiety disorder subscales (i.e., social anxiety, panic, traumatic intrusions and avoidance, and claustrophobia) were used as covariates in analyses.

3. Results

3.1. CU versus non-user differences in ERP measures

CU demonstrated a significantly enhanced RewP to initial attainment of monetary rewards compared to non-users (see Table 2), even after controlling for relevant covariates (see Table 3). CU and non-user groups did not differ on FN (see Tables 2 and 3). Of note, the covariates race/ethnicity and current psychotropic medication use were significantly related to the RewP in the ANOVA model; however, follow-up tests found no significant effect of race/ethnicity or current psychotropic medication use on the RewP (p-values > 0.05).

3.2. CU versus non-user differences in time–frequency measures

CU did not differ from non-users on reward-related delta activity ($F(1,118) = 1.44$, $p = .23$) or on loss-related theta activity ($F(1,118) = 0.00$, $p = .98$) after controlling for relevant covariates and without covariates (see Table 2).

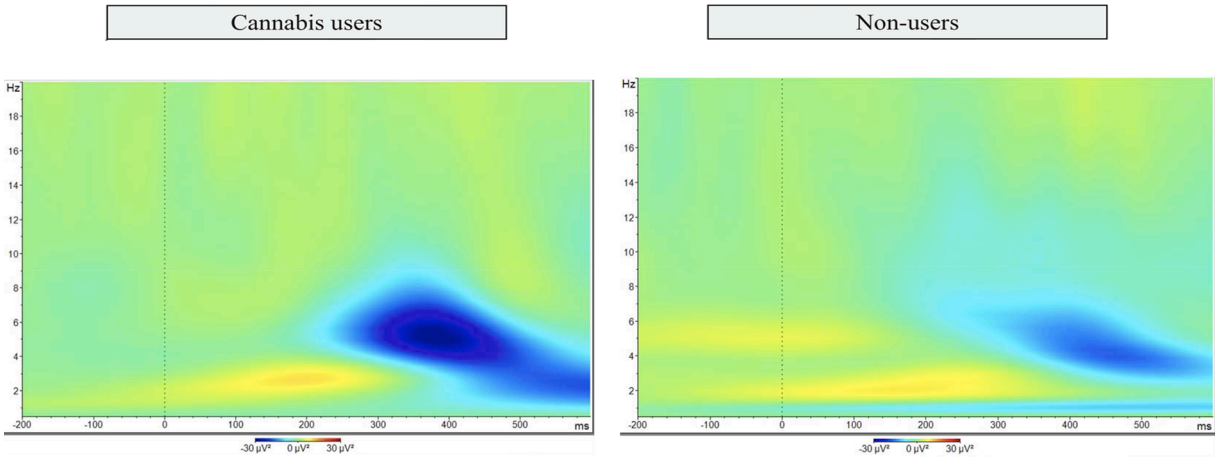

Fig. 2. Time-frequency plots for the Win minus Loss difference at FCz for all cannabis users on the left and for non-users on the right. More yellow indicates greater activity to gain relative to loss and more blue indicates greater activity to loss relative to gain. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Group Differences in EEG Measures.

	Non-Users (NU) $N = 60$	Cannabis Users (CU) $N = 67$	Group Difference	Occasional CU (OC) $n = 21$	Current CUD (cCUD) $n = 22$	Remitted CUD (rCUD) $n = 24$	Subgroup Differences
EEG Event Related Potential Measures							
RewP (residual)*	−1.18 (3.68)	1.18 (5.03)	$p = .003$	2.57 (5.71)	0.13 (5.23)	0.92 (4.06)	NU < OC
RewP Difference Score (Win-Loss)*	3.21 (3.76)	5.50 (5.00)	$p = .005$	6.78 (5.63)	4.59 (5.27)	5.22 (4.08)	NU < OC
FN (residual)	0.59 (3.77)	−0.75 (3.89)	*ns*, $p = .07$	−1.16 (4.19)	−0.74 (4.21)	−0.42 (3.42)	*ns*, $p = .24$
FN Difference Score (Loss-Win)*	−3.21 (3.76)	−5.50 (5.00)	$p = .005$	−6.78 (5.63)	−4.59 (5.27)	−5.22 (4.08)	NU < OC
Win*	10.58 (7.45)	13.98 (7.80)	$p = .009$	17.13 (9.46)	10.76 (6.38)	14.17 (6.37)	NU, cCUD < OC
Loss	7.36 (7.37)	8.47 (5.77)	*ns*, $p = .25$	10.35 (6.75)	6.17 (4.57)	8.95 (5.31)	*ns*, $p = .14$
EEG Time-Frequency Measures							
Reward-related delta (residual)	−198.59 (4413.01)	180.54 (4550.54)	*ns*, $p = .64$	2179.66 (5888.85)	−1283.46 (3773.66)	−244.40 (3148.80)	*ns*, $p = .07$
Win delta power	5185.28 (5458.60)	5944.34 (4912.59)	*ns*, $p = .41$	8042.48 (6549.82)	4675.81 (3510.33)	5242.01 (3770.20)	*ns*, $p = .12$
Loss delta power	3538.41 (6423.62)	4401.66 (5414.90)	*ns*, $p = .42$	4626.66 (3141.16)	4845.79 (8108.28)	3771.40 (3774.13)	*ns*, $p = .78$
Loss-related theta (residual)	−1095.03 (5418.48)	995.48 (6612.14)	*ns*, $p = .06$	−256.93 (5393.33)	3188.32 (8157.34)	41.48 (5652.91)	*ns*, $p = .13$
Win theta power	5350.76 (12534.73)	4252.99 (4417.62)	*ns*, $p = .51$	5305.60 (5838.09)	3242.36 (3185.04)	4258.62 (3861.60)	*ns*, $p = .81$
Loss theta power	7876.43 (11032.93)	9096.53 (7973.09)	*ns*, $p = .48$	8678.72 (6632.90)	10488.04 (9602.14)	8146.99 (7534.56)	*ns*, $p = .75$

Note. All values are means and standard deviations unless otherwise noted; ns, non-significant; *, p<.05; **, p<.01.

Table 3
ANOVA Results for ERP Measures.

	Sum of Squares	*df*	Mean Square	*F*	*p*	partial η^2
RewP (residual) as DV						
Intercept	6.76	1	6.76	0.36	0.55	
Group (NU, CU)	159.20	1	159.20	8.51	0.004	0.07
Past Other SUD	34.27	1	34.27	1.83	0.18	0.02
Past AUD	11.12	1	11.12	0.60	0.44	0.01
Current AUD	33.05	1	33.05	1.77	0.19	0.02
IDAS- Anxiety Composite	44.34	1	44.34	2.37	0.13	0.02
IDAS- Depression	1.44	1	1.44	0.08	0.78	0.00
Race	82.12	1	82.12	4.39	0.04	0.04
Taking Psychotropic Meds	80.96	1	80.96	4.33	0.04	0.04
Error	2206.90	118	18.70			
FN (residual) as DV						
Intercept	19.05	1	19.05	1.33	0.25	
Group (NU, CU)	47.13	1	47.13	3.28	0.07	0.03
Past Other SUD	22.68	1	22.68	1.58	0.21	0.01
Past AUD	1.34	1	1.34	0.09	0.76	0.00
Current AUD	29.42	1	29.42	2.05	0.16	0.02
IDAS-II Anxiety Composite	38.57	1	38.57	2.69	0.10	0.02
IDAS-II Depression	3.37	1	3.37	0.24	0.63	0.00
Race	3.80	1	3.80	0.27	0.61	0.00
Taking Psychotropic Meds	43.33	1	43.33	3.02	0.09	0.03
Error	1693.81	118	14.35			

Note. AUD, Alcohol Use Disorder; CU, Cannabis User; IDAS-II, Inventory of Depression and Anxiety Symptoms (IDAS); FN, Feedback Negativity; NU, Non-User; RewP, Reward Positivity.

3.3. Secondary data analyses

3.3.1. CU subgroups versus non-user differences in ERP measures

There was a significant effect of group (non-users, OC, cCUD, pCUD) on RewP (see Table 2), even after controlling for relevant covariates (see Supplement). Follow-up tests using Games-Howell pairwise comparison test for unequal sample sizes found OC to have an enhanced RewP compared to non-users ($p = .04$), but no other group differences. Using a one-sample *t*-test, the RewP among OC was marginally greater than zero, $t(20) = 2.06$, $p = .05$. There were no significant group differences on FN (see Supplement).

3.3.2. CU subgroups versus non-user differences in time–frequency measures

There was no significant effect of group (non-users, OC, cCUD, pCUD) on time–frequency measures, although there was a trend that OC had greater reward-related delta than the other groups (see Table 2).

3.3.3. Associations of substance use measures with ERP and time–frequency measures

Among CU, past month cannabis and alcohol use were not related to the RewP or FN or to time–frequency measures (*p*-values > 0.05). Among study 1 CU, past six-month cannabis and alcohol use were also not related to the RewP or FN or to time–frequency measures (*p*-values > 0.05). Among CUD subgroups, current or past severity of CUD was not related to the RewP or FN (*p*-values > 0.05), but higher past severity of CUD was related to less reward-related delta ($r = -0.31$, $p = .04$), and higher current and past severity of CUD was related to greater loss-related theta ($r = 0.36$, $p = .02$; $r = 0.38$, $p = .01$, respectively).

4. Discussion

The current study sought to examine whether CU show disrupted neural reward responsiveness during EEG. CU and non-user participants were drawn from larger studies of individuals with and without internalizing and externalizing psychopathology. Groups were matched on current and past psychopathology, with the exception that CU had a higher prevalence of current and past CUD, past other SUD, and current and past AUD compared to non-users. Results revealed that overall, CU demonstrated an enhanced RewP (residual) to the attainment of monetary reward compared to non-users, even after controlling for past other SUD, current and past AUD, current psychotropic medication use, race/ethnicity, and current symptoms of anxiety and depression. Secondary analyses to better understand how cannabis use history and CUD status differentially affects reward responsiveness among CU found that OC, but not cCUD or rCUD, showed enhanced RewP compared to non-users. CU did not differ from non-users on FN (residual), suggesting

that CU, and OC in particular, have enhanced neural activity to reward, but not to loss. There were no significant differences in reward-related delta and loss-related theta time–frequency measures between groups. These findings support growing evidence that sensitivity to reward is disrupted in CU (Yanes et al., 2018), and extend the prior literature by showing that the extent of disruption may be related to CUD status.

To our knowledge, this is the first study to show preliminary evidence that CU demonstrate an enhanced initial reward responsiveness (i.e., an enhanced RewP residual) compared to non-users. Accumulating evidence indicates that the RewP likely originates from the striatum (Foti et al., 2011) and that the RewP is related to BOLD and EEG activation of brain regions implicated in reward, including the striatum and medial prefrontal cortex during reward attainment (Becker, Nitsch, Miltner, & Straube, 2014; Carlson et al., 2011; Foti et al., 2011; Gehring & Willoughby, 2002). Therefore, our findings expand upon previous fMRI studies that found CU show enhanced activation in neural reward circuitry during reward processing (Yanes et al., 2018). In addition, our secondary analyses suggest that among CU subgroups, OC who have never met criteria for CUD exhibit enhanced initial reward responsiveness, while cCUD and rCUD do not differ from non-users. Therefore, it is possible that enhanced initial reward responsiveness is a risk factor for cannabis use and/or CUD, but that after CUD develops enhanced initial reward responsiveness is no longer seen, even among rCUD—perhaps reflecting a scar effect. This is in line with previous research that individuals at risk for SUD show hyperactive brain reward response to rewards (see Heitzeg et al., 2015), but as substance use progresses and SUD develops, brain reward circuitry becomes hypoactive, or less sensitive to rewards (Luijten et al., 2017; Volkow et al., 2016). This effect has also been documented among CU (Martz et al., 2016). We did not find that frequency of cannabis use during the past month or the past six months was related to reward responsiveness (or loss responsiveness), but our measures did not capture amount of cannabis consumed or duration of cannabis use, which may be related to reduced reward responsiveness among heavy CU or CUD. It is important to note that some evidence suggests that structural abnormalities in reward circuitry in SUD seem to normalize after prolonged abstinence (Gould et al., 2014; Volkow et al., 2015), but it is not known if hypoactive reward responsiveness in SUD remains in remitted SUD, after prolonged abstinence. On the other hand, it is also possible that enhanced initial reward responsiveness in OC is a protective factor for CUD risk, as it is not seen in cCUD or rCUD. Most of the sample (85% of total sample and 95% of OC) were young adults aged 18–25, a group who has relatively high cannabis use (about 1 in 5 young adults reporting use in the past month in the U.S.; SAMSHA, 2019) and have greater risk for CUD in their life compared to younger and older age groups (Hasin et al., 2016). However, the OC group in our sample had not yet developed regular use or CUD in this age window, so it may be that they represent a resilient group who have protective factors that decrease the likelihood they will develop CUD. More research is needed to better understand if greater neural reward sensitivity among CU represents a risk factor or protective factor for CUD.

In addition, we found that CU and non-user groups did not differ on the FN, although there was a trend toward CU demonstrating less FN than non-users. Although few studies have examined neural response to loss among SUD and/or CU populations, one previous study had similar findings to the current study. Specifically, an fMRI study that examined neural response to reward and loss among heavy CU during cannabis withdrawal using the MID task found that although CU did not differ from healthy non-users, a pattern emerged such that heavy CU had greater neural activation to reward (vs. loss), while the non-users had greater neural activation to loss (vs. reward) (Filbey, Dunlop, & Myers, 2013). Despite significant methodological differences, these studies both indicate that CU may have greater neural response to reward and slightly less, although not significantly so, neural response to loss than non-users. Future studies should examine loss processing among larger samples of CU to better understand how CU may differ from non-users on neural measures of loss.

Although CU, and OC in particular, showed an enhanced RewP compared to non-users, the groups did not differ on reward-related delta or loss-related theta time–frequency measures. However, it is important to note that there was a trend that OC had greater reward-related delta than the other groups. In addition, a pattern suggested that cCUD had greater loss-related theta, followed by rCUD, OC, and non-users. It is possible that differences among CU subgroups may emerge in future studies with larger sample sizes of OC and CUD groups. Interestingly, among CUD subgroups, higher past severity of CUD was related to less reward-related delta and higher current and past severity of CUD was related to greater loss-related theta. This extends the idea that hypoactivation to rewards is seen in CUD, and that severity of CUD impacts the magnitude of reward and loss measures. Previous studies indicate that reward-related delta or loss-related theta time–frequency measures are independent components that contribute to the time-domain ERP measures RewP and FN, but that these time–frequency measures also contribute additional variance that the RewP and FN do not capture (Foti et al., 2015; Nelson et al., 2018; Webb et al., 2017). Therefore, reward-related delta or loss-related theta time–frequency measures may be capturing different reward-related processes than the RewP or FN. Some evidence indicates that reward-related delta may represent salience and motivational relevance (Knyazev, 2007), while loss-related theta may index error processing (Cohen et al., 2007; Nelson et al., 2018). Therefore, greater CUD severity, may be related to less salience for rewards and greater error processing. Given this relationship was seen for both current and past CUD, it is possible that these disruptions are seen even in remitted CUD. Future studies should examine how time–frequency measures may contribute to time-domain ERP measures to better understand disrupted reward and loss responsiveness among CU.

Although the study has strengths, including the inclusion of individuals with and without internalizing and externalizing psychopathology (an important methodological feature given that approximately 24–37% of individuals with psychopathology used cannabis in the past month, see Satre, Bahorik, Zaman, & Ramo, 2018); it is important to note the current study's limitations. First, CU reported more frequent alcohol consumption and had higher prevalence of AUD and SUDs relative to non-users. We controlled for these variables in statistical analyses, but it is possible that these differences may still have influenced the results. Second, given that many CU participants currently use cannabis and alcohol, and about a third of the OC subgroup had a past SUD (but no current SUD, lifetime CUD, or lifetime AUD), the current study is limited in its ability to assess whether our findings of an enhanced RewP in OC reflects a risk factor versus consequence of cannabis use (or other substance use). Finally, the current study is cross-sectional in nature and does not follow individuals to measure substance use over time.

5. Conclusions

The current study provides preliminary evidence that CU, and OC in particular, demonstrate an enhanced RewP, a neurophysiological marker of initial response to reward, compared to non-users. We found that CU did not differ from non-users on the FN, indicating that CU, and OC in particular, have enhanced neural activity to reward, but not to loss. Our findings support growing evidence that greater neural reward sensitivity to reward is seen among CU, although this may only be seen among occasional CU, not necessarily among CU with current or past CUD. More studies are needed to better understand if greater neural reward sensitivity represents a risk factor or protective factor for CUD.

6. Author agreement

All authors have seen and approved the final version of the manuscript. This manuscript is original research and is not currently being

considered for publication in any other journal.

7. Contributors

All authors have participated sufficiently in the work and take responsibility for authorship and publication. NAC made substantial contributions to the design, analysis, and writing of the manuscript. CJF made substantial contributions to the data analysis and writing of the manuscript. KLP and SAS led the project administration and provided supervision for the team. KLB, HK, KLP, and SAS made substantial contributions to the preparation and writing of the manuscript. All authors contributed to interpreting the results and have approved the final manuscript.

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Appendix A. Supplementary data

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