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Co-occurring tobacco and cannabis use in adolescents: Dissociable relationships with mediofrontal electrocortical activity during reward feedback processing

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ABSTRACT

Differences in corticostriatal neural activity during feedback processing of rewards and losses have been separately related to cannabis and tobacco use but remain understudied relative to co-use in adolescents. Using high-density EEG (128 electrode system, 1000 Hz sampling), we examined event-related potentials (ERPs) elicited by monetary reward, neutral, and loss feedback during performance on a non-learning four-choice guessing task in a sample of non-deprived daily-cigarette-smoking adolescents (n = 36) who used tobacco and cannabis regularly (TC adolescents), and non-smoking healthy control adolescents (HCs) (n = 29). Peak amplitudes and latencies of mediofrontal ERPs indexing feedback-related negativities (FRNs) were used as outcomes in repeated-measures ANOVAs. No differences in FRNs were observed between TC and HC adolescents. Within TC adolescents, cannabis-use and tobacco-use variables had distinct relationships with the FRN, with cannabis-related problem severity being positively correlated with FRN amplitude during reward feedback and tobacco-related problem severity being negatively correlated with FRN latency during non-loss feedback (i.e., reward and neutral). These findings suggest that co-occurring cannabis and tobacco use may have dissociable relationships with feedback processing relating to each drug and support an incentive salience model of addiction severity related to cannabis use in adolescents.

1. Introduction

Tobacco and cannabis are among the most commonly used substances by adolescents worldwide. In 2019, 27.1% U.S. high school students and 22.3% of U.S. high school seniors reported past-30-days use of tobacco products and cannabis, respectively, with 2.4% and 6.4% of U.S. high school seniors using cigarettes and cannabis on a daily basis, respectively (Gentzke et al., 2019; Johnston et al., 2020). Cannabis is often used in combination with combustible tobacco by young people. Approximately 14% of young adults in the U.S. report combustible tobacco and cannabis co-use within the past month (Schauer et al., 2015). Adolescents using combustible tobacco are 9 to 15 times more likely to use cannabis than non-smoking adolescents, while over half of U.S. adolescents between the ages of 12 and 17 years who smoke cigarettes report past-month use of cannabis (Mathers et al., 2006; SAMHSA, 2004). Co-use of cannabis and tobacco may interact, both acutely during co-administration and chronically over time, leading to complex immediate-, shorter-, and longer-term effects on cognition, brain, and behaviors. The co-occurrence of cannabis and tobacco use is concerning given its association with greater frequency of use and addiction severity, and poorer treatment outcomes related to both cannabis use disorders (CUDs) and tobacco use disorders (TUDs) (Agrawal et al.,

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2012).

Although co-use of tobacco and cannabis is common among youth, little is known about the combined effects of combustible tobacco and cannabis on brain function and structure. Two groups independently found gray-matter volume differences in the putamen, thalamus, hippocampus, precentral gyrus, cerebellum, and prefrontal cortical (PFC) regions between tobacco-using, cannabis-using and tobacco and cannabis co-using adults (TC adults) (Filbey et al., 2015; Wetherill et al., 2015b). Distinct and overlapping relationships with tobacco and cannabis measures and brain function and network connectivity at rest and during reward anticipation have also been described in TC subjects (Filbey et al., 2018; Karoly et al., 2015; Wetherill et al., 2015a). Across studies, differences in brain volume and activation patterns between TC, mono-drug-using, and non-smoking subjects are most consistently observed in core regions and networks involved in cognitive control, attention, and reward processing. How brain activation patterns in these regions during reward processing relate to tobacco and cannabis addiction severities is poorly understood (Bjork and Pardini, 2015; Casey and Jones, 2010; Hammond et al., 2014; Hommer et al., 2011) and could reflect transdiagnostic or substance-specific processes in TC adolescents. Understanding the potential effects of tobacco and cannabis on reward processing in TC adolescents has significant public health implications.

Event-related potentials (ERPs) are well suited to evaluate mechanisms underlying reward processing during rapid decision-making (Luck, 2005). The feedback-related negativity (FRN), also termed reward positivity, feedback error-related negativity, and medial frontal negativity (MFN) [see (Sambrook and Goslin, 2015) and (Hauser et al., 2014) for reviews], is an ERP component over mediofrontal areas of the scalp occurring between 200 and 300 ms after reward-related feedback and is observed during human trial-and-error learning and guessing tasks (Gehring and Willoughby, 2002). Localized to the anterior cingulate cortex (ACC), it is described as the difference in ERP amplitude (defined as an increase or decrease in microvoltage (μV)) between positive and negative feedback and incorporates elements of valence, saliency, and expectancy (Gehring and Willoughby, 2002; Heydari and Holroyd, 2016). The FRN is sensitive to a reward prediction error signal that is generated when transient shifts in midbrain dopamine levels, in response to positive versus negative feedback of varying probabilities, signal disinhibitory neurons in the dorsal ACC (Holroyd and Coles, 2002; Schultz et al., 1997).

The FRN may emerge primarily from loss feedback and reflect a binary evaluation of good versus bad outcomes, with no difference between neutral and loss outcomes (Hajcak et al., 2007; Holroyd et al., 2006). This interpretation is based upon two lines of evidence. First, early studies of the FRN found it to be insensitive to the magnitude of reward and loss feedback (Gehring and Willoughby, 2002; Hajcak et al., 2007; Holroyd et al., 2006). This insensitivity to magnitude has been called into question by multiple studies and a recent meta-analysis (Sambrook and Goslin, 2015). Second, Holroyd, Hajcak, and colleagues observed that in EEG studies using trial-and-error learning or gambling tasks that included win, loss, and neutral conditions, no difference in amplitude was found between neutral and loss conditions (Hajcak et al., 2007; Holroyd et al., 2006). The binary function theory of FRN has not been tested in pediatric samples or examined developmentally.

To date, few published studies have examined FRN in relation to SUDs, and results across studies have been mixed (Baker et al., 2016, 2011; Kamarajan et al., 2010; Parvaz et al., 2015; Torres et al., 2013). Joyner and colleagues (2019) recently examined FRN in relation to SUD problems in a large sample of adults and found that FRN, measured as the net difference between win- and loss-related activation, was negatively correlated with SUD symptomatology (Joyner et al., 2019). Our group has published two studies examining the FRN in high-risk adolescents both aligning with the reward deficiency model of addiction vulnerability (Blum et al., 2000). Adolescents who had been prenatally exposed to cocaine demonstrated decreased FRN amplitude in response to losses compared to gains when compared to matched controls (Crowley et al., 2009). Yau and colleagues observed a blunted feedback for both win and loss conditions during a risk-taking task in adolescents with at-risk or problematic internet use (Yau et al., 2015). No studies to date have examined the FRN in tobacco-using or TC adolescents.

Here we examined differences in mediofrontal electrocortical activity elicited by monetary reward, neutral, and loss feedback conditions, indexed by the FRN, in relation to cannabis-related and tobacco-related problem severity in adolescents with biochemically verified daily tobacco smoking who regularly use cannabis and tobacco, and a matched group of non-smoking (cigarette or cannabis) healthy control (HC) participants. We predicted that the FRN amplitude would differentiate between reward and non-reward outcome, with no difference between neutral and loss feedback, consistent with FRN studies in adults (Holroyd et al., 2006). Based upon previous feedback-related ERP studies in high-risk youth and substance-using adults, (Crowley et al., 2009; Joyner et al., 2019) we hypothesized that FRN amplitude across feedback conditions would be decreased in tobacco-smoking adolescents compared to controls. We also predicted that cannabis- and tobacco-related problem severity would be negatively correlated with FRN amplitude among smoking adolescents. Earlier ERP studies of feedback processing in samples of high-risk adolescents and adults with SUDs have not reported latency outcomes; thus, we had no direct data to inform our latency hypotheses. Based upon indirect evidence of opposing effects on orientation and processing speed from acute cannabis and tobacco administration (D'Souza et al., 2012; Houston and Ceballos, 2013), we anticipated seeing shorter FRN latencies in relation to tobacco use and longer FRN latencies in relation to cannabis use.

2. Methods

2.1. Participants

Physically healthy adolescents, aged 14–21 years, who smoked cigarettes daily and age-matched, gender-matched, and grade-level-matched non-smoking typically developing adolescents (HCs) were recruited from local high schools in the greater New Haven area in conjunction with an NIH-funded tobacco cessation study and via flyers, peer referrals, and advertisements between July 2012 and June 2014.

2.2. Procedures

A telephone interview was administered to adolescents and their parents/guardians prior to study entry. Participants who met inclusionary criteria, and whose parents provided consent if under age 18 years, were then scheduled for a single 3-hour study session. In the session, participants completed self-report questionnaires, behavioral assessments, biochemical measures, and the EEG scan. For smoking adolescents, inclusion criteria included current daily cigarette use and current or past history of smoking 5 or more cigarettes on a daily basis for at least a 6-month period, urine cotinine level above 500 ng/ml at study visit, no current illicit substance use and a urine drug screen (UDS) negative for drugs other than cannabis. For HCs, criteria included never smoking daily, no history of regular patterns of smoking, urine cotinine level lower than 100 ng/ml at study visit, no history of illicit substance use (<5 lifetime experiences with cannabis, no previous use of any other illicit drug, negative UDS for cannabis and other illicit drugs), and not meeting criteria for heavy drinking (Calahan et al., 1969). For all participants, criteria included ages 14–21 years, English language fluency, full scale IQ (FSIQ) > 70, no chronic medical illnesses, no evidence of serious mental illness (psychosis, autism, bipolar disorders), no history of lifetime or current DSM-IV-TR diagnosis of dependence on another psychoactive substance (other than alcohol, cannabis, and tobacco). Additional exclusion criteria included neurological conditions (e.g. seizures, migraines), head trauma with loss of consciousness > 2 min, use

of any psychoactive drugs including anxiolytics and antidepressants unless the adolescent had been taking the medication consistently for 3 months, and pregnancy or lactation. Participants provided consent/assent, and participants under age 18 years also had a parent/guardian provide consent. This study was approved by the Yale University School of Medicine Human Investigation Committee.

All participants were instructed to abstain from alcohol or drugs other than cannabis or tobacco for 24 h on scan days. Participants were not instructed to modify their cannabis and tobacco use but were informed that if they presented for the scan day showing signs of overt intoxication (e.g. slurred speech, unsteady gait, and disorientation) that they would be rescheduled. Smoking participants were given an opportunity to smoke a tobacco cigarette prior to initiating study procedures. All participants were asked their last day and time of use cannabis, tobacco, and alcohol, assessed for signs/symptoms of intoxication, and were tested for recent drug and alcohol use and for expired carbon monoxide (CO) levels via breathalyzers and urine biospecimen collection. From the urine biospecimen, three biochemical measures were obtained: (1) the presence of drugs of abuse (cannabinoids, cocaine, opioids, methamphetamines, benzodiazepines) were assessed via a qualitative UDS; (2) urine cotinine levels were assessed via a semi-quantitative urine cotinine test (Acutest NicAlert® urine semi-quantitative cotinine test, Jant Pharmacal Co.); and (3) quantitative urine cannabinoid level (THC-COOH, creatinine-corrected, ng/dL) were assessed via mass spectroscopy (Quest diagnostics).

2.3. Self-report measures

We assessed clinically relevant constructs using validated and commonly used self-report instruments described in detail elsewhere (Hammond et al., 2020). As the smoking group regularly used cannabis and combustible tobacco, we focused on measures characterizing addiction severity, frequency of use, and withdrawal related to these substances. Cannabis-related problem severity was assessed with the *Cannabis Use Disorder Identification Test – Revised (CUDIT-R)* (Adamson et al., 2010), an 8-item self-report measure assessing symptoms of DSM-5 CUD over the past six months. Severity of nicotine dependence (termed tobacco-related problem severity here) was assessed with the *modified Fagerström Test for Nicotine Dependence (FTND)* (Prokhorov et al., 1996), a 7-item instrument that has been adapted for youth populations. Substance-use frequencies for cannabis, combustible tobacco, and alcohol were assessed using the *Timeline Follow-back (TLFB),* characterizing past-90-day patterns of use (Sobell and Sobell, 1992). Severity of nicotine withdrawal was assessed with the *Minnesota Nicotine Withdrawal Scale (MNWS)*, a 20-item measure assessing cognitive, affective, and somatic symptoms of nicotine withdrawal in people with daily tobacco use (Hughes and Hatsukami, 1986).

2.4. ERP reward-feedback task

A four choice gambling task modeled after Holroyd et al. (2003) (Holroyd et al., 2003) presented the participant with four lifelike balloon images of different colors (red, blue, orange, and green) that randomly appeared in different serial positions along a row centered on the screen (Supplemental Fig. 1). The object of the game, titled "Money Maker", was to select balloons, one at a time, to win money. Participants responded with their right and left middle and index fingers on a four-button response pad. Participants were told to try to win as much money as possible, and that they would receive this money at the end of the game. After each selection, all the balloons disappeared, and a green dollar sign (indicating a reward of 25¢), a white circle (indicating 'breaking even' with no win or loss of money), or a red X (indicating a loss of 25¢) appeared. Subsequent to balloon selection on each trial, feedback was delayed by 1 s. Feedback lasted 1000 ms followed by a 1000–2000 ms crosshair, and a 100 ms blank screen before the balloons reappeared. Participants made balloon choices at self-paced intervals.

Although there were four options (balloons to choose from) on a given trial, feedback was rigged to have the probability of 33.3% reward, 33.3% neutral, and 33.3% loss across the task. Feedback was random, meaning that there was no pattern of certain balloons predicting specific outcomes, but adolescents were led to believe that some people 'can figure out a pattern some of the time'. Participants were reminded to look at the screen and not at their hands, as they would in a video game to reduce eye-movement artifact.

Participant earnings were displayed numerically on the screen, centered just below the middle two balloons. There were four blocks of trials with approximately 45 trials in each block. After each block, a clear glass coin jar appeared to reflect cumulative winnings to that point. Realistic quarter images appeared in the jar, one by one, each followed by a coin sound. Prior to beginning the game there were 3 practice trials, which introduced the game and coin jar. A total of 180 trials (60 per condition) were administered for the purpose of computing ERPs. Total winnings from the ERP reward-feedback game were $7.25 for each participant. Participants received this payment as part of a larger fixed compensation for completion of the whole study.

2.5. EEG acquisition

Each participant was seated 24 in. in front of a 19 in. computer LCD monitor. Each participant's head circumference was measured to determine the appropriate net size and to mark the Cz as the juncture of the halfway point between naison to inion and left and right preauricular notches. Next, a Hydrocel high-density array of 128 Ag/AgCl electrodes arranged into a net (Geodesic Sensor Net, EGI Inc.) was placed on the participant's head using standard procedures. Before this, the net was soaked in warm potassium chloride solution (KCl) that served as the electrolyte (concentration: 1.5 tsp per liter of water). The KCl solution enabled EEG collection even through hair and without the need for abrading the participant's scalp.

Brain wave data were recorded using the Netstation v.4.4 software package (EGI, Inc.) and EGI high impedance amplifiers, sampling at 1000 Hz (EGI, Inc. Series 300 amplifier). The online filters were set at 0.1–1000 Hz. All electrodes were referenced to Cz for recording and then re-referenced offline for data analysis. All impedances remained at or under 40 kΩ as indicated by impedance measures made immediately before and after the test session. The E-prime v.2.0 (PST, Inc.) software package controlled the stimulus presentation. Each participant's EEG and behavior were continuously monitored across the session so that stimulus presentation occurred only when the participant was sitting still and looking at the monitor.

2.6. EEG preprocessing

Offline post-processing occurred in the Netstation v.4.4 software package (EGI, Inc.) The EEG data were first processed through a 0.3 Hz first-order high-pass filter and a 30 Hz low-pass filter. Then they were segmented to epochs that contained a 100 ms pre-stimulus baseline and 600 ms post-stimulus interval. Bad eye channels were manually marked and interpolated by surrounding channels. In the next step, artifact rejection was applied, in which bad segments (threshold 200 μV) were marked. Epochs with any eye blink or eye movement (threshold 150 μV) were rejected. Epochs with more than 10 bad channels (40% or more segments marked bad) were rejected as well. Then the remaining bad segments were replaced by surrounding channels. The single trial data were re-referenced from the vertex (Cz) to an average reference of all electrodes because the latter was thought to be a better representation of true zero (Junghöfer et al., 1999). The data were baseline-corrected to a 100 ms pre-stimulus interval. Finally, single-trial data were averaged respectively for each condition (reward, neutral, loss). Participants providing at least 30 artifact-free trials per condition were included (n = 19). Data for participants with fewer than 30 artifact-free trials per condition received additional preprocessing with statistical eye-blink

removal (blink threshold 14 μV/ms) (Gratton et al., 1983). Participants whose data yielded 30 good trials per condition with this additional approach (n = 46) were then included in the overall statistical analysis (n = 65). The participants receiving artifact removal were not significantly different from those not receiving artifact removal in terms of reward/neutral/loss ERP amplitude, latency, age, sex, IQ, or group status (smoking, non-smoking) (*t's* = 0.45–1.57, all *p's* > *0.05*).

Past work on the feedback negativity has localized the FRN to the medial frontal region along the midline at site Fz (10–10 system). We relied on the average signal of four electrodes over the midline in this region, specifically electrode numbers 11 (Fz), 12, 5, and 6 (Supplemental Fig. 1) consistent with prior studies (Crowley et al., 2009, 2013; Yau et al., 2015). For ERP analysis, the FRN amplitude was defined as the mean ± 25 ms around the negative peak amplitude between 200 and 350 ms within our electrode cluster. Latency for the negative peak of the FRN was assessed over the same channels and in the same 200–350 ms window.

2.7. Data analysis

Analyses were conducted using IBM SPSS Statistics Analytic software V25.0 (IBM, Armonk, NY). For both FRN amplitude and latency data, analyses employed repeated measures analysis of variance (RM-ANOVAs). All F-tests are reported with Greenhouse-Geisser correction (Greenhouse and Geisser, 1959). RM-ANOVA consisted of condition (reward vs. neutral vs. loss) as the within-subjects factor and group status (smoking vs. non-smoking) as the between-subjects factor. Age, sex, ethnicity/race, and FSIQ were included in the models as covariates of no interest. To link altered mediofrontal electrocortical activity with clinically relevant constructs, we conducted *a priori* hypothesized multivariate general linear models (GLMs) using RM-ANOVAs between identified FRN amplitude and latency values and CUDIT-R and FTND scores among the smoking group. The p-values resulting from these *a priori* correlation analyses were Bonferroni corrected (*p = 0.013* for the 4 comparisons examining CUDIT-R and FTND scores each in relation to FRN amplitude and latency). To further link feedback-related electrocortical activity with self-reported and biochemical measures of drug use and withdrawal from smoking, we conducted post-hoc exploratory correlations between FRN amplitude and latency and each smoking adolescent's nicotine withdrawal score, cannabis and tobacco use frequency, and biochemical assays. These exploratory correlation analyses were not Bonferroni-corrected for multiple comparisons. Inspection of the data on cannabis use frequency in TC adolescents showed a bimodal distribution suggesting two cannabis-related subgroups (Hammond et al., 2020). Based upon this observation, supplemental group-based analyses were also performed, stratifying the TC adolescents by daily cannabis use status (supplemental data section 4). Lastly, a series of sensitivity analyses were performed to determine if individual differences in alcohol use and recency and frequency of cannabis and tobacco use measured via self-report and biochemical assay accounted for variance in the FRN outcomes. These analyses were done by rerunning the main analyses: (1) controlling for alcohol use; (2) excluding TC adolescents with fewer than 100 lifetime cannabis use episodes and who did not use cannabis in the past 30 days; and (3) after restricting the smoking sample to TC adolescents who had used cannabis and/or tobacco in the past 24 h, and had a positive cannabis UDS, and who elected to smoke a cigarette on the scan day (i.e., 'sated-smoking' status).

3. Results

Sociodemographics, drug use, and self-report questionnaire data are presented in Table 1 and described elsewhere (Hammond et al., 2020). FRN results are presented in Table 2 and visually represented in Fig. 1 (total sample) and 2 (group effects).

Table 1
Study Sample Characteristics by Group.

Characteristics	TC Adolescents (n = 36)	Healthy Controls (n = 29)
Male, *n* (%)	24 (69%)	18 (62%)
Age (years)	17.8 (1.15)	17.6 (1.41)
Caucasian, *n* (%)*	16 (46%)	22 (76%)
WASI Full Scale IQ Score[a***]	98.4 (10.33)	107.9 (11.15)
N (%) with over 100 or more lifetime episodes of cannabis use[b***]	29 (82%)	0 (0%)
Cannabis use days per month, past 3 months***	16.9 (12.26)	0.0 (0.14)
CUDIT-R Total Score [c**]	11.8 (7.71)	0.4 (1.32)
Tobacco use days per month, past 3 months***	27.3 (5.88)	0.0 (0.00)
Cigarettes smoked per day, current***	8.2 (5.05)	–
FTND Total Score[d***]	4.1 (1.61)	0.0 (0.00)
Minnesota Nicotine Withdrawal Scale score[e]	8.0 (6.00)	7.6 (5.19)
Alcohol use days per month, past 3 months*	2.2 (2.56)	0.8 (2.45)
Binge drinking days per month, past 3 months*	1.6 (2.39)	0.5 (1.84)
Days since last cannabis use	45.6 (155.12)	–
Days since last cigarette smoked	0.1 (0.40)	–
Urine toxicology screen, qualitative positivity for cannabinoids, *n* (%)***	26 (77%)	0 (0%)
Urinary cannabis level (ng/ml)[f]	140.56 (133.26)	–
Carbon Monoxide level, ppm**	4.7 (4.29)	0.9 (0.39)
Breath Alcohol Level	0.00 (0)	0.00 (0)

*= p < 0.05; **= p < 0.01; ***= p < 0.001
a = Wechsler Abbreviated Scale of Intelligence (WASI) Full Scale IQ Score based upon two subtests, vocabulary and matrix t-scores
b = Lifetime episodes of cannabis use obtained from Youth Risk Behavior Survey (Brenner et al., 1995).
c = Cannabis Use Disorder Identification Test-Revised (CUDIT-R) (Adamson et al., 2010).
d = Fagerstrom Test for Nicotine Dependence (FTND).
e = Minnesota Nicotine Withdrawal Scale score was obtained in 41 participants including 26 smokers and 15 healthy controls.
f = Urine cannabis level represents creatinine corrected cannabis metabolite level (ng/ml) obtained during mass spectrometry in 27 participants who's qualitative urine toxicology screening was positive for cannabinoids.

3.1. Feedback-related condition effects

A significant condition effect for FRN amplitude ($F_{1,64} = 19.87$, $p < 0.001$) and latency ($F_{1,64} = 15.54$, $p < 0.001$) was observed. For amplitude analyses, pairwise comparisons indicated that the loss condition had a more negative amplitude than the neutral condition (Mean Difference (I-J) = 0.44 μV, SE = 0.19, $p = 0.025$) and the reward condition (Mean Difference (I-J) = 1.30 μV, SE = 0.24, $p < 0.001$), and that the neutral condition had a more negative amplitude than the reward condition (Mean Difference (I-J) = 0.86 μV, SE = 0.20, $p < 0.001$) after adjustment for multiple comparisons. For latency analyses, pairwise comparisons indicated that the neutral condition had a shorter latency than the reward (Mean Difference (I-J) = -24.43 ms, SE = 4.90, $p < 0.001$), and loss (Mean Difference (I-J) = -9.35 ms, SE = 3.83, $p = 0.018$) conditions and that the loss condition had a shorter latency than the reward condition (Mean Difference (I-J) = -15.08 ms, SE = 4.47, $p = 0.001$) after adjustment for multiple comparisons. FRN condition effects for amplitude and latency can be seen on visual inspection of the grand average ERP waveforms from the total sample (Fig. 1) and group samples (Fig. 2).

3.2. Group effects in feedback-related electrocortical activity

No group effect or group × condition effect for FRN amplitude (group: $F_{1,64} = 0.76$, $p = 0.39$; group × condition: $F_{1,64} = 0.01$, $p = 0.99$) or FRN latency (group: $F_{1,64} = 0.00$, $p = 0.99$; group × condition: $F_{1,64} =$

Table 2
Feedback Related Negativity (FRN) Amplitude and Latency by group.

Variable (Mean ± SD)	Smoking (n = 36)	Non-smoking (n = 29)	Total Sample (n = 65)
FRN Amplitude (μV)			
Reward	−1.53 ± 2.65	−2.09 ± 2.97	−1.78 ± 2.79
Neutral	−2.38 ± 2.01	−2.95 ± 3.02	−2.64 ± 2.51
Loss	−2.85 ± 2.32	−3.36 ± 2.97	−3.08 ± 2.62
Condition[a]			$F_{1,65} = 19.87$, $p < 0.001$
Group			$F_{1,65} = 0.76$, $p = 0.39$
Condition × group			$F_{1,65} = 0.01$, $p = 0.99$
FRN Latency (ms)			
Reward	286.78 ± 44.27	282.66 ± 40.07	284.91 ± 42.14
Neutral	257.93 ± 34.49	262.65 ± 33.62	260.07 ± 33.91
Loss	269.85 ± 29.27	269.41 ± 24.88	269.66 ± 27.16
Condition[b]			$F_{1,65} = 15.54$, $p < 0.001$
Group			$F_{1,65} = 0.00$, $p = 0.99$
Condition × group			$F_{1,65} = 0.50$, $p = 0.59$

Note: EEG data were analyzed using Repeated Measures ANOVAs with Greenhaus-Geisser correction. Table shows means +/- standard deviations. Statistical analyses are presented without covariates.
a = Post-hoc pairwise analyses using Least Significant Difference of feedback condition effects demonstrated significant between condition differences in FRN amplitude for reward vs. loss (Mean Difference (I-J) = -1.30, SE = 0.24, $p < 0.001$), reward vs. neutral (Mean Difference (I-J) = -0.86, SE = 0.20, $p < 0.001$), and neutral vs. loss (Mean Difference (I-J) = 0.44, SE = 0.19, $p = 0.025$) after adjustment for multiple comparisons.
b = Post-hoc pairwise analyses using Least Significant Difference of feedback condition effects demonstrated significant between condition differences in FRN latency for reward vs. loss (Mean Difference (I-J) = 15.08, SE = 4.47, $p = 0.001$), reward vs. neutral (Mean Difference (I-J) = -24.43, SE = 4.90, $p < 0.001$), and neutral vs. loss (Mean Difference (I-J) = -9.35, SE = 3.83, $p = 0.018$) after adjustment for multiple comparisons.

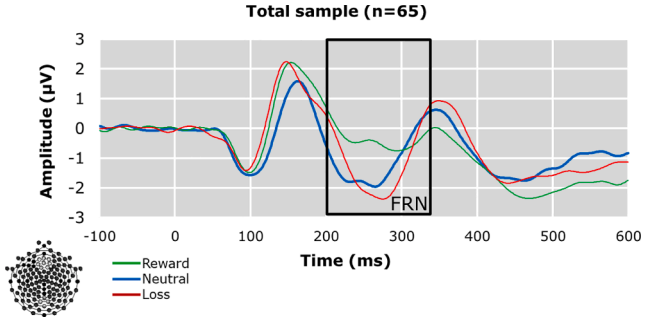

Fig. 1. Feedback Related Negativity for Total Sample.

0.50, $p = 0.59$) were observed (Table 2).

3.3. Relationships between biochemical substance-use measures and feedback-related electrocortical activity

Given the absence of main effects we conducted exploratory analyses incorporating biochemical assays (positive cannabis UDS, urine cotinine levels, and urine cannabis levels) and self-reported alcohol use. Group effects and group × condition effect results were unchanged in these analyses, but a main effect of positive cannabis UDS on FRN amplitude ($F_{1,54} = 6.29$, $p = 0.02$) emerged. Based upon this finding we conducted a simplified ANOVA to examine the effects of positive cannabis UDS status on FRN amplitude in the total sample and smoking adolescents. For the amplitude analyses, the main effect of positive cannabis UDS on FRN remained significant in the total sample ($F_{1,54} = 6.29$, $p = 0.02$) and the smoking adolescents ($F_{1,32} = 9.95$, $p = 0.003$). Post-hoc analyses revealed that positive cannabis UDS status was associated with increased FRN amplitude across reward, neutral, and loss conditions. An interaction effect between urine cotinine level and feedback condition on FRN latency ($F_{1,56} = 3.70$, $p = 0.03$) also emerged in the exploratory group analyses incorporating biochemical substance-use measures, but did not consistently show significance across post-hoc analyses.

3.4. Relationships between self-report substance-use measures and feedback-related electrocortical activity

For FRN amplitude analyses, a condition × CUDIT-R interaction effect ($F_{1,35} = 6.05$, $p = 0.004$) was observed. No main effect for CUDIT and no main or interaction effects for FTND were observed. In sensitivity analyses, the condition × CUDIT-R interaction effect remained significant after individually and collectively covarying for cannabis level, cotinine level, breath CO, last day of cannabis use, tobacco-related problem severity, and self-reported past-30-day cannabis use, tobacco use, and alcohol use. Post-hoc comparisons showed that CUDIT-R scores accounted for variance in reward ($\beta = 0.118$, $t = 2.096$, $p = 0.04$) but not neutral ($\beta = 0.062$, $t = 1.409$, $p = 0.17$) or loss (β = -0.001, t = -0.28, p = 0.98) feedback (Fig. 3).

For FRN latency analyses, no main or interaction effects for CUDIT-R scores were observed. A main effect for FTND on FRN latency ($F_{1,35} = 6.91$, $p = 0.01$) was observed. Main effects for FTND remained significant after controlling for demographics and after individually covarying for breath CO levels, cotinine levels, cannabis levels, last day of cannabis use, cannabis-related problem severity, and self-reported past-30-day uses of cannabis, tobacco, and alcohol. Post-hoc comparisons showed that FTND scores were significantly associated with feedback latency for reward (β = -11.855, t = -2.747, p = 0.01) and neutral (β = -8.505, t = -2.488, p = 0.02) but not loss conditions (β = -3.362, t = -1.082, p = 0.29) (Supplemental Fig 3).

Exploratory analyses in smoking adolescents showed that increased FRN amplitude in response to loss feedback correlated with higher nicotine withdrawal scores (β = -0.512, t = -2.85, p = 0.009) (Fig. 4). In supplemental subgroup analyses, no significant group differences were observed, and daily cannabis use status was unrelated to FRN amplitude and latency (supplemental data section 4). In sensitivity analyses, excluding participants based upon their recency and frequency of cannabis and tobacco use had negligible effects on the main FRN outcomes.

4. Discussion

We investigated cannabis- and tobacco-related differences in feedback-related electrocortical activity following monetary reward, neutral, and loss outcomes during a non-learning guessing task in a biochemically verified sample of adolescents with daily cigarette smoking who use tobacco and cannabis regularly (TC adolescents) and matched individuals (HCs). Regarding condition effects, we observed amplitude and latency differences between monetary reward, neutral, and loss feedback. Regarding group effects, no differences in FRN amplitude or latency were seen between TC and HC adolescents. Exploratory analyses suggested that residual cannabis levels influenced feedback processing in non-deprived TC adolescents. Among TC adolescents, FRN amplitude was associated with cannabis-related problem severity (for reward feedback) and nicotine withdrawal (for loss feedback), whereas FRN latency was associated with tobacco-related problem severity. Together, these results suggest that cannabis and tobacco may produce dissociable effects on feedback processing, supporting an incentive salience model of cannabis addiction in TC adolescents.

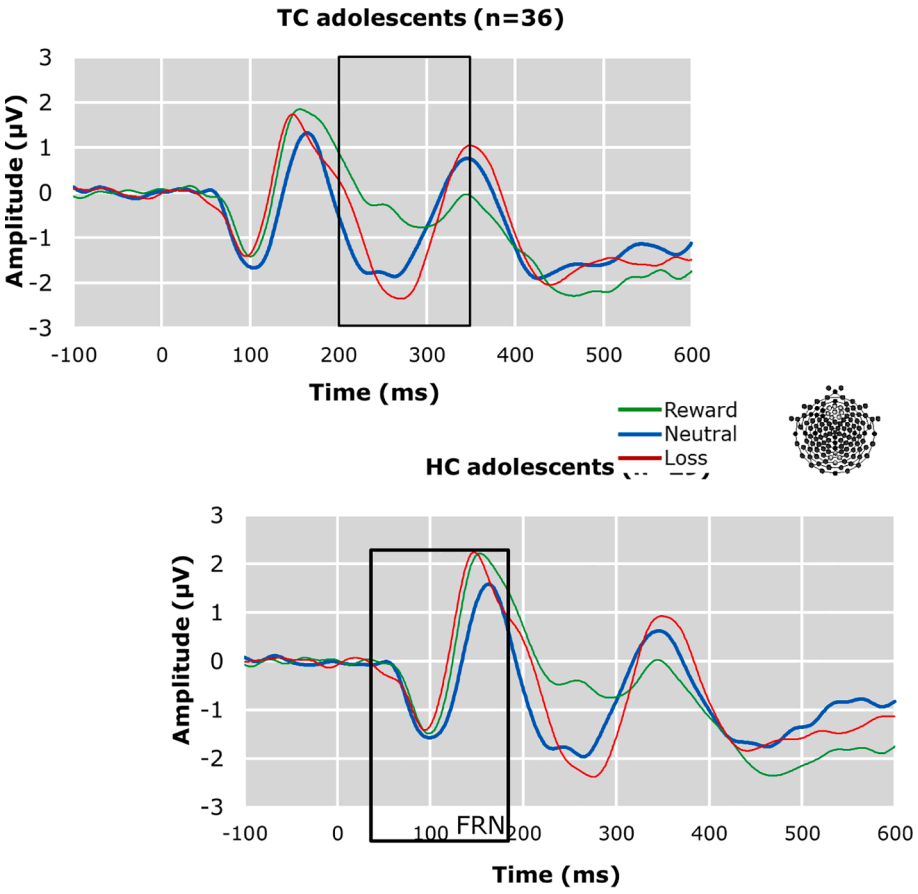

Fig. 2. Feedback-Related Negativity for Adolescents with and without Daily Smoking.

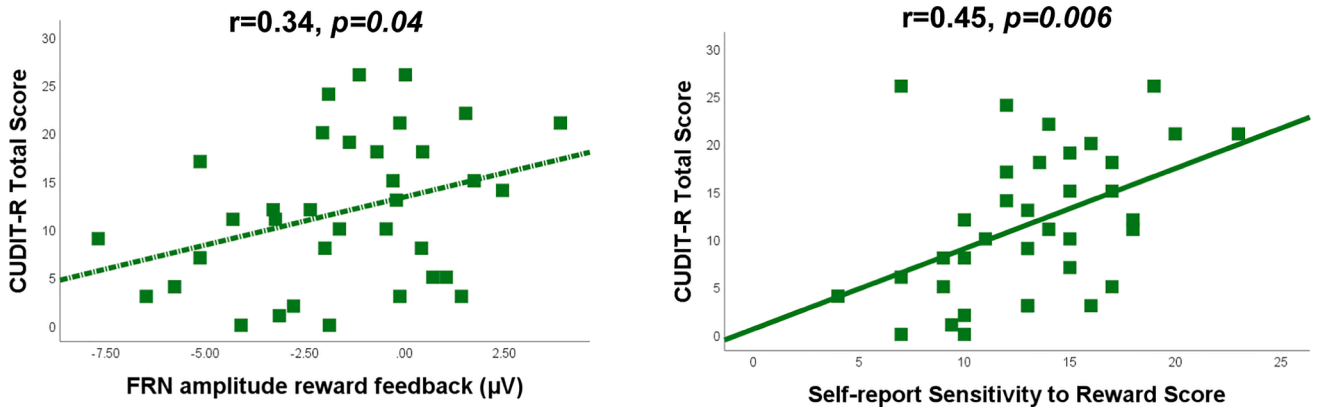

Fig. 3. Correlations between cannabis-related addiction severity, electrocortical response to reward feedback, and self-reported sensitivity to rewards in TC adolescents.

Our main findings regarding feedback-related condition effects, did not support our *a priori* hypothesis that feedback-related electrocortical activity would differentiate between reward and anti-reward feedback with no differences between neutral and loss conditions. We observed differences in FRN amplitude and latency across conditions, with increasing amplitude from reward to neutral to loss, and increasing latency from neutral to loss to reward, supporting a step-wise as opposed to binary function of feedback processing. This finding diverges from previous studies of the FRN in adults (Hajcak et al., 2006, 2007; Holroyd et al., 2006). Differences from prior studies may be due to developmental effects (Crowley et al., 2013; Ferdinand et al., 2016) or differences in study design, task parameters, electrode selection, electrode density and scalp coverage, or data acquisition and processing techniques. Despite the divergence with prior FRN study findings, our results do align with evidence from other fields suggesting a distinction between responses to neutral vs. rewarding and punishing stimuli at neurochemical, neuroanatomical, neurophysiological, and behavioral levels (Boksem et al., 2008; Gardner, 2011; Haber and Knutson, 2010; Lammel et al., 2014; Urcelay and Miller, 2014).

Our main hypothesis that FRN would be decreased across feedback conditions in smoking relative to non-smoking adolescents was not supported. We observed no group or condition × group interaction effects in TC relative to HC adolescents for feedback-related electrocortical activity. These findings are not consistent with prior studies in

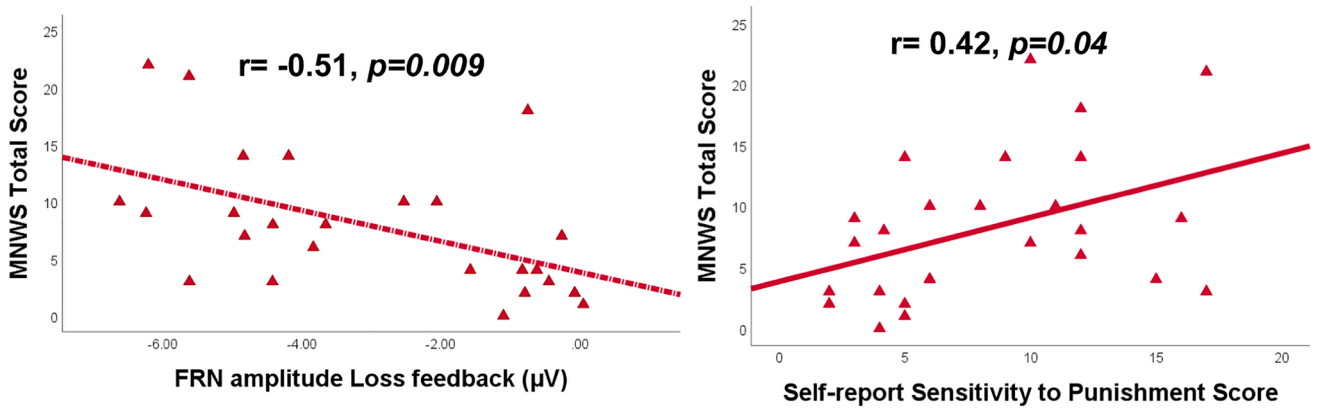

Fig. 4. Correlations between nicotine withdrawal severity, electrocortical response to loss feedback, and self-reported sensitivity to punishment in TC adolescents.

abstinent adults with SUDs (Baker et al., 2016, 2011; Parvaz et al., 2015) and at-risk youth (Crowley et al., 2009; Yau et al., 2015) which show decreased FRN amplitudes relative to matched controls (alternatively see (Torres et al., 2013)). Differences from prior studies may relate to different study sample characteristics, experimental designs, and data analysis approaches. For example, a probabilistic reward learning task could identify impairments in reward learning that may not be detected with a feedback processing task. Another possible explanation for our negative between-group findings is that tobacco and cannabis may exert directionally opposite effects on the EEG signal (D'Souza et al., 2012; Domino, 2003; Houston and Ceballos, 2013) with co-use of tobacco and cannabis canceling out EEG effects that might otherwise be observed in tobacco-only-using or cannabis-only-using individuals. Our post-hoc exploratory analyses, showing directionally opposing effects of cannabis and tobacco variables on feedback-related electrocortical activity, provide indirect support for this. Multiple fMRI studies also suggest divergent patterns of neural activity during reward and loss processing relating to cannabis use versus tobacco use (Cousijn et al., 2013b; Peters et al., 2011). Thus, the combined effects of cannabis and tobacco, acutely and/or chronically, may alter brain function in complex ways that could mask individual effects that either drug may produce in isolation.

Similarly, effects related to acute or residual nicotine or cannabis levels or withdrawal-related negative affect in TC adolescents could potentiate or mitigate existing underlying abnormalities observed on EEG. As TC adolescents in our study were assessed in a non-deprived state, acute or residual nicotine or cannabinoids may have affected the EEG signal. Prior studies in nicotine-deprived cigarette-smoking adults report that disrupted EEG signaling during evoked stimuli and attention processing "normalizes" with cigarette smoking or nicotine administration (Cui et al., 2013; Domino, 2003; Evans et al., 2015). Our findings relating the severity of withdrawal to FRN amplitude during loss feedback converges with previous work from our group showing differences in self-report measures of punishment sensitivity in TC adolescents (Hammond et al., 2020) (Fig. 4), consistent with studies showing that increased neural reactivity during loss processing is related to sensitivity to punishment in non-smoking individuals (Boksem et al., 2008) and to withdrawal severity in abstinent cigarette-smoking individuals (Addicott et al., 2012).

Among TC adolescents, cannabis-related and tobacco-related problem severities were related to different aspects of the FRN profile, with cannabis-related problem severity being associated with amplitude and tobacco-related problem severity being associated with latency. Our findings linking cannabis-related and tobacco-related problem severities with FRNs remained significant in analyses that accounted for addiction severity to the other drug (cannabis-related problem severity for tobacco analyses and vise-versa) and concurrent and recent use of alcohol, cannabis, and tobacco (assessed via self-report measures and biochemical assays). The cannabis-related-problem-severity-FRN-amplitude relationship was only found in relation to reward feedback (positive correlation). This suggests that TC adolescents may exhibit a neural sensitivity to reward feedback associated with cannabis addiction severity, converging with our previous work using self-report measures of reward sensitivity (see Fig. 3). Our results are consistent with prior studies showing increased cortico-striatal-limbic activity in response to drug-cues (Cousijn et al., 2013a; Filbey and DeWitt, 2012; Filbey et al., 2016) and monetary rewards (Filbey et al., 2013; Nestor et al., 2010; Stice et al., 2013; van Hell et al., 2010) in adolescents and adults who use cannabis, and diverges from studies of tobacco use showing decreased striatal activity in response to monetary rewards (Karoly et al., 2015; Martin et al., 2014; Peters et al., 2011). This suggests that youth with higher CUD symptomatology may exhibit dysfunctional feedback processing and show a hyper-responsiveness to reward receipt in dACC, medial PFC, and striatal brain regions believed to contribute to the generation of the FRN signal(Becker et al., 2014; Gehring and Willoughby, 2002; Heydari and Holroyd, 2016). Preclinical models indicate that cannabinoids modulate reward-seeking behaviors by enhancing phasic dopamine burst signals in the midbrain dopaminergic system believed to be the source of the FRN signal (Wenzel and Cheer, 2014). Further, animal models suggest that cannabis exposure during adolescence may result in long-lasting disruption in cortical-striatal-limbic circuits along with enhanced dopamine signaling in response to drug-related rewards (Lee and Gorzalka, 2012; Pistis et al., 2004). The present study's findings linking cannabis-related problem severity and FRN reward amplitude lends additional support to an incentive salience model for adolescent CUD. The cannabis-related reward sensitivity could be a result of adolescent cannabis use sensitizing the brain's motivational systems. Alternately, heightened neural sensitivity to reward receipt could represent an endophenotype predating substance use onset and increasing the risk for development of cannabis-related problems. These explanations are not mutually exclusive—both may contribute to the observed association. That the reward sensitivity association was related to addiction severity for cannabis but not tobacco suggests a substance-specific effect for cannabis on reward signaling. Increased electrocortical activity following reward receipt could represent a cannabis-specific endophenotype not observed in relation to tobacco or alcohol, which may be better characterized by reward deficiency models. Interestingly, we also found that biochemical substance-use measures influenced feedback processing in TC adolescents. The presence of cannabinoids, indexed by positive cannabis UDS, was associated with increased feedback-related electrocortical activity across conditions. This finding suggests that relatively acute cannabis use may produce broad cross-valence effects on feedback processing that differ from addiction-related effects which are unique to reward feedback. Determining whether reward sensitivity predates, tracks-with, or is the consequence of adolescent cannabis use should be further

explored.

The present study is the first to examine cannabis-use- and tobacco-use-behavior-related latency effects during an EEG reward-processing task. We found that tobacco-related problem severity was associated with a decrease in mean FRN latency, suggesting that TC adolescents with more severe tobacco addiction had increased speed of processing motivational outcomes. This result is consistent with EEG studies in tobacco-smoking adults demonstrating that acute nicotine administration or cigarette smoking improves attention and information processing and shortens ERP latencies across multiple cognitive tasks (Domino, 2003; Hall et al., 1973; Houlihan et al., 1996; Ilan and Polich, 1999, 2001; Pritchard et al., 2004). Post-hoc analyses indicated that the strength of this association was valence-specific: unique to reward and neutral but not loss feedback. As negative affective states (i.e., depression, anxiety) are implicated in the development and maintenance of cigarette smoking and nicotine dependence (Patton et al., 1998, 2006; Richards et al., 2011; Sinha, 2008; Wills et al., 2001), modulation of attention bias away from negative stimuli may be one mechanism by which tobacco-smoking alters negative affect (Adams et al., 2015; Rzetelny et al., 2008). Our findings are consistent with other studies of attention bias in tobacco-smoking adults showing a tobacco-related shift in attention bias away from negative stimuli (Gilbert, 1997; Gilbert et al., 2008, 2007). Attentional biasing may be a central mechanism for affect regulation in cigarette-smoking adolescents. Further research in this area is warranted.

Some study limitations should be considered. Our study was cross-sectional; thus, causal relationships could not be inferred. Longitudinal designs could be used in future studies to investigate premorbid functioning and EEG patterns prior to drug exposure. Additionally, while none of our study participants had to be rescheduled due to intoxication, scanning in the non-deprived state made it difficult to isolate acute and chronic effects of tobacco and cannabis, despite our controlling for CO, cotinine, and cannabis level in our analyses. Further, we did not systematically query for all methods of administration and use patterns of different types of tobacco products (e-cigarettes, hookah, cigarillos) or cannabis products (vaporized, edibles, concentrates). Over the past several years, cannabis and nicotine vaping has increased dramatically among U.S. adolescents. It is important to note that vaping was less frequent among youth at the time of data collection (2012–2014) for the study, exemplified by identification of only one individual in the sample who endorsed dual e-cigarette and combustible cigarette use. Removal of this participant from analyses did not impact the study's results. Given this, our results only characterize combustible tobacco-use and cannabis-use use associations. As the inclusion/exclusion criteria were framed primarily around tobacco use, we were limited by the natural heterogeneity of cannabis use behaviors in the smoking sample. Thus, while we conducted multiple additional analyses, the high frequency of co-occurrence of tobacco and cannabis use in our smoking sample made it difficult to examine the unique effects of cannabis and tobacco on feedback processing. To better characterize isolated and interactive effects, future studies should seek to recruit separate groups of tobacco-naïve adolescents who use cannabis and cannabis-naïve adolescents who use tobacco in addition to TC adolescents.

5. Conclusion

In conclusion, this study has several important implications. Our data suggest that FRN amplitudes and latencies differentiate between monetary reward, neutral outcomes, and loss feedback following a stepwise function in adolescents. While these findings require replication, they suggest that the FRN reward learning theory may require revision. Regarding smoking effects, our findings converge with a growing literature indicating that cannabis and tobacco may produce dissociable substance-specific effects on brain function and extend this evidence to feedback processing in TC adolescents (Filbey et al., 2018; Wetherill et al., 2015a). While no group-level differences in feedback processing were observed in non-deprived TC adolescents (relative to HCs), multiple cannabis-use and tobacco-use variables accounted for variance in the FRN signal. Among TC adolescents, cannabis-related and tobacco-related problem severities were associated with different aspects of the FRN signal, suggesting divergent mechanisms. Cannabis-related problem severity was associated with FRN amplitude during reward feedback, supporting an incentive salience model of cannabis-related problem severity, whereas tobacco-related problem severity was associated with FRN latency during non-negative feedback pointing to possible attention bias mechanisms for affect regulation. These outcomes provide preliminary evidence linking feedback-related mediofrontal electrocortical activity with more acute drug- and withdrawal-related facets and longer-term addiction-related facets of cannabis and tobacco use in adolescents.

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CRediT authorship contribution statement

Christopher J. Hammond: Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Jia Wu:** Formal analysis, Data curation, Writing - review & editing. **Suchitra Krishnan-Sarin:** Conceptualization, Methodology, Investigation, Writing - review & editing. **Linda C. Mayes:** Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing - review & editing, Supervision. **Marc N. Potenza:** Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing - review & editing, Supervision. **Michael J. Crowley:** Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing - review & editing, Supervision.

Conflict of interest and financial disclosures

None of the authors have any conflicts of interest. Dr. Hammond serves as a scientific advisor for the National Courts and Science Institute and as a subject matter expert for the Substance Abuse Mental Health Services Administration (SAMHSA) related to co-occurring substance use disorders and severe emotional disturbance in youth. Dr. Krishnan-Sarin has received investigational medications from Astra Zeneca and Novartis for studies on alcohol drinking behaviors. Dr. Potenza has consulted for Rivermend Health, Opiant Therapeutics, Addiction Policy Forum, Game Day Data, Idosia and AXA; has received research support (to Yale) from Mohegan Sun Casino and the National Center for Responsible Gaming; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse-control disorders or other health topics; has consulted for and/or advised gambling and legal entities on issues related to impulse-control/addictive disorders; has provided clinical care in a problem gambling services program; has performed grant reviews for research-funding agencies; has edited journals and journal sections; has given academic lectures in grand

rounds, CME events and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts. Dr. Mayes reports no disclosures. Dr. Crowley received grant funding from the NIH (T32 MH018268).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102592.

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